PERITONEAL DIALYSIS PRIMER

Editors

Dakshinamurty KV
Siva Kumar V
Ram R
Sangeetha Lakshmi B

First Edition 2017

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Ram R, Swarnalatha G, Pai BS, Rao CS, Dakshinamurty KV. Cloudy peritoneal fluid attributable to non-dihydropyridine calcium channel blocker. Perit Dial Int. 2012;32(1):110-1.

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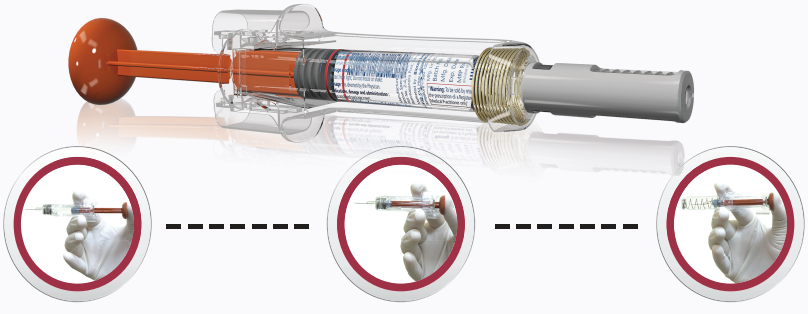

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Dakshinamurty KV, Siva Kumar V, Ram R, Sangeetha Lakshmi B

Editors

PERITONEAL DIALYSIS

PRIMER

First Edition

Peritoneal Dialysis Primer is dedicated to Prof. Dimitrios G. Oreopoulos, MD, PhD

It is a sacred opportunity to pay respects, gratitude and homage to our loving teacher Prof DG Oreopoulos.

Physicians of utmost fame were called at once; but when they came they answered, as they took their fees 'there is no cure for this disease"- Hilaire Belloc

We all agree "Urem ia" was one such entity in the yester years. In the company of many of his compatriots, Prof. D G Oreopolus offered a seemingly simple, yet perfectly scientific innovation "CAPD" with his gentle hands and brought hope and cheer in many a life over the years of his practice.

Dear sir, we your students are grateful to you for the training and values you imparted to us. Sir, in one voice, we reiterate, that you are forever in our memories for your blessings to make us lead a meaningful life in the care of needy and sick fellow beings. It is said, the nicest place to be is in someone's thoughts, the safest place to be is in someone's prayers, and the best place to be is in God's hands.

May god bless our teacher and his family for all their affection towards us.

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PREFACE

Peritoneal dialysis is now an accepted treatment ofpatients with end stage renal disease. Peritoneal dialysis restores not merely life but an acceptable quality of life to the patients. The proportion of patients with end stage renal disease receiving peritoneal dialysis is far less than the proportions of haemodialysis and renal transplantation. Nevertheless, few of us would have even imagined ten years ago that peritoneal dialysis has become a relatively common procedure than before.

The major impediment for expansion of peritoneal dialysis is that all the nephrology teaching programmes in our country do not impart training in peritoneal dialysis to the desired standards. One of the reasons for this lack of training is the want of a textbook that teaches fundamentals, emphasizes on the crucial topics and also presents an overview of developing areas.

The doctor whom doctors want to see, when they or their kith are ill, is the one they recognize as having great knowledge, exceptional experience, and good judgement, of patients and their disease. We have asked such doctors to write for this book. All the authors and we hope that this book will be a literate as well as a comprehensive guide to the peritoneal dialysis.

We acknowledge the unrestricted and unconditional academic grant extended by Biocon Limited for publication of this book.

We are grateful to Dr. Shivali Arora, Knowledge Isotopes Pvt. Ltd., (www.knowledgeisotopes.com), India, a medical writing company for helping us to edit, proofread, format and also offer critique services for our manuscripts.

Our debts are to our parents, families, teachers, students, technicians and to our patients.

Authors

Foreword

The Peritoneal Dialysis Primer is the first text book authored by renowned academicians actively practicing in peritoneal dialysis therapy in India. The lead authors Prof. K .V. Dakshinamurty, Prof. V. Sivakumar, Prof. R. Ram, Dr. B. Sangeetha Lakshmi have done a commendable work in formulating and editing the Primer. The book starts with history of peritoneal dialysis followed by a scholarly and comprehensive review of the science and clinical practice of peritoneal dialysis which is included in sixty chapters. This is a valuable resource for all those who are interested in the therapy. This comprehensive Primer is targeted at medical students, junior doctors, nephrology trainees, nephrologists research scholars, nurses, dieticians, pharmacologists and many others. The chapters review details of peritoneal dialysis in neonates, infants and children, women including pregnant women, adults and elderly. Further, the chapters cover organization of peritoneal dialysis program in India, newer solutions, cardio renal syndrome, diabetics, use of information technology, economics of therapy, outcomes comparing haemodialysis, infectious and non-infectious complications, nutrition, acute kidney injury, adequacy and automated Peritoneal Dialysis.

This Primer is being published at a time when peritoneal dialysis is being underutilized in India and the South Asian countries. One of the main reasons for underutilization of peritoneal dialysis as a renal replacement therapy is clearly a lack of knowledge and experience with peritoneal dialysis among the medical profession. Nephrology training programs are expected to provide education and experience in peritoneal dialysis. Many programs are poorly equipped and motivated to spread the knowledge of peritoneal dialysis, far and wide.

I join with my esteemed colleagues who have devoted their time and effort in writing the chapters in the Peritoneal Dialysis Primer, dedicating this comprehensive book to the memory of late Prof. D. G. Oreopoulos who was a mentor and teacher to many of us. My hope is that Primer with a state-of-the-art knowledge about peritoneal dialysis will be an academic tool for many in India and abroad.

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Acronyms and Abbreviations

3,4-DGE	3,4-Di-Deoxyglucosone-3-ene
3DG	3 Deoxyglucosone
5-HMF	5-Hydroxymethyl-Furfural
AAs	Amino Acids
ACE	Angiotensin-Converting Enzyme
ACEi	Angiotensin-Converting Enzyme Inhibitor
ADP	Adenine Di-Phosphate
AGEs	Advanced Glycation End products
ALP	Alkaline Phosphatase
ANZDATA	Australia and New Zealand Dialysis and Transplantation
AOPP	Advanced Oxidation Protein Products
APC	Antigen Presenting Cells
APD	Automated Peritoneal Dialysis
APEX	Accelerated Peritoneal Examination
ARB	Angiotensin Receptor Blocker
BIA	Bioelectrical Impedance
BMI	Body Mass Index
BP	Blood Pressure
CANUSA	Canada-United States
CAPD	Continuous Ambulatory Peritoneal Dialysis
CCPD	Continuous Cycling Peritoneal Dialysis
CCr	Creatinine Clearance
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CPD	Chronic Peritoneal Dialysis
CPD	Continuous Peritoneal Dialysis
CQI	Continuous Quality Improvement
CRP	C-reactive Protein
CT	Computerized Tomography
CTP	CT Peritoneography
CTPD	Continuous Tidal Peritoneal Dialysis
CVD	Cardiovascular Disease
D/P sodium	Dialysate/Plasma ratio sodium
DATT	Dialysis Adequacy Transport Testing
DEXA	Dual Energy X-ray Absorptiometry
DFR	Dialysate Flow Rate
DIPD	Daytime Intermittent Peritoneal Dialysis
EAPOS	European Automated Peritoneal Dialysis Outcome Study
EBPG	European Best Practice Guideline

ECW	Extracellular Water
EMT	Epithelial Mesenchymal Transformation
EPS	Encapsulating Peritoneal Sclerosis
ESI	Exit Site Infecions
ESR	Erythrocyte Sedimentation Rate
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
FM	Fat Mass
FP	Fungal Peritonitis
FWT	Free Water Transport
G6PD	Glucose 6 Phosphate Dehydrogenase
GDH	Glucose Dehydrogenase
GDH-PQQ	Glucose Dehydrogenase Pyrroloquinolinequinone
GDPs	Glucose Degradation Products
GFR	Glomerular Filtration Rate
GO	Glucose Oxidase
GP	Glucose Polymer
H_2O_2	Hydrogen Peroxide
Hb	Hemoglobin
HBV	Hepatitis B
HCG	Human Chorionic Gonadotrophin
HCV	Hepatitis C
HD	Hemodialysis
HDL	High Density lipoprotein
HGS	Handgrip Strength
HK	Hexokinase
HPDU	Home Peritoneal Dialysis Unit
HPMC	Mesothelial Cells
IAP	Intra-Abdominal Pressure
IDPN	Intra Dialytic Parenteral Nutrition
IGF	Insulin-like Growth Factor
IL	Interleukins
IPP	Intra-Peritoneal Pressure
IPV	Intra-Peritoneal Volumes
ISPD	International Society for Peritoneal Dialysis
ISRNM	International Society of Renal Nutrition and Metabolism
ITT	Intention to Treat
KDOQI	Kidney Foundation Dialysis Outcomes Initiative
LAL	Limulus Amebocyte Lysate
LBM	Lean Body Mass
LDL	Low Density Lipoproteins
LPSs	Lipopolysaccharides
MALDI-TOF	Matrix-Assisted Laser Desorption Ionization-

	Time of Flight
MALDI-TOF MS	Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry
MBP	Major Protein
MCP	Monocyte Chemoattractant Protein
MGO	Methyl Glyoxal
MHC	Major Histocompatibility Complex
MIC	Minimal Inhibitory Concentration
MIS	Malnutrition Inflammation Index
MMP-9	Matrix Metalloproteinase-9
MTAC	Mass Transfer Area Coefficient
MW	Molecular Weight
NAD	Nicotine Adenine Dinucleotide
NADP	Nicotine Adenine Dinucleotide Phosphate
NECOSAD	Netherlands Cooperative Study on the Adequacy of Dialysis
NF-B	Nuclear Factor B
NGAL	Neutrophil Gelatinase-Associated Lipocalin
NIPD	Nocturnal Intermittent Peritoneal Dialysis
NMR	Nuclear Magnetic Resonance
NO	Nitric Oxide
NTM	Nontuberculous Mycobacteria
NTPD	Nightly Tidal Peritoneal Dialysis
NYHA	New York Heart Association
OCG	Osmotic Conductance to Glucose
ONOO	Peroxynitrate
oxLDLs	Oxidizes Low Density Lipoproteins
PAA	Phenylacetic Acid
PAF	Platelet Activating Factor
PAMP	Pathogen Associated Molecular Patterns
PCR	Polymerase Chain Reaction
PD	Peritoneal Dialysis
PDF	Peritoneal Dialysis Fluid
PDSI	Peritoneal Dialysis Society of India
PEM	Protein Energy Malnutrition
PET	Positron Emission Tomography
PET	Peritoneal Equilibration Test
PEW	Prevalence of Wasting
PG	Prostaglandin
PL	Peritoneal Lymphocytes
PMNc	Polymorphonuclear Cells
PQQ	Pyrroloquinoline Quinone
PRR	Pattern Recognition Receptors
QOL	Quality of Life
RBP	Retinol Binding Protein

RKF	Residual Kidney Function
RRF	Residual Renal Function
RRT	Renal Replacement Therapy
SC	Sieving Coefficient
SERS	Surface Enhanced Raman Spectroscopy
SGA	Subjective Global Assessment
SPA	Standard Peritoneal Permeability Analysis
Tb	Tuberculosis
THP	Tamm-Horsfall Protein
TLR	Toll-Like-Receptors
TNF	Tumor Necrosis Factor
TW	Toronto Western
TWH	Toronto Western Hospital
UFF	Ultrafiltration Failure
USRDS	United States Renal Data System
UTI	Urinary Tract Infections
VLDL	Very Low Density Lipoprotein
WBC	White Blood Cell
WHO	World Health Organisation

Chapter 1

History of

Peritoneal Dialysis

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History of Peritoneal Dialysis

"The Generation which Ignores History has no Past and No Future"

– George Orwell.

Introduction

The history of peritoneal dialysis (PD) should actually begin from the description of peritoneal cavity first mentioned in Ebers papyrus in 1550 and was demonstrated by the Egyptians. Ebers papyrus is a scroll documenting ancient Egyptian medicine.

PD in Initial Stage

There were experiments conducted in the late eighteenthand early nineteenth century demonstrating permeability of peritoneum. I am not detailing it here as I could not get hold of the original paper.

George Ganter in 1923 first performed PD in rabbits and guinea pigs as mentioned by the various authors [1]. The original paper is in German language [2]. Fine and colleagues in 1940 successfully treated an anuric patient with peritoneal irrigation. The method adopted was more like a peritoneal lavage [3].Though PD was attempted earlier than hemodialysis (HD) in the treatment of renal failure, it did not gain popularity due to associated problems such asaccess failure,hemorrhage and infection leading to a very early drop out.

Peritoneal Catheters

In 1960's, intermittent PD was practiced in some centres. The patient would come to the hospital once or twice a week for dialysis. These were the patients who were not accepted on HDdue to non-availability of HD machines or not suitable for HD.

The patient had to undergo insertion of stiff peritoneal catheter repeatedly each time with a fear of complications like bowel perforation or bleeding [4]. This was circumvented by Norman Deane who designed a prosthesis which was inserted between the skin and peritoneal cavity keeping the tract patent. Everytime, the stylet catheter was inserted through the tract after removing the prosthesis. As this prosthesis was not commercially available, this was indigenously made,at Toronto Western Hospital [5].

Until 1940, different devices were used for peritoneal access without much success.These were needles, glass cannulas, stainless steel coil and Foley's catheter. The glass tubes either had straight end or mushroom head.Nylon catheters, polyethylene, plastic tubes with side holes were tried during the 1950's.Russell Palmer Canadian physician from Vancouver in 1964 designed a permanent peritoneal catheter made of silicone rubber which was 84 cm long, had long subcutaneous tunnel segment without cuffs and the tip in the peritoneal cavity being coiled [6, 7]. At the middle was a triflange step for placement between the fascia

K. C. Prakash

and the peritoneum. This catheter though better than stiff catheter did not reduce number of peritonitis.Tenchkoff in 1968 invented silicon rubberized catheter similar to Palmer catheter but with two Dacron cuffs [8].This catheter was either straight orterminally coiled like that of Palmer. This was permanently placed in the peritoneal cavity and was used for intermittent PD. Since then there havebeen many modifications in the design of the catheter in order to reduce complications such as migration, fluid leak, mesenteric wrapping and peritonitis. The other modifications were:

1. Attaching three discs in the intra-peritoneal segment of the catheter named as Toronto Western hospital catheter designed by Oreopoulus and Zellerman. This was further designed into two types. Type-1 had double cuff straight catheter with two silicon discs in the intra-peritoneal segment and type-2 had Dacron disc and silicon ring at the base of intra-peritoneal cuff [9].
2. Column disc catheterwas discontinued and changed to into Ash T-Fluted variety [10].
3. Valli catheter designed in 1983 had intra-peritoneal segment covered with silastic balloon with holes in order to prevent omental wrapping [11].
4. Swan neck catheter was introduced by Twardowski *et al,* in 1986 [9].
5. Swan neck long tunneled catheter having exit site in the pre-sternal region [9].

Despite many attempts to modify the structure of the catheter, the original version with two Dacron cuffs still holds good and not inferior in any aspect. In the earlier days, peritoneal catheters had a single hole at the end, which could get blocked due to fibrin or blood clot. Subsequent generation of catheters had terminal and multiple side holes. Present peritoneal catheters are made of either silicone rubber or polyurethane. Despite modifications, catheter failure accounts for 25% of dropouts.

Connecting Systems

With the invention of permanent peritoneal catheter by Tenchkoff, Popovich and Moncrief introduced the concept of continuous ambulatory peritoneal dialysis (CAPD). Two one litre of dialysis fluid filled in two glass bottles were used with a long tube connecting to the peritoneal catheter.They described this technique in the Annals of Internal medicine [12]. The main drawback was very high incidence of peritonitis.This was due to the connection between the catheter and glass bottle not being a closed system leading to a contamination of the dialysis fluid. Moreover, there were many steps required while performingan exchange from connection to disconnection. More the number of steps, more the chance of committing mistakes and introducing infection.

The major advancement was introduction of collapsible plastic bags which reduced the peritonitis rate. Baxter Canada was the first to design peritoneal plastic bags and was first used in the Toronto Western hospital by Oreopoulos [4]. The reduction in peritonitis rate was due to alessser number of steps for connecting and disconnecting. After instilling the fluid into peritoneal cavity, the plastic bag with

the tube was folded without disconnecting and kept in the pocket. The same bag was used for filling the drain fluid at the end of the exchange. This was more of a closed system and was called spike system.The peritonitis rate which was one episode every ten weeks with glass bottles improvedto one in ten to twelve months [4]. Peritonitis was still a major cause for drop out until 1980 when Buoncristiani from Italy designed 'Y' system also known as Perugia system or disconnect system which further reduced the peritonitis rate to one episode in every 36 patient months [13]. Despite a reduction in the peritonitis rate, this system was not accepted in the initial years in the North America. A multi-centre, randomised clinical trial comparing the 'Y' set disconnect system group to standard connecting system was conducted in Canada. The peritonitis rate was better in the 'Y' set group than the standard group [14]. The main reason for this improvement was the introduction of 'flush before fill' technique and use of disinfectant solution (sodium hypochlorite). The disinfectant solutionafter disconnecting is maintained in the line till the drainage. Peritonitis can occur due to bacteria spreading from various routes. Of these, the main place where contamination occurs is at the time of spiking. So, using flush before fill technique can flush the bacteria from the tube into drain bag before filling the peritoneal cavity. The potential risks of disinfectant usage are accidental introduction into peritoneal cavity leading to pain, chemical peritonitis.This can damage the peritoneal membrane reducing the clearance. Various studies show accidental introduction of disinfectant solution occurred once in 2500 bag exchanges to once in 4380 bag exchanges [15, 16]. There were many modifications in connecting systems mainly aiming for reducing peritonitis rate. Following connecting systems were used in the past.

1. Straight line - (spike system).

2. 'O' set.

4. 'Y' set

3. Ultra 'Y' set.

In the 'O' set, there are three connections to be made and the tube is used for four to six weeks. In between exchanges sodium hypochlorite solution (disinfectant) is filled into the tube to prevent bacterial growth. 'Y' set is also a reusable system filled with disinfectant solution at the end of exchange and disconnection. Ultra 'Y' set has two connections to be made but not reused. It comes with drain bag pre-fixed. The two connections to be made are at the patient end to the transfer set and one spiking into PD fluid bag. Now, most centres use "Twin Bag" system. The difference in these connecting systems is the number of connections. Lower the number of connections, lesser the chances of contamination thus reducing the incidence of peritonitis. Twin bag comes with attached drain bag and fluid bag. It has only one connection to be made at the patient end to the transfer set. This system is for single use.

PD cycler

The growth of PD lead to a development of cyclers as this procedure could be done overnight. In 1962, Lasker introduced simple gravity assisted cycler. The system consisted of a cycler, two litre bottles filled with dialysis fluid, plastic tubing for filling and a drain bag [4]. Warm dialysis fluid was delivered with a heater in the system. Subsequent improvement in the technology made the cyclers' more compact, precise volumetric controlled, easy to operate, driven by hydrolic pump and not by gravitation. Boen also introduced first automated PD cycler [17]. After initial attempts with the cycler, the interest died down due to simplicity of CAPD. But over long term new problems cropped up like recurrent peritonitis due to repeated spiking, patient burn out and inadequate dialysis due to drop in residual renal function requiring more exchanges and volume. Diaz-Buxo and his associates introduced PD cycler which were automated delivering three exchanges at night. The main aim was to reduce manual exchanges [18].

Peritoneal Dialysis Fluid

In the early stages, the fluid that was used for PD was either normal saline, 5% dextrose or Ringer's lactate solution. The major complications seen frequently with the use of these solutions was pulmonary edema or electrolyte imbalance.The PD fluid now available is with minor modifications and was composed by Morton Maxwell [19].

The glucose in conventional peritoneal dialysis fluid which is very high when compared to physiologic levels has potential advantages and disadvantages. It could act as an osmotic agent for ultrafiltration and a source of energy. Gotolib *et al,* in 1985 showed basement membrane changes in peritoneal membrane venules in non-diabetic patients on long term PD [20]. The dialysis fluid has been shown to cause peritoneal injury, which is been attributed to glucose. Glucose degradation products (GDP) and advanced glycosylation end products (AGE) have been shown to accumulate in peritoneal tissue causing inflammation and interstitial fibrosis. This also gets absorbed into the systemic circulation [21]. Also, it aggravates long term metabolic complications such as hyperlipidemia and obesity. This has led to the development of bio-compatible solutions either by reducing the glucose load or by increasing the pH. In 1990's, polyglucose or icodextrin was substituted instead of glucose in PD solution. Icodextrin is a starch derived glucose polymer derivedfrom maltodextrin which acts as an iso-osmolar osmotic agent by colloid osmosis without increasing the blood glucose and insulin level. It can induce sustained ultrafiltration over long dwell time over twelve hours period [22].

The other problem is the acidic nature of the PD fluid and this is due to lactate which is added as a buffer and to combat acidosis in renal failure. There is no bicarbonate in the PD fluid as this can precipitate calcium to form calcium bicarbonate.Such type of acidic fluid with lactate and no bicarbonate is bio-incompatible and can lead to mesothelial degradation and loss of integrity of

peritoneum. Also, bicarbonate based PD solution corrects acidosis better, improves nutrition, better growthrate in children and preserves residual renal function [23].

To overcome this problem, the peritoneal bag has been divided into two compartments. One compartment has glucose and the electrolytes with calcium. The other compartment has bicarbonate. As the bicarbonate is separated from calcium, there is no precipitation. The two solutions are mixed at the time of infusion.

Malnutrition is frequently found in patients on CAPD leading to an increased morbidity and mortality [24, 25]. PD fluid containing 1.1% amino acids solution (Nutrineal) was tried using as an osmotic agent and for improving hypoalbuminemia and malnutrition [26]. This fluid can replace the protein and amino acid losses in the peritoneal fluid and also can replace carbohydrate [27]. Studies have shown Nutrineal to be safe with extended use, is associated with improvement in the albumin levels, maintaining adequate body weight and lower mortality rates [28]. Since the first attempt of peritoneal lavage, there has been constant effort to improve the out come of PD over the decades. Different players have contributed in improving the therapy. The effort is to reduce complications leading to drop out, improving bio-compatibility and better survival. PD history will not stop at this point as what is today will become history tomorrow.

References

1.Diaz-Buxo, J. A., 2005: Clinical use of dialysis. *Clinical Dialysis*.In Allen, R. Nissenson, and N. Richard, Eds., McGraw-Hill, 421- 89.

2.Ganter, G., 1923:UeberdieBeseitigunggiftigerStoffeausdemBlutedurch Dialyse. *Munch. Med. Wochschr.,* **70,** 1478.

3.Fine, J. H., H. A. Frank, and A. M. Seligman, 1946: The treatment of acute renal failure by peritoneal irrigation. *Ann. Surg.,* **124,** 857-875.

4.Oreopoulus, D. G., and T. Elias, 2010: The History of Peritoneal Dialysis: Early Years at Toronto Western Hospital. *Dial. Transplant.,* **2010,** 338- 343.

5.Bigelow, P., D. G.Oreopoulos, and G. A. deVeber, 1973: Use of Deane's prosthesis in patients on long term peritoneal dialysis. *CMAJ*, **109,** 999-1001.

6.Palmer, R. A., W. Quinton, and J. E. Gray, 1964: Prolonged peritoneal dialysis for chronic renal failure. *Lancet,* **1,** 700-702.

7.Palmer, R. A., J. E. Newell, E. J. Gray, W. E. Quinton, 1966: Treatment of chronic renal failure by prolonged peritoneal dialysis. *NEJM*, **274,** 248-254.

8.Tenchkoff, H. A., and H. A. Schechter, 1973: Bacteriologically safe peritoneal access device. *Trans. Am. Soc. Artif. Intern. Organs,* **19,** 363-370.

9.Twardowski, Z. J., 2006: History of peritoneal access development. *Int. J.Artif. Organs,* **29,** 2-40.

10. Ash, S. R., and E. M. Janle, 1993: T-Fluted peritoneal catheter. *Adv. Perit. Dial.,* **9,** 223-226.

11. Valli, A., U. Crescimanno, O. Midiri, K. Arw, P. Reigler, W. Huber, and N. Cabassa, 1983: 18 months experience with a new (Valli) catheter for peritoneal dialysis. *Perit. Dial. Int.,* **3,** 22-24.

12. Popovich, R. P., J. W. Moncrief, and K. D. Nolph, 1978: Continuous ambulatory peritoneal dialysis. *Ann. Intern. Med.,* **88,** 449-456.

13. Oreopoulus, D. G., 1998: A backward look at the first 20 years of CAPD. *Perit. Dial. Int.,* **18,** 360-362.

14. Churchill, D. N., D. W. Taylor, and S. I. Vas, 1989: Peritonitis in continuous ambulatory peritoneal dialysis (CAPD): a multi centre randomised clinical trial comparing the Y connect disinfectant system to standard systems. *Perit. Dial. Int.,* **9,** 159-163.

15. Oreopoulus, D. G., M. Robson, S.Izatt, S. Clayton, and G. A. de Veber, 1978: A simple and safe technique for CAPD. *Trans. Am. Soc. Artif. Intern. Org.,* **24,** 484-489.

16. Canadian CAPD Trial Group, 1989: Peritonitis in continuous ambulatory peritoneal dialysis (CAPD); a multicentre randomized clinical trial comparing Y connector disinfectant system to standard system. *Perit. Dial. Int.,* **9,** 159-163.

17. MacBride, P., T. S. Fred, and M. D. Boen, 1982: The man who brought science to the art of peritoneal dialysis. *Perit. Dial. Int.,* **2,** 50-53.

18. Diaz-Buxo, J. A., C. D. Farmer, P. J. Walker, J. T. Chandler, and K. L. Holt, 1981: Continuous peritoneal dialysis – a preliminary report. *Artif. Organs,* **5,** 157-161.

19. Maxwell, M. H., R. E. Rockney, C. R. Kleman, and M. R. Twiss, 1959: Peritoneal dialysis. *JAMA,* **170,** 917-924.

20. Gotolib, L., P. Bar-Sella, and A. Shostak, 1985: Reduplicated basal lamina of small venules and mesothelium of human parietal peritoneum. *Perit. Dial. Bull.,* **5,** 212-215.

21. Zeier, M., V. Schwenger, R. Deppisch, U. Haug, K. Weigel, U. Bahner, C. Wanner, H. Schneider, T. Henle, and E. Ritz, 2003: Glucose degradation products in PD fluids: Do they disappear from the peritoneal cavity and enter the systemic circulation? *Kid. Int.,* **63,** 298-305.

22. Mistry, C. D., R. Gokal, and E. M. Peers, 1994: MIDAS Study Group. A randomised multicenter clinical trial comparing isomolarico-dextrin with hyperosmolar glucose solution in CAPD. *Kid. Int.,* **46,** 496-503.

23. J. A. Diaz-Buxo, 2005: Bicarbonate solutions update. *Adv. Perit. Dial.,* **21,** 115-119.

24. Avram, M. M., P. Goldwasser, M. Erroa, and M. D. Fein, 1994: Predictors of survival in continuous peritoneal dialysis patients: the importance of pre albumin and other nutritional and metabolic markers. *Am. J. Kid. Dis.,* **23,** 91-98.

25. CANADA-USA (CANUSA) Peritoneal Dialysis Study Group, 1996: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: associated with clinical outcomes. *J. Am. Soc. Nephrol.,* **7,** 198-207.

26. Kopple, J. D., D. Bernard, J. Messana, R. Swartz, J. Bergstrom, B. Lindholm, and V. Lim, 1995: Treatment of malnourished CAPD patients with amino acid based dialysate. *Kid. Int.,* **47,** 1148-1157.

27. Faller, B., M. Aparicio, D. Faict, C. De Vos, V. de Précigout, N. Larroumet, R. Guiberteau, M. Jones, and F. Peluso, 1995: Clinical evaluation of an optimized 1.1% amino acid solution for peritoneal dialysis. *Nephrol. Dial. Transplant.,* **10,** 1432-1437.

28. G. S. Taylor, V. Patel, S. Spencer, R. J. Fluck, and C. W. McIntyre, 2002: Long term use of 1.1% amino acid dialysis solution in hypoalbuminemic continuous ambulatory peritoneal dialysis patients. *Clin. Nephrol.* **6,** 445-450.

Chapter 2

History of Peritoneal Dialysis in India

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History of Peritoneal Dialysis in India

In the year 1986, I was given the opportunity to work as a senior clinical fellow at the University of Toronto, the leading hospital called Toronto Western (TW) division. The division of Nephrology had distinguished staff members; Professor.D.G Oreopolos, Professor Robert Uldal, Dr, Carl J.Cardella Dr.George dereber and Dr.Joanne M Bargman. The entire nephrology and transplant programme including kidney and heart were performed at the TW hospital. Ihappened to the be the second Indian nephrologist to join the programme along with Prof. Hugh Brady (current V.C of Bristol University, UK) and Prof. Moshe Zlotenik (Israel) and a year later Prof. Peter Blake (Professor University of Western Ontario) from Ireland joined us. The CAPD programme was run by Prof Oreopolos and Dr.Bargman with the able support of Sharron Izatt who was the nurse manager in charge. The nurses in the home PD unit shown in **(Figure 1)** came from different countries, and there was a strong bonding between the doctors and the Home peritoneal dialysis unit (HPDU) nurses.

Figure 1 : Toronto Western Hospital HPDU staff with doctors (Center: DG Oreopoulos 1987)

The system used in Toronto was a straight spike system and the patients were doing 2L exchanges 4 times a day. There were nearly 260 patients on treatment in the HPDU. A few patients who had no home support, who could not do self dialysis, were on intermittent PD using a cycler for 24 hours, 3 times a week, in the hospital who were brought and sent back. A very good support system existed between the HPDU and the maintenance hemodialysis and the transplant programme. The home PD unit provided CAPD training as an inpatient for 5 – 10 days with trained nurses.

The patients were taught about techniques of spiking the bag, hygienic aseptic care, exit site care, blood glucose monitoring in Diabetes Mellitus, the concentration of fluids to be used and dietary advice and to deal with trouble shooting. A certain number of patients were assigned to a particular nurse who was responsible for the primary care of the patient. The patients were seen once a month in HPDU clinic by the doctors, nurses, dieticians, social workers and blood work was supported by the laboratory. Patients first direct contact point was the HPDU nurse. Betty Kalman was the nurse educator for the PD programme who always supported the nurses in their learning process. There were no portable PD cyclers or the double bag system (Y system) available at that time. A modification of the current "Y'' system, the ''O'' system **(Figure 2)** was introduced in 1989 which was a system we started using in India in 1991 by Padma. The ''O'' system is a reusable Y system which was filled with Amukin after each use (Sodium hypocholorate) and many patients accidently infused the Amukin in to the peritoneal cavity which produced severe abdominal pain. Permanent flexible PD catheters were not available in India in 1990. When we initiated the first person on CAPD in Chennai, India, the catheters were accessed from Toronto which included double cuffed straight Tenckhoff catheter, a few coiled catheters and TW hospital catheters. Dialysis fluid was not available in 2 liter bags for CAPD. The first catheter was implanted for the first patient by Dr.K.Sriram **(Figure 3)**.

Fig. 10.4 The O-set CAPD system. (a) connected, (b) disconnected

Figure 2: The Original O-Set (reusable Y-set) CAPD system, used in 1991

This patient was an elderly gentleman with diabetes mellitus with severe LV failure who was not tolerating hemodialysis. The difficulty in procuring supplies for CAPD were enormous and it was not possible as the Department of health, Govt of India had very little knowledge of CAPD. Every time a patient required dialysis bags and accessories, the patients were asked to deposit a huge amount to the finance department as customs duty before hand as the fluid in the collapsible bags were imported from either from far East or Europe. Based on an individual's needs and requirements, the deposits were returned back to the patients at a later date. Many

patients lost their lives waiting for the fluid to arrive at different seaports in India which was a real tragedy. Late Prof. Vidya Acharya and myself travelled to Delhi to meet the Director General of health service with support from central minister, past ministers, beurocrats and nephrology colleague in the early 90's. However, after 3 years, in 1994 permission was granted to include the PD fluid and accessories in the open general license import. Other colleagues Dr. K.C Prakash, Dr. K. S. Naik, Dr. Amit Gupta, Dr. Rajan Ravichandran and Dr. D.S. Rana took active interest in promoting CAPD in the early years. The support of Prof. Dimitrios Oreopoulos (Late), Dr.Ramesh Khanna, Prof. Joanne Bargman, Prof. Ram Gokal, Dr. Peter Blake and Prof. Sara Prichard in the early years by conducting CME programmes in India with support from Baxter is commendable. The first child with chronic kidney disease (CKD) was put on CAPD in 1993 at Chennai which got wide spread print media attention **(Figure 4)** and paediatric nephrologists also participated in promoting PD in India.

Figure 3: Celebrating 1 year of CAPD programme with patients in India, 1991

Figure 4: PD use in one year old reported by the media, 1993

The Peritoneal Dialysis Society of India (PDSI) was established in 1997 and the first congress was held at Bangalore under the chairmanship of Dr.Sundar Shankaran. I was unanimously elected as the founder president of PDSI. The guest speaker for the first meeting was Prof. Steven Vas (Late) from T.W hospital who pioneered the definition for the diagnosis of peritonitis and guidelines for the treatment. **Figure 5** shows the speakers and participants of the first PDSI congress in Bangalore. The Indian Journal of Peritoneal Dialysis is the official journal of PDSI which was edited by Dr. K.C Prakash and Dr. Amit Gupta. Since 2005, two issues per year are regularly published as hard copy with the support of my esteemed editorial board members. This journal is currently connected to Peritoneal Dialysis International. Although, the first patient was initiated in 1991 at Tamilnad Hospital, many nephrologists, nurses and technicians from India and abroad (**Figure 6**) were trained by my senior nurse Padma at Tamil Nadu Hospital, Sri Ramachandra Medical College Hospital and Madras Medical Mission Hospital, Chennai. These doctors and nurses came from Nepal, Srilanka, Pakistan, Middle East, Sudan, Tanzania, Dr.Congo, Nigeria, Fiji and Seychelles.

Figure 5: Formation of Peritoneal Dialysis Society of India, 1997 with members

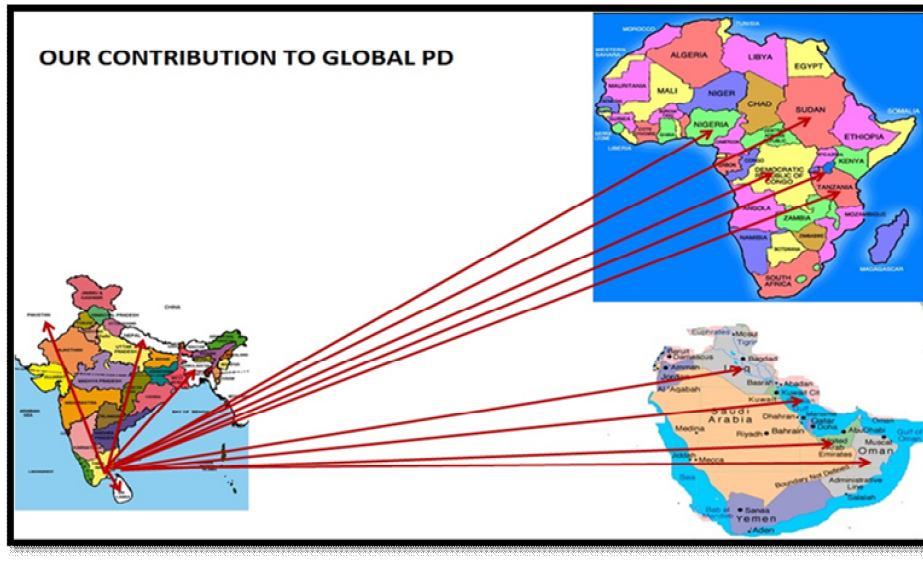

Figure 6: Map Showing the Countries from where Nephroplogists and Nurses Came for CAPD Training

Figure 7: Celebrating 10 years of PD in India with a CAPD patient, 2001

The manufacture of fluid in 2 L collapsible bags with double bag connection system in the late 90's by different companies was a boost to the PD programme. When

comparing the cost, India set standards for the cheapest CAPD programme in the world. The first portable cycler was used by us in 1997 to initiate patients on automated peritoneal dialysis (APD). We currently have 2 anuric ladies on CAPD for 14 and 15 years doing their own exchanges 4 times a day. (**Figure 7**) As peritonitis continues to be the Achilles' heel of CAPD, a PD to peritonitis workshop is conducted every year at the Madras Medical Mission, Chennai since 2012 in memory of Professor DG Oreopoulos. Hands-on training on collection and processing of dialysis effluent and recent culture techniques are demonstrated at the workshop conducted by Dr Anusha Rohit. A strong dietary department to advise the patient on the importance of diet in CAPD is the cornerstone of any PD programme. PD colleges were conducted in various parts of India by faculty from India and abroad including Peter Blake, Sara Prichard, Simon Davis, Joanne Bargman, Ram Gokal, who are all pioneers of peritoneal dialysis (**Figure 8**). I was awarded the lifetime achievement award named after Prof. DG Oreopoulos by the International Society for peritoneal dialysis in 2012 which was a recognition for the tireless efforts by the Indian peritoneal dialysis professionals to expand PD programme in South Asia. PDSI is a registered society with an elected President, Secretary and Treasurer. It has conducted annual conferences across India since 1997 with participants from India and abroad. The unique feature of this conference is the separate educational activity for nurses and technicians for interaction, learning and patient care. Continuous education and interaction is an integral part of a successful CAPD programme. Continuous quality improvement (CQI) is mandatory with regard to infections, cardiovascular disease, physical activity, nutrition, CKD-MBD, hypertension control, maintenance of residual renal function, anemia correction, electrolyte balance and psychological well being of the patients. The co-ordinated efforts by nephrologists, nurses, technicians, skilled nutritionists and clinical co-ordinators have set high standards for CAPD in south Asia. There are many more hurdles to overcome.

Figure 8: Receiving DG Orepoulos Lifetime Achievement Award for Contributions Peritoneal Dialysis by the ISPD, 2012

Figure 9: Madras Medical Devices Donates PD Catheters to Saving Young Lives Programme in Africa at WCN Cape Town, 2015

The Madras Medical Devices was set up to manufacture flexible catheters for PD. These catheters were donated for training programme at the World Congress of Nephrology in Cape Town, 2015 (**Figure 9**).

The future of chronic PD is safe in the hands of young nephrologists in India. There are many unserved geographical areas in the South Asian region where there is little access, maintenance hemodialysis or transplantation. CAPD is a suitable renal replacement therapy.

References

1. Abraham, G., G. Padma, M. Mathew, and S. Shroff, 1999: How to set up a peritoneal dialysis program: Indian experience. *Perit. Dial. Int*., **19,** 184-186.
2. Reddy, Y. N.V., G. Abraham, M. Mathew, R. Ravichandran, and Y. N. V. Reddy, 2011: An Indian model for cost-effective CAPD with minimal man-power and economic resources. *Nephrol. Dial. Transplant*., **26,** 3089-3091.
3. Abraham G., B. Pratap, S. Sankarasubbaiyan, P. Govindan, K. S. Nayak, R. Sheriff, and S. A. J. Naqvi, 2008: Chronic peritoneal dialysis in South Asia-challenges and future. *Perit. Dial. Int.,* **28,** 13-19.

Chapter 3

How to Organize a Peritoneal Dialysis Programme?

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How to Organize a Peritoneal Dialysis Programme?

Role of peritoneal dialysis (PD) in the management of End Stage Renal Failure (ESRF) has been well established, notwithstanding the unfair comparison of PD with hemodialysis (HD) and transplantation. It has provided a means of managing some patients who would have been denied treatment because HD and transplant would be inappropriate, unavailable or failed. PD and HD, far from being competitive modalities, complement each other so well to give better solution to the ESRF population.

Different trends of PD prevalence are emerging in various parts of the world. When PD utilization is declining in many Western countries, like, United States, which has shown a drop in the PD utilization rate to 7% in 2010 from 14% in 1995, it is robustly growing in Latin America, the Middle East and Asia. The different growth trajectories reflect prevailing social structure, economic status, availability of expertise, HD facility prevalence, insurance and government support in these populations.

Perplexing US Data: The decline in PD utilization in US is particularly perplexing, as recent USRD data has shown a definite survival benefit of PD over HD during the first two years and significant patient and the technique survival in the recent years compared to the past [8, 11]. (**Figure 1, 2**)

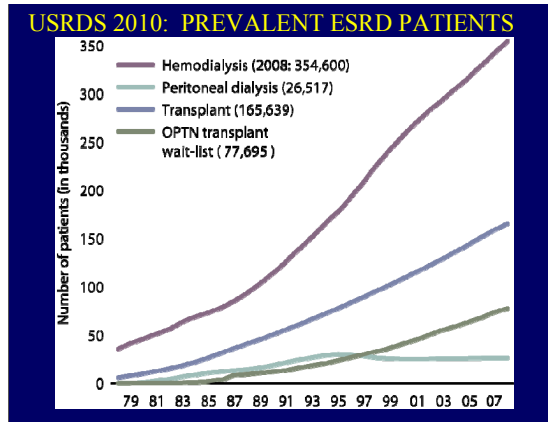

Figure1: ESRD Patients on Different Modalities

J. Balasubramaniam

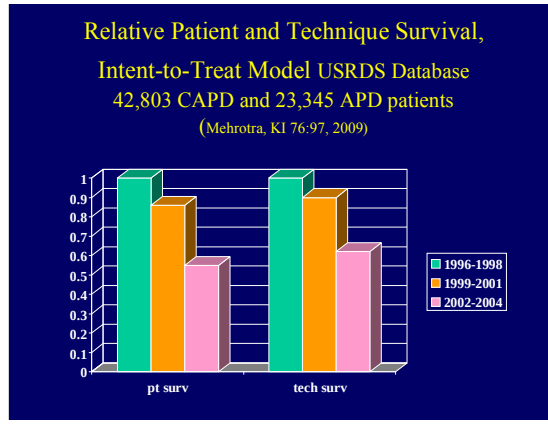

Figure 2: Relative Patient and Technique Survival (USRDS Database)

When Dr. Georgi Abraham, a protégé of Dr. Dimitrios G Oreopoulos, introduced PD in India in the early 1990's, it appeared that it would be a definite non-starter. India, a tropical country with poor connectivity and sanitation has a predominantly poor rural population without adequate access to health care, making it an unfavourabledestination for PD.But, PD being versatile and being the best option for a particular group of patients has put its foot strongly in India. Now, more than 750 out of the 2500 nephrologists are using PD, managing around 8500 prevalent PD patients [1-4, 15, 18, 19]. So, the process of setting up of PD centre would find an important place in health care planning.

Establishing a PD programme

Essential requirements for PD Unit

1. Place

•Suitable location.

•Rooms for PD training: single room/designated area.

•Outpatient facilities.

•Back up HD facilities.

•Inpatient Beds.

2. Staff

• Adequate and experienced medical, nursing staff 24hr on call.

• Multidisciplinary approach.

• Staff orientation/training.

3. Training

- Teaching plans and training manual.
- Establishment of protocols.
- Continuous education programmes.

4. Equipment

- Reliable and suitable equipment for patient.
- Storage space.
- Home delivery system.

5. Finance

- Adequate funding.

Motivated Leader

The most important prerequisite for a successful PD programme is the strong 'belief' in the therapy by the nephrologist and his ability to pass on the 'trust'to the PD team and the patients. In any ESRF population, there exists a group of patients who would be best helped by PD. This may be due to medical or other practical circumstantial reasons. This fact would be appreciated by a shrewd and concerned nephrologist within a short time of starting his practice.Hence, a renal unit cannot go on for long without facility for PD.

Multidisciplinary Approach

The importance of multidisciplinary approach and team work is nowherebetter exemplified than in PD programme. The team should consist of a nephrologist, PD nurse, dietician, coordinator and a social worker. Stronger the coordination and team spirit, higher the patient survival and success of the programme. To start with, the team need not necessarily be big – one can double or even triple the roles and give effective outcome.

PD Nurse

It is true that doctors, especially nephrologists are familiar with acute care but not with chronic care. Hence, the doctor should be empowering the nurse and both should join hands to empower the patient. Although, with the same motive and intention, doctors and nurses differ very much one cannot play the others role. The doctor diagnoses the patient and plans the treatment protocol, focuses more on physiological issues; whereas, the nurse implements the treatment protocol, promotes lifestyle changes and improves patient's compliance to the treatment protocol. A holistic approach in patient care promotes rehabilitation.

Dietician and Social worker

The role of correct diet in success of PD is significant. With limited ultrafiltration capcity of PD, fluid and salt restriction is mandatory in controlling hypertension and preventing pulmonary edema. Dietitian should keep track of dialysate protein loss, serum albumin, phosphate, potassium levels and modify the diet accordingly after consulting the nephrologist. This will reflect on the quality of life (QoL) and rehabilitation and ultimately the morbidity and mortality of patients on PD.

Assessing family burden, caregiver's problems, ability of the patient to cope with the all new environment and the attitudes of others towards his new way of life will be done by the social worker. He will liaison with each one of them and the PD team members and minimize the traumas and misgivings. Mental depression and procedure fatigue are quite common amongst PD patients. Periodic counselling and encouragement by the social worker goes a long way in making them cope with their new way of life, and reducing PD drop outs for non medical reasons. There will be occasions when roles of dietitian and social worker have to be combined in new centres, to start with.

Standardized Protocols

Whenever a project involves multiple service providers and especially if they have to change or play multiple roles, devising standardised protocol is mandatory. Or else, there will be too many errors. Vague and contradicting instructions to the patient can confuse him and make him lose faith in the procedure. This will predictably lead tomore complications and patient loss. The protocols should be designed to suit the local needs keeping in mind the size and economic stature of the unit, the social structure and customs of the target population. The written protocols should be freely available to the members of the team. New entrants to the team should essentially be made to familiarize with the protocols before getting inducted into the field.

The patients and the junior team members should not be given multiple choices or permission to modify the protocols by themselves. This will slowly compromize the quality and end up in more failure rates.

Essential protocols for PD programme

- CAPD exchange.
- Dialysate and urine collection for adequacy assessment.
- PET.
- Exit site care (pre, peri and post implantation).
- Administration of IP medications.
- Transfer set change procedure.

- Treatment of infections: peritonitis, exit site care.
- Managing complications.
- Cycler set up.
- PD regimes: IPD, APD.
- Follow up care: discharge plans.

Monitoring, Recording and Reporting

The patient progress and their performance should be periodically monitored and recorded. Separate records should be maintained by the PD nurse, coordinators and the patient. The format should be kept compact and user friendly. If too elaborate, it would be often incomplete - with some redundant notes but many missing vital data.

Centre size

Several studies have stressed the importance of center size on the outcome of PD in terms of peritonitis rates and technique failure rates [21]. The reasons for this impact are probably related to nursing and physician experience, the ability to develop a 'support team', and the development of effective quality control programmes. This need not necessarily be true always. There are several small centres that have shown remarkable PD survival rates [18]. Many a times, it is a charismatic and concerned team member who is responsible for the success story in these small centres. But as the centre size grows, it is the strength of the protocols and relentless and continuous quality maintenance that matters and not the brilliance of teammembers.

Education programmes

Continuing education is an important component of PD programme and it should involve not only the clinical team but also the patients, families and care givers. Nephrologists should get familiarized with the basic principles of PDduring their training period itself. PD being predominantly a home treatment, opportunity for nephrology trainees to show interest and gain experience is limited in many teaching institutions. With surgeons undertaking the catheter insertions, PD nurses doing the exchanges and coordinators and social workers doing the follow up, nephrologists for long didn't show interest. But things are changing with the realization that PD is an integral part of renal replacement therapy (RRT) and the advent of percutaneous PD catheter insertion by nephrologist, the 'belief' in PD has risen significantly.

PD nurse training in the basic PD techniques like bag exchanges, exit site inspection and management, monitoring the health parameters and maintaining records is not all. Making them understand the basic principles of physiology

behind PD goes a long way in the success of the

PD centre

Dieticians and social workers are the ones who make the lives of patients on PD more meaningful. Educating them in the recent trends and nuances of diet and lifestyle management is vital.

Patients, caregiver, family- In this busy world, health care professionals would spend only a few hours per year with patients with chronic diseases. Rest of the time the patient has to take care of himself. Hence, self-management of chronic illness like chronic kidney disease (CKD) is imperative - patient has to be both a service consumer and a provider. That is the reason why considerable time is spent in a PD programme for the patient education and empowerment.

CKD education **(Figures 3, 4, 5)** should start well ahead of the PD initiation. If the patient should do the selection of mode of RRT, he should be well informed about CKD and various RRT options. CKD education of the patient by the PD team should aim at making him knowledgeable about renal failure, help retard the progression of the disease and empower him to choose the best option for RRTand not merely motivating him for PD. Pre dialysis education can positively impact the both the PD and the patient survival [16, 17, 20].

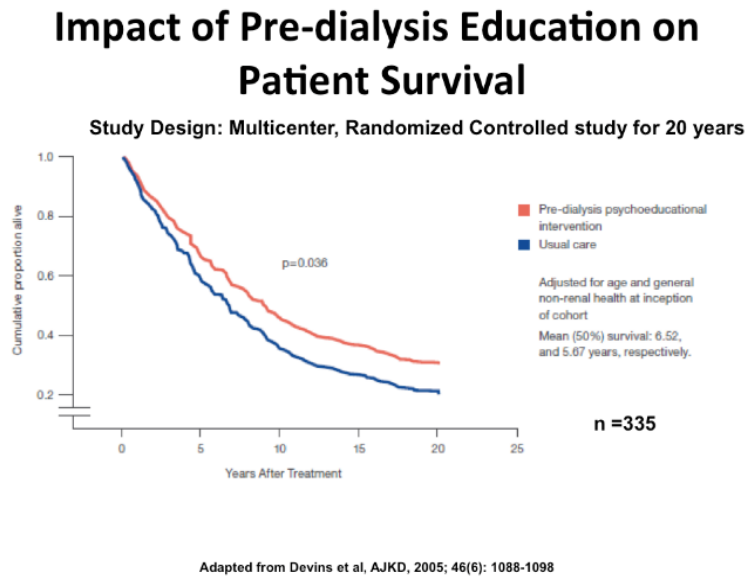

Figure 3: Impact of Pre-Dialysis Education on the Patient Survival

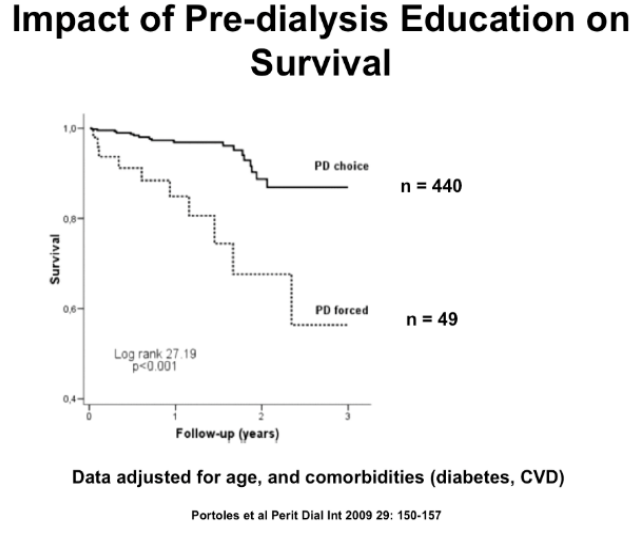

Figure 4: Impact of Pre-Dialysis Education on the Patient Survival

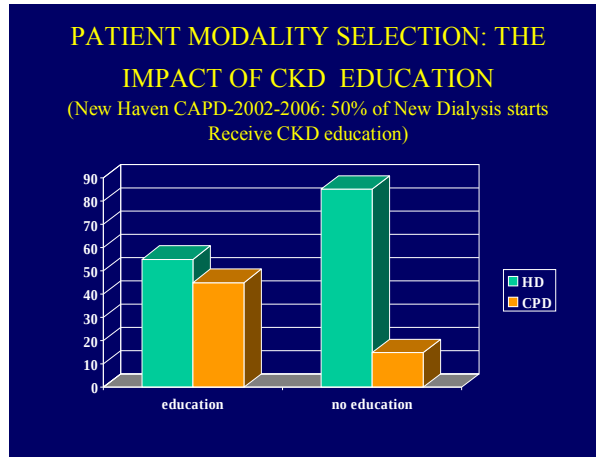

Figure 5: The Impact of CKD Education

Study in New Haven during 2002 – 2006 showed that only 50% of the ESRD patients and family received CKD education in the eve of dialysis initiation. The impact of CKD education on the selection of RRT modality made a whopping 200% (15% to 45%) shift towards PD. Once PD is selected as anoption, the systematic education should begin for the patient and the family. Selection of the caregiver should go more by their attitude, earnestness and concern towards the patient rather than their smartness. Overconfident relative who feigns quick learning can be more dangerous than the slow learning, bashful one.

Continuous Quality Improvement (CQI) Activities

It has been shown that the quality improvement activities can effectively improve clinical outcomes. A 5-fold reduction in peritonitis rates has been documented by CQI activities [14].

CQI methodology

• Identify aspects of practice important for quality monitoring.

• Collecting data to monitor quality.

• Analyzing quality data to identify opportunities for improving practice.

• Formulating and implementing recommendations to improve quality and patient outcome.

A model of CQI for peritonitis reduction [15]:

- Track infection rates by organism and overall.
- Monthly meetings to evaluate root causes of each infection.
- Subsequent plan for interventions to prevent recurrence.
- Chart trends and revaluate protocols of PD programme.

Involve all the members of the PD team.

Interventional Nephrology: The involvement of the treating nephrologist in PD catheter placement and management of complications goes a long way in gaining the confidence of the patient and the success of the PD programme. The advantages of catheter placement by nephrologist over that of by surgeon havebeen observed by Sampath *et al* [13].

Use of Electronics: Vastness and lack of connectivity and transport was expected to be a big impediment for PD growth in India. Indians have shown uncanny knack of getting over problems by ingenious methods. Simple mobile phones, SMS, WhatsApp imaging have been effectively utilized for filling up the gaps and reducing the delays. Nayak KS has described and put to use this novel method effectively. This is to be emulated and incorporated in new centres. Reminders and enquiries from call centressomehow don't work well with our population, especially in the rural and semi urban centres. Our patients need a known person to relate to, when they receive these electronic communications [12].

Patient groups and meetings: Periodic patient meetings should be organized and they should be made to learn from each other's experience and mistakes. During these meetings, the PD team should reinforce the patient's knowledge by discussing in detail about actual problems encountered by them like peritonitis and exit site infection. As a group they should be encouraged to find where they went wrong and make them believe that complications don't happen without reasons. This would give them the confidence that peritonitis and other complications are not inevitable.

Issues specific to developing countries: Understanding the issues specific to developing countries would help us to better plan our strategies while setting up the PD unit. Inherent positive factors can be taken full advantage of and the negative factors can be alleviated and circumvented.

Factors that favourPD over HD

- No need for sophisticated equipment.
- Lack of HD facility.
- Shortage of skilled technicians.
- Can be performed away from nephrology centres which are few and far apart.
- Government support for PD in some regions to compensate for lack of HD facility.
- Availability of good family and social support.

Problems

- PD is not cheaper than HD, as it is in developed countries.
- Patient's inability to understand the economic and other practical implications of PD in spite of counseling.This leads to frustration and displeasure with the doctor and the motivators.
- Lack of facility in the house – many live as joint family, without privacy.
- Difficulty in transport of supplies.
- Relative lack of personal hygiene and clean environment.
- Late diagnosis and referral of CKD precludes most patients with good residual renal function, who are actually the ideal patients for PD.

PD suite (Figure 6)

It is good to have PD suit in the renal unit from the beginning. This would be a multipurpose room. Mere 12x12 feetspace can give -

- Much prestige and grace to the image of PD patients.
- Privacy and a feeling of belonging.
- Place for bag exchanges.
- Meeting point for patients.
- Prospective patients can have first hand witness.
- Counseling for old and new patients.
- Learning centre for PD team, patients, family and students.
- Maintain records, literature.

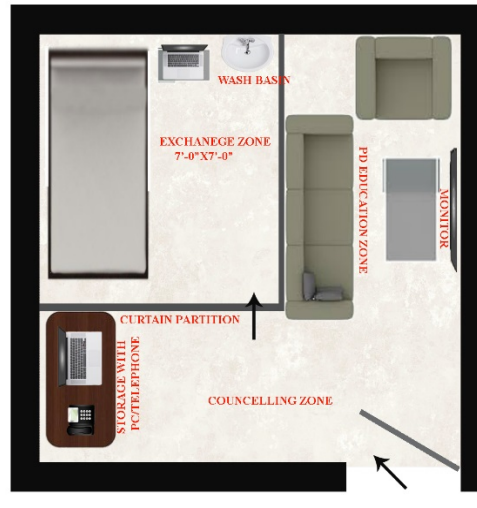

Figure 6: A Model PD Suite

Tirunelveli PD Centre

This centre, located in a place endowed with all the 'Indian' disadvantages - remote, rural, economically backward, lack of expertise, hot and arid climate-came into being in 1992. Although renal transplant was started in 1996, PD programme got a reluctant start only in 2000. The delay was partly due to the nephrologist, who although was familiar with PD, believed that PD was irrelevant to this place and people. But once started, number of initiation went up to 144 with significant PD survival within a short time.The relevance of PD as an RRT option became very evident [18, 19]. Some pertinent factors brought out from the experience are

1. Optimal size of the unit need not be very big.
2. PD nurse multitasking as coordinator and social worker to start with, could be an advantage.
3. Close and cordial relationship of the PD team with the patient worked well. But this sometimes stressed the coordinator because he was expected to be at their beck and call for even minor issues.
4. Proper patient selection is very important. Social and other non medical factors should also be given equal importance. Some jump into PD wagon inappropriately because of fear of other options like HD and transplantation (not for lack of donor or cost). Such ill-advised patients often turn hostile at times and blame the nephrologist and the coordinator for the wrong choice. Such patients soon become bad ambassadors for the PD programme.
5. Meticulous care in the catheter placement.
6. Expertise ininterventional nephrology and adoption of percutaneous catheter insertion very early.

Lifetime scheme was very reasonably priced at that time and there were many takers. The best of PD was brought to light by these patients under scheme because of good compliance, resulting in long PD survival. Freedom from economic burden given by these schemes gives them as much psychological wellbeing as physical wellbeing given by PD. Hence more affordable and attractive lifetime schemes should again emerge.

Conclusion

With PD becoming an important limb of RRT management in developing countries like India, early commencement of PD unit in every renal centre and hospital is imperative. Although general guidelines have been outlined, it can be planned and built imaginatively to suit the local requirements and the available resources.

References:

1. Abraham, G., S.Bhaskaran, P.Soundarajan, R. Ravi, S.Nitya, G. Padma, and V. Jayanthi, 1996: Continuous ambulatory peritoneal dialysis. *J. Assoc. Physicians India,* **44,** 599–601.

2. Nayak, K. S., 2004: Asia, a melting pot for peritoneal dialysis practices: redefining and expanding peritoneal dialysis horizons in Asia.*Perit. Dial. Int.,* **24,** 422–423.

3. Nayak, K. S., M. V. Prabhu, K. A. Sinoj, S. V. Subhramanyam, and G. Sridhar, 2009: Peritoneal dialysis in developing countries. *Contrib. Nephrol.,* **163,** 270–277.

4. Abraham, G., B. Pratap, S. Sankarasubbaiyan, P. Govindan, K. S. Nayak, R. Sheriff, and S. A. J. Naqvi, 2008: Chronic peritoneal dialysis in south Asia: challenges and future. *Perit. Dial. Int.,* **28,** 13–19.

5. Aditi, N. K., A. K. Sinoj, and M. V. Prabhu, 2010: Improving peritoneal dialysis (PD) outcomes in rural patients compared to urban by employing novel and practical initiatives [Abstract]. *Perit. Dial. Int.,* **30,** 65.

6. Nayak, K. S., K. A. Sinoj, S. V. Subhramanyam, B. Mary, and N. V. Rao, 2007: Our experience of home visits in city and rural areas. *Perit. Dial. Int.,* **27,** 27–31.

7. Nayak, K. S., 2007: Key success factors for a quality peritoneal dialysis program. *Perit. Dial. Int.,* **27,** 9–15.

8. Heaf, J. G., H. Lokkegaard, and M. Madsen, 2002: Initial survival advantage of peritoneal dialysis relative to haemodialysis. *Nephrol. Dial. Transplant.,* **17,** 112.

9. Maiorca, R., E. Vonesh, G. C. Cancarini, A. Cantaluppi, L. Manili, , C. Camerini, ., and A. Strada, 1988: A six-year comparison of patient and technique survivals in CAPD and HD. *Kid. Int.,* **34,** 518.

10. Serkes, K. D., C. R. Blagg, K. D. Nolph, E. F. Vonesh, and F. Shapiro, 1990: Comparison of patient and technique survival in continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis: a multicenter study. *Perit. Dial. Int.,* **10,** 15.

11. Mehrotra, R., Y. W. Chiu, K. Kalantar-Zadeh, J. Bargman, and E. Vonesh, 2011: Similar outcomes with hemodialysis and peritoneal dialysis with similar outcomes for endstage renal disease treatment in United States. *Arch. Intern. Med.,* **171,** 110-118.

12. Nayak, A., A. Karopadi, S. Antony, S. Sreepada, and K. S. Nayak, 2012: Use of a Peritoneal Dialysis Remote Monitoring System in India. *Perit. Dial. Int.,* **32,** 200–204.

13. Sampathkumar, K., A. R. Mahaldar, Y. S. Sooraj, M. Ramkrishnan, A. Kumar, and R. Ravichandran, 2008: Percutaneous CAPD catheter insertion by a

nephrologist versus surgical placement: A comparative study. *Ind. J. Nephrol.,* **18,** 5-8.

14. Bender, F. H., J. Bernardini, and B. Piraino, 2006: Prevention of infectious complications in peritoneal dialysis: best demonstrated practices. *Kid. Int.,* **70,** 44–54.

15. Personal communications with M/s Baxter India Ltd and M/s Mitra Industries Pvt Ltd.

16. Devins, G. M., D. C. Mendelssohn, P. E. Barré, K. Taub, and Y. M. Binik, 2005: Predialysis Psychoeducational Intervention Extends Survival in CKD: A 20-Year Follow-Up. *AJKD*, **46,** 1088-1098.

17. Portoles, J., G. del Peso, M. J. Fernández-Reyes, M. A. Bajo, and P. López-Sánchez, 2009: Previous co-morbidity and lack of patient free choice of technique predict early mortality in peritoneal dialysis. *Perit. Dial. Int*., **29,** 150-157.

18. Balasubramaniam, J., CAPD Versus Hemodialysis in rural/semi urban population in India: Data from Kidney Care Centre, Tirunelveli.

19. Balasubramaniam J., 1988: Prescription and practice of Renal Replacement Therapy (RRT) for End Stage Renal Failure (ESRF) in rural India. ERA-EDTA, Rimini, Italy.

20. Finkelstein, F. O., K. Story, C. Firanek, P. Barre, T. Takano, S. Soroka, S. Mujais, K. Rodd, and D. Mendelssohn, 2008: Perceived knowledge among patients cared for by nephrologists about chronic kidney disease and end-stage renal disease therapies. *Kid. Int.,* **74,** 1178-1184.

21. Finkelstein, F. O., 2006: Organization and structure of a PD program. *Kid. Int.,* **103,** 118-121.

Chapter 4

Functional Anatomy of Peritoneum

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Functional Anatomy of Peritoneum

Peritoneal Membrane

- The peritoneum is a thin, transparent and large serous membrane lining the abdominal cavity. The surface area of peritoneum is nearly equal to the body surface area.

- It is composed of a monolayer of mesothelium supported by a thin layer of connective tissue.

- At the peritoneal side, mesothelial cells have numerous microvilli with anionic charge [1].

- The function of the peritoneum is to support and cover the organs inside abdomen. Besides, the mesothelial cells secrete a serous fluid to function as a lubricant

- The peritoneum is divided into 1) parietal layer and 2) visceral layer.

Parietal Peritoneum

- Peritoneum lining the inner surface of the abdominal and pelvic walls and the lower surface of the diaphragm is called the parietal peritoneum.

- It is loosely attached to the walls by extra-peritoneal connective tissue and can be easily stripped

- Parietal peritoneum receives nerve supply from the somatic innervations, thus it is pain sensitive.

Visceral Peritoneum

- The peritoneum investing the viscera is called visceral peritoneum.

- The visceral peritoneum invaginates to cover the abdominal viscera.

- It is firmly adherent and cannot be stripped.

- Visceral peritoneum receives the nerve supply from the autonomic innervations, so it causes pain when viscera is stretched, ischemic or distended.

Folds of Peritoneum

- Many organs within the abdomen are suspended by folds of peritoneum and are rendered mobile.

R. Padmanabhan

- The peritoneal folds provide pathways for passage of vessels, nerves and lymphatics

Peritoneal Cavity

- The parietal and visceral layers of peritoneum are separated from each other by capillary films of peritoneal fluid secreted by the mesothelial cells.

- This serous fluid lubricates the peritoneal surfaces, enabling the viscera to move on each other without friction.

- The peritoneal cavity is closed in males but in females, there is a communication with the exterior through the fallopian tubes, uterus and vagina.

Arterial supply

- The visceral peritoneum and the underlying structure are supplied by the superior mesenteric artery.

- The parietal peritoneum is supplied by the intercostals, Epigastric, and lumbar arteries.

Venous drainage

- Venous drainage of the visceral peritoneum is by the portal circulation.

- Venous drainage of the parietal peritoneum is by the caval circulation.

Solute and water transport

- The peritoneal membrane is a complex, heterogenous, semi-permeable membrane with multiple pores.

- There are 6 regions of resistance for the passage of fluid from capillary blood to the peritoneal cavity.

1. Stagnant capillary fluid film on the inner aspect of endothelium of capillaries

2. Capillary endothelium

3. Capillary basement membrane

4. The interstitium

5. The mesothelium

6. The stagnant film on the surface of mesothelium

- The capillary wall remains the most important restrictive barrier for transport determining size-selectivity thro a system of pores.

- Solute and water transport across the peritoneal capillary is mediated by pores of three different sizes.

The basics of peritoneal transport described by Nolph, 1 is relevant even today

Two models of peritoneal transport have been described:

- The three pore model
- The distributed model

The three pore theory considers peritoneal membrane with three different pore size and explains the classical mechanisms of transport of molecules across peritoneal membrane like diffusive transport and convective transport.

1. Three-pore model [2]

Large Pores

- Large pores (radius 20-40nm) exist in small numbers, are actually large clefts in the endothelium and constitute < 0.1% of all pores.
- They transport macromolecules

Small pores

- Small pores (radius 4-6nm) are more numerous, believed to be smaller cleft between endothelial cells and transport small solutes and water.
- The small pores are the majority pores transporting small molecular weight substances and large pores are minority transporting macromolecules.

Ultra Pores

- Ultra-small or transcellular pores (radius <0.8nm) are water channels or aquaporin. The ultra-small pore transports 50% of water.
- The presences of water-only channels make the peritoneal membrane, more than a semi-permeable membrane.
- They transport water only and are present in the endothelial cells of the peritoneal capillaries.

2. Distributed model

This model emphasizes the importance of capillary density in the interstitium and the distance between capillaries and mesothelium for solute and water transport.

So, the transport is dependent on the surface area of the peritoneal capillaries and the proximity of capillaries to the mesothelium. The area of peritoneum close to the capillaries is considered “effective peritoneal surface area”.

Endothelial glycocalyx

The microcirculation focussed studies recently have demonstrated the critical role of the endothelial glycocalyx (a delicate layer of glycosaminoglycans and proteoglycans) as a primary barrier in trans-endothelial solute and water transport.

The structural and functional changes in peritoneum with duration of PD

During peritoneal dialysis (PD), the peritoneal membrane undergoes ageing processes that affect its function. And loss of microvilli is very common in patients receiving PD.

Exposure to non-biocompatible dialysate, inflammation, and uremia induce conformational changes in the peritoneal membrane. After a time on dialysis, mesothelial cells are injured and sometimes denuded from the peritoneal surface. After around 5 years of PD, there is a loss of mesothelial integrity with sub-mesothelial fibrosis, vasculopathy and vascular proliferation. The normal loose serial fiber matrix turns into fibrotic dense serial fiber matrix.

Peritoneal fibrosis is detected in 50% and 80% of patients on PD within one and two years, respectively. Thus, there is a temporal relationship between peritoneal fibrosis, vasculopathy, and time on PD [3].

The main risk factors of peritoneal injury are PD fluid related factors, patient factors, genetic factors and epigenetic factors.

Pathogenesis of peritoneal fibrosis

1. Epithelial to mesenchymal transition as shown by presence of mesenchymal markers and documentation of mesenchymal features.

2. The mesenchymal progenitor cells transform into myofibroblast during the process of fibrosis.

The functional anatomy of Peritoneum is determined in long term by

- Perturbations of Glycocalyx
- Inflammation- with raised IL6 production locally
- Fibrosis
- Epithelial to mesenchymal transition
- Genetics- genetic polymorphism for IL6, eNOS and RAGE genes
- Mesenchymal precursor cells

References

1. Gotloib, L., and A. Shostak, 1987: Ultrastructural morphology of the peritoneum: new findings and speculations on transpfer of solute and waster during peritoneal dialysis. *Perit. Dial. Bull.,* **7,** 119-120.

2. Rippe, B., 1993: A three-pore model of peritoneal transport. *Perit. Dial. Int.,* 1993; **13,** 35-38.

3. Williams, J. D., K. J. Craig, and N. Topley, 2002: Morphologic changes in the peritoneal membrane of patients with renal disease. *J. Am. Soc. Nephrol.,* **13,** 470–479.

Chapter 5

Physiology of Peritoneal Solute, Water and Lymphatic Transport

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Physiology of Peritoneal Solute, Water and Lymphatic Transport

The foundation of peritoneal dialysis (PD) was laid down by Thomas Graham (1805-1869) when he discovered the concepts of "diffusion", "crystalloids/colloids" and "semi-permeable membrane" [1]. He coined the term, "dialysis" for movement of solutes and water across a semi-permeable membrane and is regarded the "Father of modern day dialysis Rene Henri Joachim Dutrochet (1776-1846) who defined osmosis is regarded as the "Grandfather of dialysis" [2]. Ever since George Ganter's first attempt at PD in humans[3], the landmark discoveries in the area of physiology of PD [3] were by: George Wegener (1877) - Effect of hypertonic and hypotonic solutions in rabbit peritoneal cavity.

- Ernest Starling and Alfred Tubby (1894) – Direct and indirect lymphatic transport across peritoneal membrane.
- Cunningham (1920) - Glucose absorption from the peritoneal cavities of rats.
- Putnam (1923) - Peritoneum is a semipermeable membrane that allows bidirectional movement of water and solutes based on principles of diffusion and osmosis.
- Engel (1927) – Determinants of solute clearance across the peritoneum.
- Henderson and Nolph (1969) - definition of "dialysance" (MTAC or permeability area product)
- Henderson and Flessner (1973, 1996) - Functional surface area in contact with dialysis fluid is substantially lower than true anatomical peritoneal surface area.

Rippe and Stelin (1989) - Two pore model of peritoneal transport.

- Twardowski (1989) – clinical evaluation of peritoneal transport by peritoneal equilibration test.
- Flessener *et al*, (2001) -Transperitoneal ultrafiltration and fluid absorption occur simultaneously but not in similar areas of peritoneal membrane.

In PD, the peritoneal membrane plays the role of a semi-permeable membrane with peritoneal capillary blood and intraperitoneal dialysis solution on its either side.

The peritoneal membrane is a delicate intricately arranged serous layer lining the intra-abdominal viscera and the abdominal cavity. It is comprised of

1. Parietal peritoneum (10 - 20%)
2. Visceral peritoneum (80 – 90 %)

The anatomical surface area of peritoneal membrane closely approximates the total body surface area (TBSA), as reported by Wegener in 1877 [3]. But subsequently, the peritoneal surface area was found to be 0.6-0.8 of TBSA in adults as revealed by autopsy series [4]. Evisceration experiments in animals and neonates demonstrated

that only parietal peritoneum (10 % of TPSA) is involved in effective PD [5, 6]. Diaphragmatic peritoneum (3-8 % of TPSA) is concerned with lymphatic absorption and animal models underestimate its role in humans [7]. The visceral peritoneum receives its blood supply from mesenteric arteries and portal vein while parietal peritoneum is supplied by the vessels of the abdominal wall. The peritoneal blood flow rate is 50 - 100 ml/min.

The peritoneum is a monolayer of specialized mesothelial cells with an underlying interstitium comprising of bundles of collagen interspersed in a mucopolysaccharide hydrogel in which a network of capillaries and lymphatic vessels are present [8]. Hence, there are six layers of barrier for particle movement between peritoneal cavity and capillary blood. They are:

1. Fluid film over the capillary endothelium
2. Endothelial layer
3. Basement membrane
4. Interstitium
5. Mesothelium
6. Fluid film over the mesothelium

Of these, the capillary endothelium is the rate-limiting barrier for peritoneal transport. Several theoretical models of transport have been proposed to explain the peritoneal solute and water transport. The most popular among them are

1. Three pore model
2. Distributed model
3. Pyle-Popovich model

The distributed model is a complex mathematical model applicable only in the research settings [9]. It proposes that peritoneal transport is dependent not only on the effective peritoneal surface area (EPSA) but also on the capillary density and distribution in the interstitium such that transport is efficient in areas with more dense capillaries located nearer to the mesothelial layer.

The Pyle-Popovich model is a simplified model wherein peritoneal membrane is considered as a simple membrane placed between two compartments akin to the setting in hemodialysis [10]. The “pore theory” is the most commonly applied model for peritoneal transport in the clinical settings [11]. According to this model, capillary endothelium offers the rate limiting hindrance for peritoneal transport. Solute and water transport occurs through a system of pores. Initially it was a “two pore model” with a large set of small pores and a small set of very large pores. But, this model could not explain the discrepancy between reflection coefficient and sieving coefficient observed in peritoneal dialysis, which subsequently led to the discovery of a third set of water only, ultra-small transcellular pores. Later, this was found to be aquaporin-1, involved in free water transport and sodium sieving [12]. The three pore model can sufficiently and accurately explain most phenomena of solute and water transport across peritoneal membrane [13, 14]. The three pores are

1. Transcellular aquaporins
2. Small inter endothelial pores and
3. Large inter endothelial pores

The features of these three different types of pores are as given in **Table 1.**

Table 1: Features of Different Pore Types

Pore type	Pore radius	Transported particles	Pore density	Pore location
Large pores	Variable radii, Average > 150 Å	Macromolecules by convection	Extremely sparse	Inter endothelial (venular)
Small pores	40 – 50 Å	Small solutes (sodium, potassium, Urea, creatinine) and water by diffusion	Large	Inter endothelial (capillary)
Aquaporins	4- 5 Å	Free water transport by osmosis	Large	Trans cellular

The ultra-small pores that were assumed to be responsible for the solute sieving effect were subsequently characterized as aquaporin 1 transcellular channels. They are involved in free water transport in response to an osmotic stimulus like glucose in the peritoneal cavity. Aquaporin-1 was originally described by Peter Agre as CHIP-28, a 28 kilodalton protein, which earned him a Nobel Prize [15].

The solute and water transport across the peritoneal membrane occurs through three physiological processes that take place simultaneously. They are

1. Diffusion
2. Convection/ Ultrafiltration
3. Absorption

Diffusion

Diffusion is the major mechanism of small solute transport and it is bidirectional, *i.e.*, uremic solutes and potassium diffuse into the peritoneal cavity while glucose and lactate/bicarbonate diffuse into the peritoneal capillaries. This process is determined by concentration gradient, mass transfer area coefficient (MTAC) and dialysate flow rate.

Solute diffusion rate = Concentration gradient x MTAC

MTAC is determined by effective peritoneal surface area (EPSA), intrinsic peritoneal membrane resistance and molecular weight of the solute. Peritoneal diffusion rate can vary determined by the vascularity and the inflammatory state [16].

Convection/Ultrafiltration

Convective solute transport or "solvent drag" is the transport of solutes along with water movement resulting from the osmotic force created by glucose in the peritoneal cavity. Middle molecules and proteins are cleared by convection.

Ultrafiltration is the process of movement of water from the peritoneal capillaries into the peritoneal cavity due to the osmotic force generated by glucose or other osmotic agents. Ultrafiltration occurs through aquaporins (40 -50 %) and small pores (50 -60 %) [17]. Ultrafiltration through small pores is accompanied by solutes while ultrafiltration through aquaporins is pure water transport without any accompanying solute.

Convection/Ultrafiltration is determined by the concentration gradient of the osmotic agent, EPSA, hydraulic conductance, hydrostatic pressure gradient, reflection coefficient and sieving coefficient.

Reflection coefficient

Reflection coefficient is the ability of the osmotic agent to remain in the peritoneal cavity and effect osmotic ultrafiltration. It is expressed as a dimensionless index called the Staverman's reflection coefficient. Lower reflection coefficient means the solute dissipates easily into the capillaries resulting in poor ultrafiltration while a solute with higher reflection coefficient means that it remains in the peritoneal cavity and is ideal for longer peritoneal dwells. Glucose has a low reflection coefficient (0.02 – 0.04) while icodextrin has a high reflection coefficient (1.0) [18].

Sieving coefficient

Sieving is a phenomenon in solute transport wherein some solutes are held back in the peritoneal capillaries. It is expressed as the sieving coefficient and it is due to the free water transport occurring through the aquaporins. Sieving coefficient is a measure of the ease with which a small solute moves across the membrane and its value for small solutes is always less than unity [19]. Rapid removal of relatively more water as that can occur in an automated cycler dialysis can result in significant hypernatremia. The degree of sodium sieving can be determined by measuring the drop in first hour dialysate sodium concentration. This phenomenon is absent with icodextrin as water transport with icodextrin is aquaporin independent.

Lymphatic absorption

As ultrafiltration is happening during PD, fluid is also absorbed continuously out of the peritoneal cavity both

- directly into the lymphatic vessels situated in the diaphragmatic peritoneum (direct transport), and
- Indirectly into the abdominal wall which ultimately finds its way into the lymphatic vessels (indirect transport).

This occurs at the rate of 1 – 2 ml/min or 250 – 500 ml per four hour dwell. Lymphatic transport offsets both solute and water clearance achieved through diffusion and convection, such that

- Net solute clearance = (Diffusive clearance + convective clearance) – Absorption
- Net ultrafiltrate = Transcapillary ultrafiltrate – Absorption

Solute transport

Low Molecular Weight Solutes

The principal mechanism by which the transport of low molecular solutes such as urea, creatinine and uric acid occurs is by diffusion. Diffusion is predominantly a size selective process, while other factors such as concentration gradient, surface area and permeability of peritoneum determine rate of transport.

Restriction coefficient is used to express the size selectivity of the peritoneal membrane. It is calculated by utilising the mass transfer area coefficients and the free diffusion coefficients in water. The size-selective permeability of the peritoneum is lower as the restriction coefficient raises [20].

MTAC is a theoretical value of diffusion obtained before any solute transfer has occurred that represents maximal peritoneal clearance. The equation for MTAC [21] when there is negligible contribution of convection is

$$\mathbf{MTAC = Vt/t \ ln[(P-D0)/(P-Dt)]}$$

Vt – drained dialysate volume

t – time

D0, Dt – dialysate solute concentration at start and time‘t’

P – Plasma solute concentration

It is used as a research tool. Since inaccurate values are obtained at shorter dwells due to convection, assessment is usually performed after 4 to 6 hour dwell. The MTAC values for different solutes are given in **Table 2** and dwell times are represented in **Figure 1**.

Table 2: MTAC Values for Different Solutes.

MTAC	Ml/min per 1.73m^2
MTAC $_{UREA}$	17.5
MTAC creatinine	10.2
MTAC$_{URATE}$	8.6

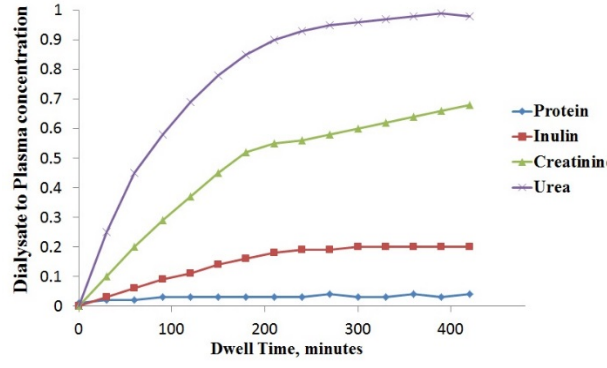

Figure 1: Dwell Time (in minutes) for Different Solutes

Low molecular weight solute transport which occurs in opposite direction from the peritoneal to vascular compartment is also dependent on molecular weight suggesting mainly a diffusive process [22].Among the various osmotic agents used, glucose has mean absorption of 66% across various concentrations, while for glycerol, it is 71% and for 73 to 90% for the amino acids. In addition, convective leak caused by lymphatic drainage from peritoneal cavity and by trans-mesothelial movement into the interstitial tissue of peritoneum is mediated by abdominal pressure. Thus, convection plays a major role in the transport of high molecular weight solutes [23].

Convection / diffusion ratio for solutes

Glucose: 0.1

Inulin: 1.0

Intraperitoneal autologous haemoglobin: 10

Absorption of molecules administered intraperitoneally occurs both by diffusion and convection with convective component increasing as the molecular weight of the solute increases. Rate of solute transport of each individual in a population is

widely variable, ranging from 'slow transporters' to 'rapid transporters' which is determined by means of the peritoneal equilibration test (PET).

High Molecular Weight Solutes

Serum proteins and other macromolecules are transported at a relatively slow rate. This transport is dependent on both the surface area and the size-selective permeability of the membrane. Peritoneal transport of large molecules is probably through large pore system through both restricted diffusion or hydrostatic convection or combination of both [24].

Distribution of large pore system determines the mechanism of transport. Size non-selective mechanism of removal of macromolecules from peritoneal cavity is by means of lymphatics in sub-diaphragmatic region and also through peritoneal interstitial region.

Electrolytes

Sodium

There is decline in dialysate sodium concentration during initial dwell period reaching a minimum by 1 hour followed by a gradual increase [25]. The initial phase of sodium sieving leads on to dilution of dialysate and hypernatremia. This is due to solute-free movement of water through ultra small pores and Na+ binding in interstitial tissue. Subsequent rise in dialysate sodium is caused by Na + diffusion from the circulation [26].

Na^+ (molecular weight 23 Da) and Cl^- (molecular weight 33Da) have MTAC values which are comparatively lower compared to urea (mol. wt. 60 Da) and, creatinine (mol. Wt. 113 Da). Hence, they have a slower rate of transport than that predicted based on their molecular weight MTAC Na+: 4 ml/min, Cl^-: 9ml/min

This is explained by the behaviour of sodium as a large molecule caused by alteration in configuration of due to hydration [27].

Potassium

The MTAC of potassium averages about 17 ml/min and it is cleared by means of diffusion. It may be as high as 24 ml/min during the initial 1 hour due to potassium release from peritoneal lining cells induced by the low initial PH and dialysate hyperosmalilty [28].

Calcium and Magnesium

The standard PD solution contains 1.75 mmol/L and 0.75 mmol/L of Ca^{2+} and Mg^{2+}, respectively which are slightly higher than the unbound plasma concentration. Hence, there is net mass transfer of these solutes from the peritoneal cavity to vessel by diffusion. The ultrafiltration induced convective transport balances the net transfer when higher glucose concentrations are used [29].

Bicarbonate

Average MTAC for bicarbonate is 9.5ml/min. HCO^{3--} loss is dependent on the bicarbonate concentration in plasma and convective loss produced by ultrafiltration. Lactate is the source of buffer in standard dialysate which counterbalances the bicarbonate loss, as lactate is metabolised by liver producing bicarbonate.

The acid base status of the patient depends on the acid production by metabolism and net 'Base Exchange'. In case of lactate buffer, maximum transfer occurs during initial period of dwell which can lead to metabolic alkalosis with increased number of exchanges. HCO^{3--} based dialysis solution is not different from fluids which are lactate based.

Fluid Transport

During dialysis, fluid transport consists of transcapillary ultrafiltration that is movement from peritoneal capillaries to the peritoneal cavity and fluid loss due to transcapillary back filtration and lymphatic system fluid uptake.

Water transport across the capillary wall through small pores is determined by hydrostatic and colloid osmotic forces, while the ultra small pore transport is determined by the osmotic gradient. Studies have shown that 40% of fluid transport occurs by aquaporins [30].

Transcapillary ultrafiltration rate is governed by the Starling's forces which depend on the ultrafiltration coefficient of membrane and the net driving force across the membrane.

$$\text{TCUF rate} = \text{UFC} \times (\Delta \text{ Hydraulic pressure} - \Delta \text{ osmotic pressure})$$

$$= \text{UFC} \times [\Delta P - (\Delta \Pi + S \Delta O)]$$

UFC – ultrafiltration coefficient which is the product of surface area and hydraulic permeability.

The number and size of pores along with intracapillary pressure are major determinants of hydraulic permeability [31].

ΔP – difference in capillary and peritoneal fluid hydrostatic pressure

$\Delta \Pi$ – colloid osmotic pressure gradient

S – Reflection coefficient

ΔO – crystalloid osmotic pressure gradient

The peritoneal capillary hydrostatic pressure is around 17 mmHg while the average intraperitoneal pressure is around 2 - 8 mmHg, depending on the position of patient.

It may exceed 20 mmHg while walking. This is also determined by the instilled dialysate volume [32].

Studies have shown that the net ultrafiltration is reduced by 1.1 ml/min for a 10 mmHg rise in intraperitoneal pressure due to enhanced lymphatic absorption and decreased transcapillary ultrafiltration [33].

Average colloid osmotic pressure in peritoneal capillaries is 26 mmHg, in the dialysis patients it is 21mmHg. Contribution of colloid osmotic pressure of dialysate is negligible [34]. Crystalloid component of colloid osmotic pressure is mainly determined by glucose. The resistance offered by membrane to transport of osmotic agent determines its effectiveness which is expressed as reflection coefficient. In case of glucose, it is one across ultra small pores reaching zero towards large pores due to which it acts as an effective osmotic agent despite small size. The mean value for glucose is around 0.02 to 0.05 [35].

The osmotic pressure exerted by 1.36% glucose concentration is about 23 mmHg while for 4.36% glucose it is about 104mmHg. The crystalloid osmotic pressure during dialysis dwell is maximal at the initial phase and dissipates later as the dialysate concentration of glucose decreases due to ultrafiltration induced dilution and systemic reabsorption (**Table 3**).

The average glucose absorption during 4 hour dwell is 61%, while it is about 75% during a 6 hour dwell. The glucose concentration influences the absolute not the relative absorption [36].

Table 3: Dialysate Glucose Concentration and Ultrafiltration Rates and Time

Dialysate concentration	**Maximum UF rate**	**Mean UF (4 hr)**
1.36% glucose	2.7 to 4.3 ml / min	1.0 to 1.2 ml / min
3.86% glucose	12 to 16 ml / min	3 to 4 ml / min

Colloid Osmosis

Glucose polymers such as dextrin which are relatively impermeable through peritoneal membrane are applied during PD as osmotic agents. Such colloid macromolecules in the dialysate effect fluid flow into the dialysate, known as ‘colloid osmosis’. This fluid flow occurs through small poresand is independent of aquaporin [37]. The pressure gradient exerted by icodextrin is greater than the 1.5% glucose based solution but lower than 4.25% glucose based solution.

Dissipation of gradient is slower for such colloid solutions; thus 7.5% icodextrin is used for inducing ultrafiltration based on this property as the icodextrin absorption during 8 hour exchange is 20% with mean ultrafiltration rate of 1.4 to 2.3 ml/min. Randomised controlled studies show that icodextrin compared to 1.36% dialysate glucose produced UF which is 3.5 times more at 8 hours while at 12 hours it was 5.5 times more and also demonstrated that it had equivalent efficacy with 3.86% glucose [38].

References

1. Gottschalk, C. W., and S. K. Fellner, 1997: History of the science of dialysis. *Am. J. Nephrol.,* **17,** 289–298.
2. Cameron, J. S., 2002: The science of dialysis: 'uraemic toxins'. *History of the Treatment of Renal Failure by Dialysis.* J. S. Cameron, Ed., Oxford: Oxford University Press, 15–23.
3. Khanna, R., and R. T. Krediet, 2009: *Nolph and Gokal's Textbook of Peritoneal Dialysis*. 3rd ed. Springer- New York.
4. Esperanca, M. J., and D. L. Collins, 1966: Peritoneal dialysis efficiency in relation to body weight. *J. Pediatr. Surg.,* **1,** 162–169.
5. Fox, S. D., J. K. Leypoldt, and L. W. Henderson, 1991: Visceral peritoneum is not essential for solute transport during peritoneal dialysis. *Kid. Int.,* **40,** 612–620.
6. Alon, U., J. A. Bar-Maor, and G. Bar-Joseph, 1988: Effective peritoneal dialysis in an infant with extensive resection of the small intestine. *Am. J. Nephrol.,* **8,** 65–67.
7. Pawlaczyk K., M. Kuzlan, K. Wieczorowska-Tobis, H. Pawlik-Juzków, A. Breborowicz, J. Knapowski, D. G. Oreopoulos, 1996: Species-dependent topography of the peritoneum. *Adv. Perit. Dial.,* **12,** 3–6.
8. Wiederhielm, C. A., 1972: The interstitial space. *Biomechanics: Its Foundations and Objectives.* Y. C. Fung, N. Perrone, and M. Andeker, Eds., Englewood Cliffs, NJ: Prentice-Hall, 273–286.
9. Devuyst, O., and E. Goffin, 2008: Water and Solute Transport In Peritoneal Dialysis: Models and Clinical Applications. *Nephrol. Dial. Transplant.,* **23,** 2120-2123.
10. Pyle, W. K., R. P. Popovich, and J. W. Moncrief, 1981: Mass transfer in peritoneal dialysis. *Adv Perit Dial.,* 41–46.
11. Aguirre, A. H., 2011: Protective measures against ultrafiltration failure in peritoneal dialysis patients. *Clinics*, **66,** 2151-2157.
12. Rippe, B., G. Stelin, and B. Haraldsson, 1991: Computer simulations of peritoneal fluid transport in CAPD. *Kid. Int.,* **40,** 315–325.
13. Rippe, B., 2008: Free water transport, small pore transport and the osmotic pressure gradient three-pore model of peritoneal transport. *Nephrol. Dial. Transplant.,* **23,** 2147–2153.
14. Rippe, B., D. Venturoli, O. Simonsen, and J. de Arteaga, 2004: Fluid and electrolyte transport across the peritoneal membrane during CAPD according to the three-pore model. *Perit. Dial. Int.,* **24,** 10–27.
15. Preston, G. M., T. P. Carroll, W. B. Guggino, and P. Agre, 1992: Appearance of water channels in Xenopus oocytes expressing red cell CHIP 28 protein. *Science,* **256,** 385–387.
16. Yung, S., and T. Chan, 2012: Pathophysiological Changes to the Peritoneal Membrane during PD-Related Peritonitis: The Role of Mesothelial Cells. *Mediators Inflamm.*, **2012:** 1-21.
17. Smit, W., D. G. Struijk, M. M. Ho-dac-Pannekeet, and R. T. Krediet, 2004: Quantification of free water transport in peritoneal dialysis. *Kid. Int.,* **66,** 849–854.

18. Leypoldt, J. K., 1993: Interpreting peritoneal osmotic reflection coefficients using a distributed model of peritoneal transport. *Adv. Perit. Dial.,* **9,** 3–7.
19. John, K. L., 2002: Solute Transport across the Peritoneal Membrane. *JASN*, **13,** 84-91.
20. Ho-dac-Pannekeet, M. M., J. G. Koopmans, and D. G. Struijk, 1997: Restriction Coefficients of Low Molecular Weight Solutes and Macromolecules during Peritoneal Dialysis. *Adv. Perit. Dial.,* **13,** 72-76.
21. Henderson, L. W., and K. D. Nolph, 1969: Altered Permeability of the Peritoneal Membrane after Using Hypertonic Peritoneal Dialysis Fluid. *J. Clin. Invest.,* **48,** 992-1001.
22. Krediet, R. T., E. W. Boeschoten, D. G. Struijk, and L. Arisz, 1987: Pharmacokinetics of intraperitoneally administered 5-fluorocytosine in continuous ambulatory peritoneal dialysis. *Nephrol. Dial. Transplant.,* **2,** 453.
23. Struijk, D. G., R. T. Krediet, G. C. M. Koomen, E. W. Boeschoten, H. J. Reijden van der, and L. Arisz, 1990: Indirect measurement of lymphatic absorption with inulin in continuous ambulatory peritoneal dialysis (CAPD) patients. *Perit. Dial. Int.,* **10,** 141–145.
24. Rankin, F. M., 1979: Relation of capillary morphology to transport of fluid and large molecules: a review. *Phsiol. Scand.*

25. Raja, R. M., R. E. Cantor, C. Boreyko, H. Bushehri, M. S. Kramer, and J. L. Rosenbaum, 1972: Sodium transport during ultrafiltration peritoneal dialysis. *Trans. Am. Soc. Artif. Intern. Organs,* **18,** 429.

26. Nolph, K. D., J. E, Hano, and P. E. Teschan, 1969: Peritoneal sodium transport during hypertonic peritoneal dialysis. Physiologic mechanisms and clinical implications. *Ann. Intern. Med.,* **70,** 931.

27. Heimbürger, O., J. Waniewski, A. Werynski, and B. Lindholm, 1992: A quantitative description of solute and fluid transport during peritoneal dialysis. *Kid. Int.,* **41,** 1320.

28. Imholz, A. L., G. C. Koomen, D. G. Struijk, L. Arisz, and R. T. Krediet, 1994: Fluid and solute transport in CAPD patients using ultralow sodium dialysate. *Kid. Int.,* **46,** 333.
29. Merchant, M. R., A. J. Hutchinson, S. J. Butler, H. Boulton, R. Hintchliffe, and R. Gokal, 1992: Calcium, magnesium mass transfer and lactate balance study in CAPD patients with reduced calcium/magnesium and high lactate dialysis fluid. *Adv. Perit. Dial.,* **8,** 365.
30. Yang, B., H. G. Folkesson, J. Yang, M. A. Matthay, T. Ma, and A. S. Verkman, 1999: Reduced osmotic water permeability of peritoneal barrier in aquaporin 1 knockout mice. *Am. J. Physiol.,* **276,** 76-81.
31. Stelin, G. and B. Lippe, 1990: Pharmacological interpretation of variation in dialysate volume with dwell time in CAPD. *Kid. Int.,* **38,** 465-472.
32. Twardowski, Z. J., R. Khanna, K. D. Nolph, A. Scalamogna, M. H. Metzler, T. W. Schneider, B. F. Prowant, and L. P. Ryan, 1986: Intraabdominal pressures

during natural activities in patients treated with continuous ambulatory peritoneal dialysis. *Nephron.,* **44,** 129-135.
33. Imholz, A. L., G. C. Koomen, D. G. Struijk, L. Arisz, and R. T. Krediet, 1993: Effect of an increased intraperitoneal pressure on fluid and solute transport during CAPD. *Kid. Int.,* **44,** 1078-1085.
34. Ho-dac-Pannekeet, M. M., N. Schonten, M. J. Lagendi, J. K. Hiralall, D. R. de Waart, D. G. Struijk, and R. T. Krediet, 1996: Peritoneal transport characteristics with glucose polymer based dialysate. *Kid. Int.,* **50,** 979-986.

35. Leypoldt, J. K., 1993: Interpreting peritoneal membrane osmotic reflection coefficients using a distributed model of peritoneal transport. *Adv. Perit. Dial.,* **9,** 3-7.

36. Heimbürger, O., J. Waniewski, A. Werynski, and B. Lindholm, 1992: A quantitative description of solute and fluid transport during peritoneal dialysis. *Kid. Int.,* **41,** 1320-1332.

37. Mistry, C. D., and R. Gokal, 1993: Can ultrafiltration occur with a hypoosmolar solution in peritoneal dialysis? the role for 'colloid' osmosis. *Clin. Sci.,* **85,** 495–500.

38. Mistry, C. D., R. Gokal, and E. Peers, 1994: A randomized multicenter clinical trial comparing isosmolar icodextrin with hyperosmolar glucose solutions in CAPD. MIDAS Study Group. Multicenter Investigation of Icodextrin in Ambulatory Peritoneal Dialysis. *Kid. Int.,* **46,** 496-503.

Chapter 6

Animal Models in Peritoneal Dialysis

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Animal Models in Peritoneal Dialysis

Why the Need of Animal Models?

The use of peritoneal dialysis (PD) in human beings has given us some insight in the understanding of various aspects of PD. Principally,

1. Physiology of peritoneal membrane;
2. Solute and water transport across the membrane;
3. Effect of inflammation on peritoneal membrane, solute and water transport in the inflammatory state;
4. The culprit behind peritoneal injury, whether it is fluid or infection; and
5. Encapsulating peritonitis the dreaded complication.

Even if we can avoid peritonitis, the PD procedure *per se* injures the peritoneum. Exposure to solution with low pH and high glucose results in various pathological changes in the peritoneal membrane [1]. Thus, we often have a question-Is there a half life of peritoneal membrane? If so, can it be prolonged? A number of attempts are being made to address this issue and that is the reason we have newer more biocompatible PD solutions and newer

therapeutic agents. So on the one hand, we want to know about solute and water transport across the peritoneal membrane of newer solutions and on the other hand, we wish to prolong the life of the membrane. We need to know underlying mechanisms [2].The newer agents need to be tested before being put to clinical practice. Jorres and Witowski [3] defined three periods in the history of PD and its associated research. The first period, pre 1980 focused mainly on the clinical PD, peritoneal cavity access and PD procedure. In the second period mid 1980 to early 1990s, there was an emergence of basic research on host defence mechanism and fluid biocompatibility using peripheral and peritoneal WBCs. In the third phase, from mid 1990s, the focus shifted towards the longevity of the peritoneal membrane. Sophisticated cell cultures and animal models are being used to achieve this purpose.

Limitations of Human Studies

As per Di Paolo and Sacchi, the ideal methodology for studying peritoneal membrane related to PD should involve the following steps:

1. Study of the healthy peritoneum;
2. Prospective biopsies of the same individuals in different stages of CKD; and
3. Studying during PD treatment and subsequently effect of infection/ inflammation on the peritoneal membrane. This seems impossible due to ethical as well as technical reasons [4].

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Technically, it is complicated to perform biopsy of the peritoneum (diaphragmatic and visceral peritoneum) as it is inaccessible during standard surgical procedures. Moreover, catheter placement is needed to obtain such biopsy which is painful and traumatic for the patient. Due to these ethical and technical issues, animal models are required. These models enable both *in vivo* and *ex vivo* research of the healthy peritoneal membrane, sequential changes during dialysis and also the effect of newer solutions on the peritoneum [5, 6].

Animal models

Peritoneal structure is similar in all the mammals so it is expected that the results obtained from animal models should be similar to human beings.

Characteristics of an Ideal Animal Model

An ideal animal model should have the following characters:

1. Easy and affordable breeding;
2. Adequate life expectancy;
3. Adequate survival on PD;
4. Similar size of the parietal- peritoneum and the ratio of peritoneal surface to body surface area as that of the humans ;
5. Easy peritoneal catheter insertion;
6. Should allow the study of transport characteristics of the peritoneal membrane as well as;
7. Time related structural and functional changes of peritoneal membrane; and
8. Ability to study the underlying pathogenetic mechanisms.

However, a number of practical problems have to be sorted to conduct proper experiments and interpretation of the in an animal model.

Animal models: Practical Issues to be Tackled

The main goal is to have a model which is almost similar to the human PD. A number of challenges are encountered and have to be overcome irrespective of the animal and type of model to get the desired information about peritoneal transportation, structural changes of peritoneal membrane and local defence mechanisms.

Peritoneal Access Related Issues

These are of major concerns in rats. In acute PD model, under anaesthesia, either PD fluid is instilled by direct abdominal puncture by 22G needle or by inserting a temporary catheter [3]. There are three ways to secure the peritoneal access [7].

1. With or without anesthesia: PD fluid is instilled by direct blind abdominal puncture with 22G needle. The drawback is that the repeated punctures can lead to bleeding and infection which can affect the results of the experiment [8].

Additionally, anesthesia can influence peritoneal transport by its action on the lymphatic drainage [9].

2. Permanent indwelling catheter is inserted subcutaneously from the neck to the peritoneal cavity. In this "open method" dialysate is instilled and subsequently removed from the peritoneal cavity through the catheter. Though, there is no anesthesia requirement but there is a high risk of infection and catheter obstruction [2].

3. In the "closed system" unlike open method, the catheter is attached to a subcutaneous reservoir in the neck, thus, making it a closed system. Dialysate remains in the peritoneal cavity untill it is absorbed. Infection rate is low but obstruction remains a problem [2].

In rabbits, the peritoneal access is easier, a permanent catheter can be implanted, for this purpose a double lumen central venous catheter has been used and some have even used the infusion system [2, 10].

To avoid catheter obstruction, omentectomy or heparin has been tried [11, 12]. Heparin coated catheters solve the above problems as it decreases the obstruction with no changes in the peritoneum characteristics [5]. Prophylactic antibiotics prevent peritonitis without any functional or structural changes in the peritoneum.

Peritoneal Dialysis Exchanges: Rats have a peritoneal surface area of around 600 cm^2 as compared to 17000 cm^2 of that of humans. Thus, 70 ml of volume instilled in rats should equal to that practiced in the human beings in a clinical scenario [13, 14]. But, generally 10 ml is used as higher volumes that leads to respiratory distress and leakage [15]. In rabbits, usually 40 ml/kg dialysis solution is instilled which matches in proportion to that of the humans [16]. Gradual increase in volume prevents respiratory distress [11]. Multiple exchanges with drainage after every dwell closely resembling human PD has also been used.

Peritoneal Membrane Sampling and Analysis

How long after exposure to fluid does the peritoneal membrane get altered? Immediately post catheter insertion, a self limiting non specific inflammatory reaction is seen. [17]. A three month period is at least required, however it is subject to the type of dialysis solution. To study the alterations in the structure, having a proper sample is a must. In humans, mainly parietal peritoneum is sampled due to its easy accessibility. Alterations in the parietal layer are more than that in the visceral layer, while in animals, the reverse holds true [12, 15, 18]. Thus, in the experimental models, irrespective of the animal or the type of experiment, mainly visceral peritoneum is sampled. Peritoneal tissue is very fragile, it gets dried quickly and even light touch can bring about ultrastructural changes. So, the sample has to be fixed immediately [13]. Histomorphometry provides precise quantitative analysis, it can quantify mesothelial cells as well as the sub mesothelial oedema, lumen diameter and the dimensions of different layers of vessel wall [19].

Despite limitations, animal models can give a fair understanding of the peritoneal functional and structural changes and help in studying interventions and innovations before being applied to the human beings.

Once, we have both the practical issues to be dealt with and expected information required from the animal model, there are two things to be addressed, first which animal and; second what sort of model.

Animals Used in Animal Model Studies: Which Animal to be Used?

Characteristics of an ideal animal model required for PD has been described but which animal to be used still remains unanswered. Generally, small animals like rats and rabbits have been used. **Table 1** summarises the characteristics of different animals in relation to an ideal one.

Table 1: Characteristics of Various Animals in Relation to Ideal Animal Model

Ideal animal model	Rats	Rabbits	Large animals (Dog, sheep)
Easy and affordable breeding	Yes	No	No
Adequate life expectancy and survival on PD	No	Yes	Yes
Similar size of parietal peritoneum and ratio of peritoneal surface area to BSA as in humans	No	Yes	? Yes
Easy catheter insertion	No	Yes	Yes
Adequate time frame to obtain results	Yes	Yes	No

Though, rabbits have lot of advantages as an animal model, securing peritoneal access is easy as catheter can be inserted. The life expectancy as well as survival on PD is good, thus, can be studied over a considerable time period. The ratio of peritoneal membrane surface area is somewhat akin to human beings. However, rabbits are delicate animals and unlike rats very difficult to breed. Rats, on the other have a lot of drawbacks. Due to their small size, it is difficult to secure peritoneal access and a lot of complications are observed. The peritoneal surface area to the total body surface area, is more as compared to the human beings. Thus, the results may be fallacious. But, their easy and economical breeding and fast maturation makes them a favorite for conducting experiments. In addition to small animals, large animals have also been used mainly sheep and dogs who like humans have a longer life span [2, 6, 11]. Pros and cons of different animals are described in **Table 2**.

Table 2: Pros and Cons of Different Animals used in Animal Models

	Rat (small animal)
Drawbacks	Shorter life span
	Difficulty in securing peritoneal access
	Higher complications due to small size
	Transplant characteristics not similar to humans
	Peritoneal surface area to body surface area not akin to humans
Advantages	Economical and easy breeding
	Rabbits (small animal)
Drawbacks	Extremely difficult to breed
	Delicate animals: difficult to maintain
Advantages	Easy to secure peritoneal access
	Transport characteristics similar to humans
	Peritoneal surface area to BSA ratio similar to human
	Sheep/dog (large animal)
Drawbacks	Difficult to breed, costly, need prolonged period to obtain results
Advantages	PD procedure similar to humans can be done
	Easy to secure peritoneal access

Type of Animal Models

As addressed above, since the basic purpose is two-fold; first, to study transport characteristics of the peritoneal membrane under normal as well as inflammatory state and; second what happens to the peritoneal membrane over the years. Hence, two types of animal models are used which address the above questions. (i) Acute peritoneal dialysis animal models (ii) Chronic peritoneal dialysis animal models (2, 20).

Acute Peritoneal Dialysis Animal Models

The simplest model is to introduce fluid into the peritoneal cavity and study the physiology of transport across the peritoneal membrane. Different newer solutions of varying concentrations and addition of therapeutic agents can thus be studied for clinical application in the humans. These models are for shorter duration experiments and generally use a single dwell. Any animal can be used for conducting the experiment.

In rats under short anesthesia, dialysis solution is infused in the peritoneum by an abdominal puncture with a 22G needle. At fixed intervals, rats are sacrificed and the residual dialysate is collected from the abdominal cavity. Blood samples are also taken from the heart. Solute and water transport across the peritoneal membrane can be studied easily. In another model, dialysis solution is infused *via* a temporary catheter and a volume marker radiolabelled albumin is added [21]. Peritoneal solution samples are taken over different dwelling periods. Thus, both intraperitoneal volume as well as water and solute transport across peritoneal membrane can be studied.

The next question that arises is about the peritoneal area that comes in contact with the PD fluids. This has been studied in the rat models by using either MRI [22] or radiolabelled markers [23]. Approximately, 40% of the peritoneal surface area is in contact with the fluid.

In acute model using intravital microscopy, the membrane is seen under a video-microscope in a live animal model [20]. This provides information about the different functional parameters such as blood flow rate, vessel diameter [24-27], permeability to macromolecules, capillary recruitment and lymph vessel kinetics.

Genetically Modified Mice (Knockout and Transgenic)

These are easy and economical for breeding. Despite its drawback of being extremely small in size, aquaporin-1 and its role in water transport across the membrane has come to the forefront [28]. Similarly, the role of nitric oxide synthase isoforms as well as IL-6 in inflammation has been studied using this model [28]. The biggest advantage is that the role of single proteins in solute and water transport can be studied.

Peritonitis Model

In this model, bacteria or pro inflammatory bacterial product like lipo-polysacchanoli (LPS) or *S. epidemidis* supernatant is introduced in the peritoneal cavity [30, 31]. Precaution is required as the over dose of the bacterial or pro inflammatory substance may result in the mortality of the animal. Pawlaczyk K and group D have produced LPS induced peritoneal inflammation which is akin to the human early stage of CAPD peritonitis by adding LPS to standard glucose based dialysis solution. In animal models, this results in an increased dialysate WBC

count and increased cytokines and vascular endothelial growth factor. This also results in enhanced solute transport but diminished ultrafiltration [30].

Apart from single dose of inflammatory agent in different models, an attempt has been made to have sustained peritoneal inflammation by using multiple doses of LPS or incorporating bacterial inoculum in the PD fluid [32].

Based on these results, a number of agents such as n-acetylglucosamine, hyaluronan, heparin *etc*. have been used in animal models to study their effect in reducing the inflammatory response. Similarly, prostaglandin as well as nitric oxide synthetase inhibitors have also been studied.

Chronic Peritoneal Dialysis Models

PD is not a biocompatible procedure, fluid itself causes an inflammatory reaction and progressive injury to the membrane. To know the prolonged effects of dialysis solutions on peritoneal membrane structure and thus function, a variety of chronic models have been developed, mainly in the rats.

Rats with an average life span of 2.5 years, 16 weeks of PD may be similar to that of 5 years in the humans [33]. However, to sustain rats on PD for such a long duration is very challenging. Exposure to PD fluid for at least 4 weeks gives a fair idea about the structural and functional changes of the peritoneal membrane [34]. In rat model, the catheter similar to Tenckholf catheter made from silicone tubing with cuffs in inserted. Omentectomy is usually done and while the one end is placed in the peritoneal cavity, the other end is exteriorised between the ears [34, 35]. As described earlier, it can be either “open system” or “closed system”

Subsequently, PD solutions to be tested are infused 1-4 times/day. Instilled fluid is either absorbed gradually from the peritoneal cavity or drained after completion of the dwell time. Dialysate samples can be taken at predetermined time intervals, thus solute concentration ratio of dialysis fluid and that of dialyte can be calculated. Thus, transplant across the membrane can be studied in a continuous fashion and histopathology of the peritoneum studied at the completion of the experiment [36, 37]. With this model, the function of local peritoneal cells against infection can also be studied. It was observed that solutions with low concentration of glucose and neutral pH elicit less peritoneal inflammatory reaction with improved functioning of the peritoneal white blood cells [38].

Peritoneal Fibrosis in Chronic PD Model

Advanced glycated end products (AGE) exert their action to some extent by binding to AGE receptor (RAGE). This leads to the cellular activation and production of transforming growth factor-B (TGF-B) which plays a pivotal role in the peritoneal membrane fibrosis. The role of AGE-RAGE in peritoneal fibrosis has been studied in different models, uremia *per se*, high glucose concentrate exposure and glucose degradation products containing dialysates. In all of the above, there was an

increased AGE, upregulation of RAGE and fibrosis. So, in addition to PD fluid, uremia *per se* also brings about structural changes in the peritoneal membrane [39]. In addition to glucose, low PH and low content of lactate also contribute towards fibrosis [36]. Bicarbonate buffered PD solutions reduce but can't eradicate these changes. Glutathiome, enalapril or rosiglitazone added to PD solution preserves the peritoneal morphology.

Extrapolating Results of Acute Animal Model Studies to Human Beings

Though, the peritoneal structure is similar in all the mammals but the contribution of different parts of the peritoneum to the total peritoneal surface in various animals is significantly different from the humans [11]. For interpreting the results of the experiments using the animal models, it is important to know the problems encountered and to take adequate preventive steps without affecting the results of the study. Catheter obstruction, peritonitis and use of anesthesia can bring about changes which can affect the experiment. Heparin has many pleiotropic actions which can interfere with the result of an experiment [42, 43]. Similarly, omentum itself is a defense organ of the peritoneal cavity. Anaesthesia may also affect lymphatic drainage and characterstics of the functional membrane [45, 46].

Diaphragmatic area which plays an important role in the lymphatic drainage from peritoneal cavity is larger in the humans as compared to animals [47]. Thus, the experimental animals study may underestimate the role of lymphatic drainage. Effective peritoneal surface area may be more in experimental animals, mainly rats, thus overestimating the solute and water transport [48]. With aging too, the kinetics of PD may change in the experimental models [11]. If an animal is anaesthetised, then effect of it on peritonel circulation needed to be taken in account. Thus, above points need to be kept in mind before extrapolating the results of animal studies to humans.

To conclude, the animal models help in understanding the problems faced during PD in the human beings. Newer PD solutions and different agents can be timed and tested in these models. Thus, animal models do contribute a lot in achieving the goal of PD and prolonging the life of patients with PD by helping in providing a safe and effective PD therapy.

References

1. Lameire, N., W. Biesten, M. Van Landschoot, T. Wang, O. Heimbürger, and J. Bergström, 1998: Experimental models in peritoneal dialysis: a European experience. *Kid. Int.,* **54,** 2194-2206.
2. Stojimirovic, B., J. Trbojevic-Stankovic, and D. Nesic, 2007: Animal models in peritoneal dialysis. *Scan. J. Lab. Anim. Sci.,* **34,** 281-289.
3. Jorres, A., and J. Witowski, 2005: Lessons from basic research for PD treatment. *Perit. Dial. Int.,* **25,** 35-38.
4. Di Paolo, N., and G. Sacchi, 2000: Atlas of Peritoneal histology. *Perit. Dial. Int.,* **20,** 6-87.
5. Choi, J., K. Credit, K. Henderson, R. Deverkadra, H. M. Vanpelt, Z. He, and M. F. Flesser, 2006: Antibiotic prophylaxis in an animal model of chronic peritoneal exposure. *Perit. Dial. Int.,* **26,** 249-258.
6. Nikitidou, O., V. I. Peppa, K. Leivaditis, T. Eleftheriadis, S. G. Zaroginnis, and V. Liakopoulos, 2015: Animal models in peritoneal dialysis. *Fron. Physiol.,* **6,** 244.
7. Mortier, S., N. H. Lameire, and A. S. De Vriese, 2005: Animal models in peritoneal dialysis research: a need for consensus. *Perit. Dial. Int.,* **25,** 16-24.
8. Peng, W. X., Y. Q. Guo, S. M. Liu, C. Z. Liu, B. Lindholm, and T. Wang, 2000: Comparison of three chronic dialysis models. *Adv. Perit. Dial.,* **16,** 51-54.
9. Tran, L., H. Rodela, J. B. Hay, D. Oreopoulos and M. G. Johnston, 1993: Quantitation of lymphtic drainage of the peritoneal cavity in sheep: comparison of direct cannulation techniques with indirect methods to estimate lymph flow. *Perit. Dial. Int.,* **13,** 270-279.
10. Zweers, M. M., C. E. Douma, D. R. Dewaart, A. B. Vander Wardt, M. M. Ho-Dac-Panekeet, R. T. Krediet, and D. G. Struijk, 1999: The standard Peritoneal permeability analysis in the rabbit: A Longitudinal model for peritoneal dialysis. *Perit. Dial. Int.,* **19,** 56-64.
11. Pawlaczyk, K., L. Baum, K. Schwermer, K. Hoppe, B. Lindholm, and A. Breborowicz, 2015: Animal models of peritoneal dialysis thirty years of our own experience. *Biomed. Res. Int.,* 261813.
12. De Vriese, A. S., S. Mortier, M. Cornelissen, E. Palmans, N. Vanacker, A. Leyssens, D. Faict, L. De Ridder, and N. H. Lameire, 2002: The effects of Heparin administration in an animal model of chronic peritoneal dialysis exposure. *Perit. Dial. Int.,* **22,** 566-572.
13. Di Paolo, N., G. Garosi, G. Petrini, L. Traversari, and P. Rossi, 1995: Peritoneal dialysis solution biocompatibility testing in animals. *Perit. Dial. Int.,* **15,** 61-70.
14. Rubin, J., B. S. Clawson, A. Planch, and B. S. Jones, 1988: Measurements of peritoneal surface area in man and in rat. *Am. J. Med. Sci.,* **295,** 453-458.
15. Mortier, S., M. Lameire, and A. S. De Vriese, 2005: Animals models in peritoneal dialysis research: A need for consensus. *Perit. Dial. Int.,* **25,** 16-24.
16. Struijk, D. G., C. E. Douma, R. T. Krediet, and M. M. Zweers, 2001: Nitric oxide -related experiments on peritoneal solute transport in the rabbit. *Nephrol. Dial. Transplant.,* **16,** 661-663.

17. Wieczorowska-Tobis, K., K. Korybalska, M. Radkowski, A. Polubinska, A. Breborowicz, and D. G. Oreopoulos, 1997: In vivo model to study the biocompatibility of peritoneal solutions. *J. Artif. Org.,* **20,** 673-677.
18. Williams, J. D., K. J. Craig, C. V. Ruhland, N. Topley, G. T. Williams, 2003: The natural course of peritoneal membrane biology during peritoneal dialysis. *Kid. Int.,* **88,** 43-49.
19. Garosi, G., and N. Di Paolo, 2001: The rabbit model in evaluating the biocompatibility in peritoneal dialysis. *Nephrol. Dial. Transplant.,* **16,** 664-665.
20. Lameire, N., W. V. Biesen, S. Mortier, and A. DeVriese, 2006: What did we learn from animal models in peritoneal dialysis? *Perit. Dial.,* **150,** 70-76.
21. Wang, T., H. H. Cheng, O, Heimburger, C. Chen, J. Waniewski, J. Bergstrom, and B. Lindholm, 1999: Intraperitoneal addition of hyaluronan improves peritoneal dialysis efficiency. *Perit. Dial. Int.,* **19,** 106-111.
22. Fischbach, M., A. C. Michallat, G. Zollner, C. Dheu, M. Barthelmebs, J. J. Helwig, C. Loichot, B. Escande, K. P. Schmitt, F. Schaefer, B. Haraldsson, and C. Jacques, 2005: Measurement by magnetic resonance imaging of the peritoneal membrane in contact with dialysate in rats. *Adv. Perit. Dial.,* **21,** 17-20.
23. Flessner, M. F., J. Lofthouse, and E. R. Zakaria, 2001: Improving contact area between the peritoneum and intraperitoneal therapeutic solutions. *J. Am. Soc. Nephrol.,* **12,** 807-813.
24. Mortier, S., A. S. De Vriese, J. Van de Voorde, T. P. Schaub, J. Passlick-Deetjen, and N. H. Lameire, 2002: Hemodynamic effects of peritoneal dialysis solutions on the rat peritoneal membrane: role of acidity, buffer choice, glucose concentration, and glucose degradation products. *J. Am. Soc. Nephrol.,* **13,** 480-489.
25. Zareie, M., A. A. Van Lambalgen, A. S. De Vriese, E. V. Gelderop, N. Lameire, P. M. ter Wee, R. H. Beelen, J. van den Born, and G. J. Tangelder 2002: Increased leukocyte rolling in newly formed mesenteric vessels in the rat during peritoneal dialysis. *Perit. Dial. Int.,* **22,** 655-662.
26. Zakaria, R., and D. A. Spain, 2002: Generalized dilation of the visceral microvasculature by peritoneal dialysis solutions. *Perit. Dial. Int.,* **22,** 593-601.
27. DeVriese, A. S., R. G. Tilton, C. C. Stephan¸ and N. H. Lameire, 2001: Vascular endothelial growth factor is essential for hyperglycemia- induced structural and functional alterations of the peritoneal membrane. *J. Am. Soc. Nephrol.,* **12,** 734-1741.
28. Ni, J., J. M. Verbavatz, A. Rippe, I. Boisde, P. Moulin, B. Rippe, A. S. Verkman, and O. Devuyst, 2006: Aquaporin-I plays an essential role in water permeability and ultrafiltration during peritoneal dialysis. *Kid. Int.,* **69,** 1518-1525.
29. Ni, J., R. M. McLoughlin, A. Brodovitch, P. Moulin, P. Brouckaert, B. Casadei, O. Feron, N. Topley, J. L. Balligand, and O. Devuyst, 2010: Nitric oxide synthase isoforms play distinct roles during acute peritonitis. *Nephrol. Dial. Transplant.,* **25,** 89-96.
30. Pawlacyzk, K., A. Polubinska, M. Numata, M. Nakayama, R. Pecoits-Filho, S. Czekalski,
B. Lindholm,andA. Breborowicz,2008:Vascular endothelial growth factor in dialysa

te in relation to intensity of peritoneal inflammation. *Int. J. Artif. Organs,* **31,** 535-544.
31. McLoughlin, R. M., S. M. Hurst, M. A. Nowell, D. A. Harris, S. Horiuchi, L. W. Morgan, T. S. Wilkinson, N. Yamamoto, N. Topley, and S. A. Jones, 2004: Differential regulation of neutrophil activating chemokines by IL-6 and its soluble receptor isoforms. *J. Immunol.,* **172,** 5676-5683.
32. Kim, Y. L., S. H. Kim, J. H. Kim, S. J. Kim, C. D. Kim, D. K. Cho, Y. J. Kim, and J. B. Moberly, 1999: Effects of peritoneal rest on peritoneal transport and peritoneal membrane thickening in continuous ambulatory peritoneal dialysis rats. *Perit. Dial. Int.,* **19,** 384-387.
33. Topley, N., 2005: Animal models in peritoneal dialysis: more questions than answers? *Perit. Dial. Int.,* **25,** 33-34.
34. Wieczorowska-Tobis, K., A. Polubinska, J. Wisniewska, K. Pawlaczyk, M. Kuzlan-Pawlaczyk, V. Filas, A. Breborowicz, and D. G. Oreopoulos, 2001: Multidirectional approach to study peritoneal dialysis fluid biocompatibility in a chronic peritoneal dialysis model in the rat. *Nephrol. Dial. Transplant.,* **16,** 655-656.
35. Pawlaczyk, K., C. J. Holmes, S. Czekalski, A. Breborowicz, and L. Lindholm, 2009: Effects of biocarbonate/lactate dialysis solution on the inflammatory response of spontaneous peritonitis in rats undergoing chronic peritoneal dialysis. *Blood Purif.,* **3,** 200-208.
36. Yao, Q., K. Pawlaczyk, E. R. Ayala, A. Styszynski, A. Breborowicz, O. Heimburger, J. Q. Qian, P. Stenvinkel, B. Lindholm, and J. Axelsson, 2008: The role of the TGF/Smad signaling pathway in peritoneal fibrosis induced by peritoneal dialysis solutions. *Nephron. Exp. Nephrol.,* **109,** 71-78.
37. Breborowicz, A., K. Pawlaczyk, A. Polubinska, K. Górna, A. Wieslander, O. Carlsson, P. Tam, and G. Wu, 2006: Effect of peritoneal dialysis on renal morphology and function. *Nephrol. Dial. Transplant.*, **21,** 3539-3544.
38. Pawlaczyk, K., M. Kuzlan-Pawlaczyk, K. Wieczorowska-Tobis, A. Polubinska, J. Wisniewska, D. Faict, C. J. Holmes, and A. Breborowicz, 1999: Bicarbonate/lactate dialysis solution improves in vivo function of peritoneal host defense in rats. *Perit. Dial. Int.,* **19,** 370-377.
39. De Vriese, A. S., 2005: The John F. Maher Recipient lecture 2004: rage in the peritoneum. *Perit. Dial. Int.,* **25,** 8-11.
40. Yao, Q., K. Pawlaczyk, E. R. Ayala, M. Kuzlan, A. Styszynski, A. Breborowicz, 2006: Peroxisome proliferator-activated receptor-y agonists diminish peritoneal functional and morphological changes induced by bioincompatible peritoneal dialysis solution. *Blood Purif.,* **24,** 575-582.
41. Duman, S., M. Wieczorowska-Tobis, A. Styszynski, B. Kwiatkowska, A. Breborowicz, and D. G. Oreopoulos, 2004: Intraperitoneal enalapril ameliorates morphologic changes induced by hypertonic peritoneal dialysis solutions in rat peritoneum. *Adv. Perit. Dial.,* **20,** 31-36.
42. De vriese, A. S., S. Mortier, and N. H. Lameire, 2001: Non anticoagulant effects of heparin implications for animal models of peritoneal dialysis. *Perit. Dial. Int.,* **21,** 354-356.

43. Gozdzikicwicz, J., J. Borawski, and M. Mysliwiec, 2009: Pieiotropic effects of heparin and heparinoids in peritoneal dialysis. *Clin. Appl. Thromb. Hemost.,* **15,** 92-97.
44. Beelen, R. H., 2006: Role of omental milky spots in the local immune response. *Lancet*, **339,** 689.
45. Tran, L., H. Rodela, N. J. Abrenethy, Z. Y. Yuan, J. B. Jay, D. Oreopoulos, and M. G. Johnston, 1993: Lymphatic drainage of hypertonic solution from peritoneal cavity of anesthetized and conscious sheep. *J. Appl. Physiol.,* **74,** 859-867.
46. Shin, S.K., C. D. Kamerath, J. F. Gilson, and J. K. Leypoldt, 2006: Effects of anaesthesia on fluid and solute transport in a C57BL6 mouse model of peritoneal dialysis. *Nephrol. Dial. Transplant.,* **21,** 2874-2880.
47. Mactier, R. A., R. Khanna, Z. J. Twardowski, and K. D. Nolph, 1987: Role of peritoneal cavity lymphatic absorption in peritoneal dialysis. *Kid. Int.,* **32,** 165-172.
48. Kuzlan, M., K. Pawlaczyk, K. Wieczorowska-Tobis, K. Korybalska, A. Breborowicz, and D. G. Oreopoulos, 1997: Peritoneal surface area and its permeability in rats. *Perit. Dial. Int.,* **17,** 295-300.

Chapter 7

Peritoneal Dialysis – Connectology

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Peritoneal Dialysis – Connectology

Introduction

Peritoneal dialysis (PD) connectology – refers to the delivery of PDfluid to the patient *via* the tubings and connecters. Since continuous ambulatory peritoneal dialysis (CAPD) is a home based therapy, performed by the patient or the care-giver, connectology should be such that it is simple to use and economical. The material usedshould be biocompatible, easily disposable and preferably re-cyclable. Most important of all, there should be low rate of peritonitis due to touch continuation. In this chapter, I will be restricting the discussion to connectology in CAPD with a brief discussion of automated PD. Acute PD will not be discussed. In the initial years of CAPD, there was an explosion of knowledge related to this subject. However, in the recent years this has slowed down considerably.

The early years

PD was first done by George Ganter in 1923 [1]. He used a sterile solution containing electrolytes and dextrose in large glass bottles. The fluid was instilled into the peritoneal cavity through a hollow needle connected to the bottle by a rubber tubing.

In late 1940s, a group in Massachusetts used two catheters: one for the inflow and one for the outflow of the dialysate [2]. In 1960, the Seattle group consisting of Fred Boen and B Scribner developed an automated unit for 24 hour peritoneal dialysis, which could even be done at home [3]. Henry Tenckhoff working at the same centre simplified the technique. Later he improved the silicone PD catheter [4]. In 1975 Moncrief and Popovich conceived CAPD as a modality of renal replacement therapy (RRT) by using Tenckhoff catheters, plastic tubing and one liter glass bottles [5].

However, the PD peritonitis rates were very high. The causes of PD peritonitis are transluminal (touch contamination), periluminal (around the catheter), transmural (across the intestinal wall), hematogenous and ascending (vaginal). The use of disconnect systems, which will be discussed subsequently have reduced the rates of touch contamination related PD peritonitis. Peritonitis due to periluminal causes is usually due to tunnel and exit site infections. The incidence of exit site infection is not related to connectology [1].

D. Oreopoulos at Toronto General Hospital made CAPD a practical reality by using collapsible two liter bags. The empty dialysate bag was rolled up, put into a pouch and remained strapped to the patient [6]. By this method the peritonitis rate dropped from one episode per 10 weeks to one episode per 8-11 months. The number of patients on CAPD increased in the Toronto city, and this modality soon became acceptable worldwide [7]. Hence, Oreopoulos is accepted as the "Father of CAPD".

When CAPD became prevalent as a routine mode of RRT, there were two methods

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of attaching the dialysis bag to the tubing. In the United States, the tubing had a spike, which was a rigid pointed hollow plastic tube. This end was spiked into the dialysis bag at the beginning of the procedure. The other end of the tubing was attached to the titanium adaptor.After installation of fluid into the peritoneal cavity, the empty collapsed dialysis bag and the tubing was folded and put into a pouch as described above. At the beginning of the PD cycle, the PD effluent was drained into the empty bag. The used bag containing the spent dialysate was disconnected, and a fresh bag attached as before. Obviously, the 'spike' system had a high rate of peritonitis. In the United Kingdom and Europe, apart from the spike method another method was also available. In this method, connection of the tubing to the dialysis solution bag was achieved through a luer lock system with a protective povidone iodine laden clam shell [8].

Oreopoulous modified the spike system. He developed a dialysis connector which involved a sharp needle paining through a zone of betadine solution into the delivery set, thus obtaining a disinfected connection [8]. Fresenius developed the Safe-Lock system in which an antiseptic (alcoholic betadine) solution was sprayed during connection [9]. During this era of wearable bags, various attempts at reducing touch contamination were made. One of them was the Travenol® compact exchange system, a mechanized device to facilitate connections of the tubings from the used dialysis bags to fresh bags (**Figure 1**). Also methods of sterilization of the connecting surfaces like heat and microwaves were used [8]. However, studies showed that they were actually not effective in reducing the rates of PD peritonitis.

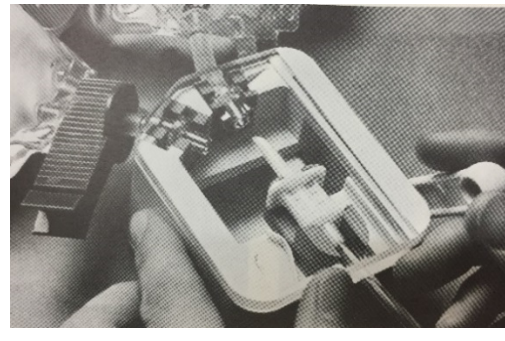

Figure 1: Travenol® compact exchange device

The advent of the 'disconnect system'

A significant improvement in connectology occurred in Italy where the 'Y' system was developed by Buoncristiani in 1980 (**Figure 2**) [10]. This was the first attempt at a disconnect system. Here, a full bag and the empty bag were attached to either end of the upper limbs, where the lower lime of the 'Y' was connected to the titanium adaptor.

The Y shaped tubing was filled with disinfectant during the dwell time. The concept of 'flush before

fill' which is the current standard of care came into vogue. Also, the patient become bag free after installation of fresh fluid during the dwell time. Subsequently, the non-disconnect CAPD system, which has been described in the previous paragraph, was refer

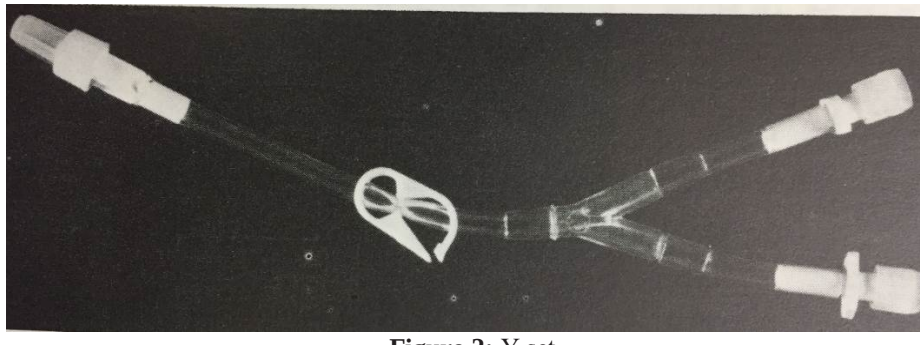

Figure 2: Y set

red to as the 'standard' system of CAPD in the scientific literature of 1980s and 1990s. It may also be noted that the term 'transfer set' relates to the tubing, which connects the PD catheter to the dialysate bags in the non-disconnect systems [1].

In India, the short tubing, which is connected to the PD catheter *via* the titanium adaptor, is called the 'transfer set'. This tubing is referred to as the 'patient extension line' internationally. In subsequent discussion in this chapter, the term transfer set will be as per the international usage.

A variation of the 'Y' of system was the development of the 'O' system and was introduced worldwide (**Figure 3**) [8].

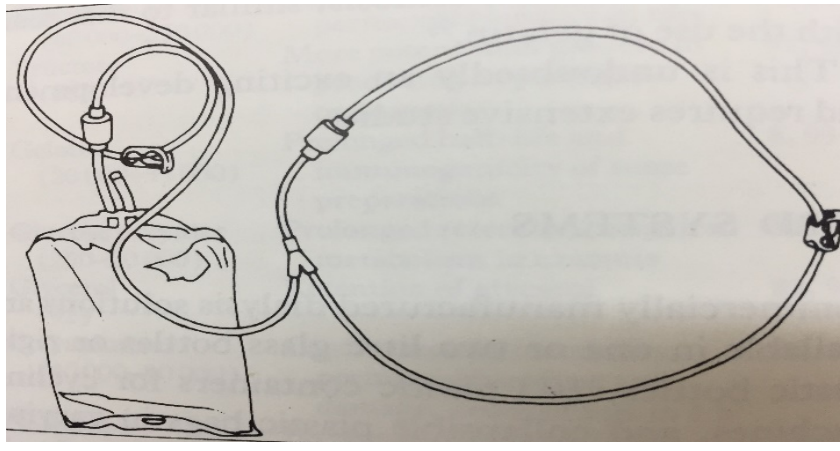

Figure 3: O set

A study from North America of 101 consecutive patients, who were compulsorily switched to the 'O'system from the standard 'spike'system showed a significant reduction in PD peritonitis. There was no reduction in the incidence of exit site infections [11]. The 'O' system also became available in India in the mid-1990s, and the author had used this system for few years. However, it was rather cumbersome and the steps needed to be followed meticulously; else there was a risk of the disinfectant in the 'O' tubing getting instilled into the peritoneal cavity at the beginning of the new cycle [12]. We have also experienced the same issue.

In a large national US study to evaluate the risk of peritonitis and technique failure by CAPD connection technique, Port etal showed that the relation risk for first peritonitis was 40% less for the Y set compared to the standard system. Similarly, technique survival was also significantly better for the Y set [13]. The patient acceptance for the disconnect system was also high leading to a rapid increase in the use of the Y-set system [14].

Current Technology

The double or twin bag system was introduced by Bazzato [15]. Here, the new bag containing the fresh solution and the empty drainage bag are already connected to the Y shaped tubing. Hence, only one connection has to be done by the patient. In the early years, the tubing was revised with a hypochlorite disinfectant during bag exchange. However, the risk of accidental infusion of the disinfectant into the peritoneal cavity was always there. Since subsequent studies showed that the procedure of flush before fill was the main preventive measure against peritonitis, this practice of rinsing with disinfectant was abandoned. Materials used for continuous ambulatory peritoneal dialysis systems include polyethylene and polyolenes. The differences in material are not known to affect technique or patient survival. In 2001, a meta-analysis of 12 trials with a total of 991 randomised

patients compared the peritonitis rates amongst three groups namely the standard, Y-set and twin bag systems [16]. Patients using either the Y-set or the twin bag system had significantly fewer peritonitis episodes as compared to those using the standard system. When the twin-bag system was compared with the Y-set system, the twin bag system was definitely better. Subsequently, two Cochrane reviews concluded conclusively that the double bag disconnect systems should be the preferred connectology in continuous ambulatory peritoneal dialysis [17, 18]. The European Best Practices Guidelines (EBPG) published in 2005 recommended the twin bag system, since they have reduced rates of peritonitis (Evidence level A). If the twin bag systems are unavailable, Y-sets is the next best alternative [19]. It may be noted that at that time about 10% European patients were still using the Y-set system.The twin bag system thusbecame the standard of care for CAPD connectology, which continues to date.

Currently commercially available systems

1. Baxter – marketed under the name 'Ultrabag®'. It is a twin bag system with a luer lock connector (**Figure 4**).

Figure 4: Baxter® Ultrabag system

2. Fresenius AG – Stay safe® and ANDY disc® are twin bag systems with a spiral connecting disc (**Figures 5-7**). After connecting this disc to the transfer set, all further steps are performed by rotating the knob of the risk. Finally, an automatically introduced pin seals the transfer set.

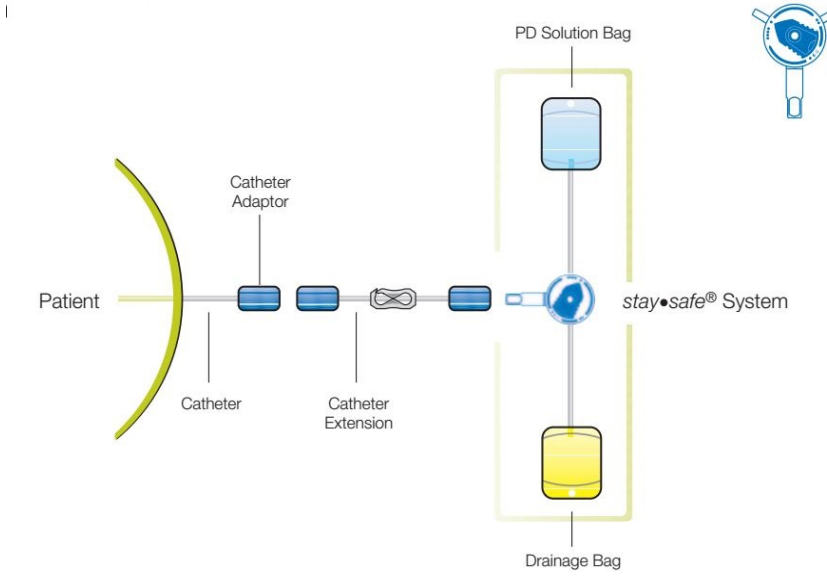

Figure 5: Fresenius® Stay-safe System

Figure 6: Fresenius® Disc and Pin

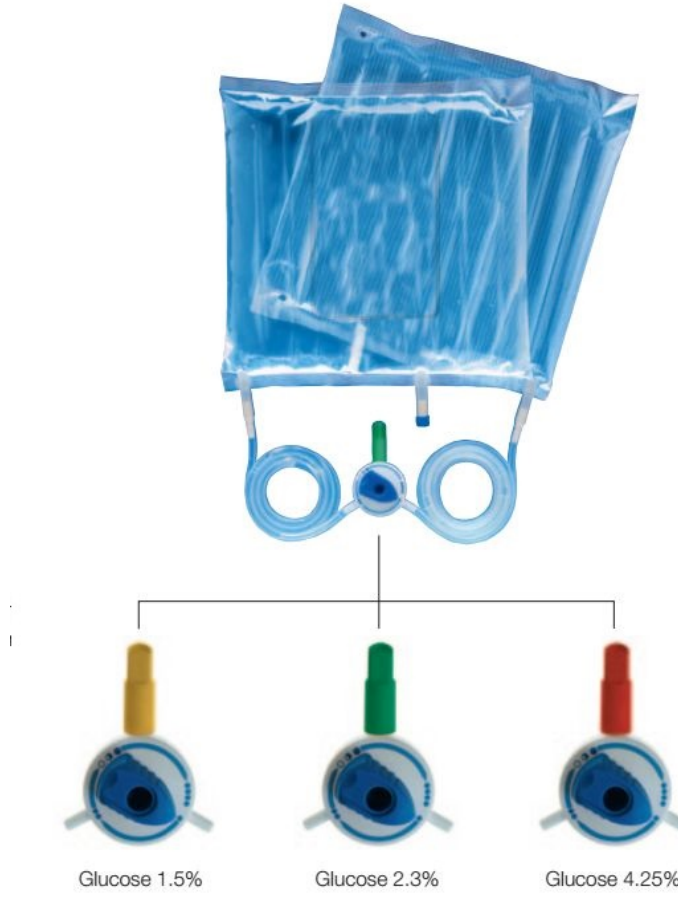

Figure 7: Fresenius® Dialysate Bags with Tubing and Disk

Gambro – The Gambrosol trio system is a twin bag system. The main difference is in the dialysate bag, which is three chambered. By appropriate mixing of the three chambers, dialysates with varying glucose concentrations (as clinically indicated) can be prepared.

3. J Mitra twin bag system.

Studies have shown that the twin bag system is easy to use by the patients. In a head to head trial of two twin bag systems namely the Stay-safe® *vs*.Ultrabag® systems, there was similar incidence of peritonitis and exit-site infection rates. The Stay-safe® system was easier to learn during the initial training period, but there was no difference after one month of training [20]. It is possible that it also has a favourable

effect on technique survival, though studies in this regard are not conclusive. Although the twin bag system is costlier than the earlier systems, this increase in price is definitely offset by the reduced rates of PD peritonitis [21].

Automated Peritoneal Dialysis

In the 1970s, chronic PD consisted mostly of CAPD. Patients on CAPD need to spend a considerable time of their day-time waking hours, often making it unsuitable for the working class. Also, with the progressive loss of residual renal functions, CAPD may be inadequate. Since the time automated peritoneal dialysis (APD) was introduced in the early 1980s, it became very popular amongst patients and nephrologists. The use of APD is based on cyclers and disposables. In the USA, in the initial years the cyclers used the spike technology, while in Europe it was the luerlock technology from the beginning [22]. Currently, in the USA too, cyclers use the luer lock technology. The Baxter Homechoice® system has a disposable tubing set with a cassette / organizer (**Figure 8**). Currently, the number of patients on APD in USA is twice the number of patients on CAPD [23]. Recently, J Mitra® too has introduced a cycler for home use. Need of power supply is one of its limitations, especially in rural India. The high costs of the fluids and disposables remain the main stumbling block. As a result, itsuse is limited to those having employer or insurance reimbursement. Discussion of details of the APD system is beyond the scope of this chapter.

Figure 8: Baxter Automated PD Connections

Conclusion

PD connectology has come a long way since its inception. The '*spike carry bag*' system with its high rate of PD peritonitis and the cumbersome technology of the 'O' system are now only of historical interest. The twin bag disconnect system in vogue since the 15 years is now universally used due to its safety and convenience. APD is popular since it provides day-time freedom.

References

1. Dombros, N., and V.Liakopoulos, 2009: Peritonel dialysis connectology. *Textbook of peritoneal dialysis.* In: R.Khanna, R.Krediet, Eds., Nolph and Gokal's, New Delhi: Springer, 267–281.

2. Frank, H. A., A. M. Seligman, and J. Fine, 1946: Treatment of uremia after acute renal failure by peritoneal irrigation. *J. Am. Med. Assoc.,* **130**, 703–705.

3. Boen, S. T., C. M. Mion, F. K. Curtis, and G. Shilipetar, 1964: Periodic peritoneal dialysis using the repeated puncture technique and an automatic cycling machine. *Trans. Am. Soc. Artif. Intern. Organs,* **10,** 409–414.

4. Tenckhoff, H., B. Meston, and G. Shilipetar, 1972: A simplified automatic peritoneal dialysis system. *Trans. Am. Soc. Artif. Intern. Organs,* **18,** 436–440.

5. Popovich, R. P., J. W. Moncrief, K. D. Nolph, A. J. Ghods, Z. J. Twardowski, and W. K. Pyle, 1978: Continuous ambulatory peritoneal dialysis. *Ann. Intern. Med.,* **88,** 449–456.

6. Oreopoulos, D. G., M. Robson, S. Izatt, S. Clayton, and G. A. de Veber, 1978: A simple and safe technique for continuous ambulatory peritoneal dialysis (CAPD). *Trans. Am. Soc. Artif. Intern. Organs,* **24,** 484–489.

7. Oreopoulos, D. G., 1979: Peritoneal dialysis is here to stay. *Nephron.*, **24,** 7–9.

8. Winchester, J., 1986: CAPD systems and solutions. *Continuous Ambulatory Peritoneal Dialysis.* In: Gokal R, Eds., Edinburgh: Churchill Livingstone, 94–109.

9. Lambert, M., C. Lage, J. Kirchgessner, 1999: Staysafe. A new PVC free system in long-term CAPD treatment. *EDTNA ERCA J.,* **25,** 28–32.

10. Buoncristiani, U., P. Bianchi, and M. Cozarri, 1980: A new safe, simple connection system for CAPD. *Nephrol. Urol. Androl.* **1,** 50.

11. Bonnardeaux, A., D. Ouimet, A. Galarneau, M. Falardeau, J. Cardinal, L. Nolin, and M. Houde, 1992: Peritonitis in continuous ambulatory peritoneal dialysis: impact of a compulsory switch from a standard to a Y-connector system in a single North American Center. *Am. J. Kid. Dis. Off. J.,* **19,** 364–370.

12. Swartz, R., J. Reynolds, P. Lees, and L. Rocher, 1989: Disconnect during continuous ambulatory peritoneal dialysis (CAPD): retrospective experience with three different systems. *Perit. Dial. Int. J. Int. Soc.,* **9,** 175–178.

13. Port, F. K., P. J. Held, K. D. Nolph, M. N. Turenne, and R. A. Wolfe, 1992: Risk of peritonitis and technique failure by CAPD connection technique: a national study. *Kid. Int*. **42,** 967–974.

14. Junor, B. J., 1989: CAPD disconnect systems. *Blood Purif*., **7,** 156–66.

15. Bazzato, G., S. Landini, U. Coli, S. Lucatello, A. Fracasso, and M. Moracchiello, 1980: A new technique of continuous ambulatory peritoneal dialysis (CAPD): double-bag system for freedom to the patient and significant reduction of peritonitis. *Clin. Nephrol,* **13,** 251–254.

16. Daly, C. D., M. K. Campbell, A. M. MacLeod, D. J. Cody, L. D. Vale, A. M. Grant, C. Donaldson, S. A. Wallace, P. D. Lawrence, and I. H. Khan, 2001: Do the Y-set and double-bag systems reduce the incidence of CAPD peritonitis? A systematic review of randomized controlled trials. *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. – Eur. Ren. Assoc.*, **16,** 341–347.

17. Daly, C., M. Campbell, J. Cody, I. Khan, K. S. Rabindranath, L. Vale, and S. A. Wallace, 2001: Double bag or Y-set versus standard transfer systems for continuous ambulatory peritoneal dialysis in end-stage renal disease. *Cochrane Database Syst. Rev.* **2,** CD003078.

18. Daly, C., J. D. Cody, I. Khan, K. S. Rabindranath, L. Vale, and S. A. Wallace SA, 2014: Double bag or Y-set versus standard transfer systems for continuous ambulatory peritoneal dialysis in end-stage kidney disease. *Cochrane Database Syst. Rev.,* **8,** CD003078.

19. EBPG Group, 2005: Continuous ambulatory peritoneal dialysis delivery systems. *Nephrol. Dial. Transplant,* **20,** 13-15.

20. Li, P. K., M. C. Law, K. M. Chow, C. C. Szeto, Y. L. Cheng, T. Y. Wong, C. B. Leung, A. Y. Wang, S. F. Lui, and A. W. Yu, 2002: Comparison of clinical outcome and ease of handling in two double-bag systems in continuous ambulatory peritoneal dialysis: a prospective, randomized, controlled, multicenter study. *Am. J. Kid. Dis.,* **40,** 373–380.

21. Mehrotra, R., and E. Boeschoten, 2009: Current status of peritoneal dialysis. *Textbook of peritoneal dialysis* In: Khanna R, Krediet R, Eds. Nolph and Gokal's. New Delhi: Springer; 19–31.

22. Piraino, B., 2017: Innovations in Treatment Delivery, Risk of Peritonitis, and Patient Retention on Peritoneal Dialysis. *Semin. Dial.*, in press.

23. Diaz-Buxo, J. A., 2014: The road to automated peritoneal dialysis: a personal reflection. *Artif. Organs,* **38,** 993–997.

Chapter 8

Use of Acute Peritoneal Dialysis

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Use of Acute Peritoneal Dialysis.

Acute kidney injury (AKI) occurs more frequently in intensive care unit (ICU) as a part of multiple organ failure and is usually associated with higher mortality. In rural areas and small cities of developing countries, AKI is usually a community-acquired condition, affecting young and previously healthy individuals. Common causes of AKI in developing countries include diarrheal disease with dehydration, snake bites and other animal venomous bites, infectious diseases like malaria, dengue, leptospirosis, native medicine intake, septic abortions *etc*. [1].

Management of AKI includes, ensuring adequate renal perfusion and at the same time avoiding volume overload, meticulous attention to acid-base balance and removal of uremic toxins. Timely initiation of renal replacement therapy (RRT) may lower mortality from AKI [2].

Georg Ganter was the first person to describe the use of peritoneal dialysis(PD) for the treatment of uremia [3] The first case of AKI treated successfully with PD using Ringers solution with dextrose was described by Frank *et al*. in 1946 [4].

In the 1970s, acute PD was a widely accepted form of RRT for the treatment of AKI. But, utilization of PD for the treatment of AKI declined in the favour of hemodialysis (HD) and continuous renal replacement therapy (CRRT) as a number of concerns were raised, especially whether sufficient clearances and ultrafiltration could be achieved, risk of peritonitis, the effects of protein loss and glucose absorption.

With the availability of safe PD solutions and improvements in PD catheter designs, outcomes improved with resultant increase in PD utilization. Over the past decade, there has been a renewed interest in the use of PD for AKI [5, 6, 7].

Advantages of acute peritoneal dialysis

PD has a number of advantages when compared to other RRT modalities. PD is widely available, technically easy to perform with minimal infrastructure and is cost effective. PD is an option for patients with difficult vascular access. Since fluid shifts are gradual, PD is better tolerated by hemodynamically unstable patients. PD carries lesser potential for dialysis disequilibrium syndrome and is better tolerated by patients with raised intracranial pressure. As there is no extracorporeal circulation, there is no predisposition to blood borne infections and local renal hemodynamics may be better preserved. PD is more physiologic and less inflammatory than other extra corporeal therapies and this fact may aid in earlier renal recovery [8]. Large pores in the peritoneal membrane allow removal of toxic cytokines and this has been shown to reduce the need for vasopressors in critically ill patients [9]. PD requires no systemic anticoagulation and can be an option in patients with abnormalities in coagulation profile. The absorbed dextrose from the

dialysate provides nutritional benefits to the critically ill patient. PD is advantageous in children since they have large peritoneal surface area with good clearance and PD access placement is relatively easier. PD is sufficient to meet treatment goals for AKI patients, maintaining adequate fluid, electrolyte, and acid base balances. In developing countries, the cost, practicability, and feasibility of CRRT may be limiting factors, whereas PD is relatively simple and inexpensive and is more widely used, thus avoiding the delay caused by referring critically ill patients to nephrologist or ICU.

Indications for acute peritoneal dialysis

The indications for acute PD can be divided into two groups: renal and nonrenal (**Table 1**) [10].

PD can be invaluable at times when a major catastrophe damages the infrastructure such as earthquakes and flash floods [11]. During disasters, crush injuries are the second most common cause of death after direct trauma, and PD can save lives [7, 12]. Besides classical renal indications for RRT, acute PD can be used to treat congestive heart failure [13] and to treat necrotizing pancreatitis with peritoneal lavage [14]. Clinically significant hypothermia or hyperthermia can be managed with PD where heated or cold peritoneal solutions can be used to maintain core temperature [15]. In fulminant liver failure, PD may help in the removal of toxins like ammonia, bilirubin, and free fatty acids, corrects fluid and electrolyte disorder and may reduce the risk of hypoglycaemia [16]. PD may be used as route for delivery of nutrients like glucose and amino acids and certain drugs in severely ill patients [16, 17].

Table 1: Renal and non-renal indications for acute Peritoneal Dialysis.

Renal indications	Non-renal indications
RRT in the treatment of AKI in children	Refractory heart failure
Hemodynamically unstable patients	Acute pancreatitis
The presence of bleeding diathesis or hemorrhagic conditions contraindicating placement of vascular access for hemodialysis or anticoagulation	Clinically significant hypothermia or hyperthermia
Patients with difficult vascular access placement	Liver failure
Removal of high molecular weight toxins	Infusion of drugs and nutrients as a supportive therapy in critically ill patients
Advanced chronic kidney disease (CKD) presenting urgently with uremia or volume overload and inability to perform any other RRT modality (urgent start PD)	

Limitations to acute peritoneal dialysis

PD is relatively contraindicated in patients with recent abdominal surgery, intra-abdominal adhesions, peritoneal fibrosis, peritonitis, known pleuroperitoneal fistula, presence of abdominal hernia, abdominal wall cellulitis, a recent aortic graft that may become infected [18]. Severe gastroesophageal reflux disease, and adynamic ileus may decrease efficiency of PD. In patients with relative respiratory insufficiency, the use of intraperitoneal fluid may increase intra-abdominal pressure and hence compromise respiratory function. PD may not be as efficient as extra corporeal blood purification techniques for the treatment of emergencies such as acute pulmonary edema or life- threatening hyperkalemia [19, 20, 21]. However, in many resource poor settings, where there is no alternative, PD may still be life-saving in these patients [22].

Acute PD in AKI is associated with significant protein losses and may aggravate malnutrition. Protein supplementation, either enteral or parenteral (1.5g/kg/d), has been recommended for patients with AKI on PD [23]. The high glucose concentrations in peritoneal dialysate may cause hyperglycemia. This can be easily corrected through intravenous or intraperitoneal administration of insulin [24].

Acute peritoneal dialysis prescription

The acute PD prescription order involves length of the dialysis session, dialysate composition, exchange volume, inflow and outflow periods, dwell time, number of exchanges, additives, and monitoring of fluid balance. The most appropriate dose for PD in the management of patients with AKI is poorly defined, because there are only a limited number of trials available to compare treatment modalities. PD orders need to be individualized depending upon the hemodynamic status of the patient, laboratory work up, and volume status. Patients must be reassessed daily and fresh orders given, as dialysis requirements fluctuate.

In acute intermittent PD (AIPD), usual dialysis session lasts for 48–72 hours and each exchange is done over one hour. The length of the PD session can be varied according to volume status, residual renal function, cause and duration of AKI, and renal recovery. Fluid removal can be optimized by mixing and matching low and high glucose concentration PD fluid or by adding 25% or 50% dextrose solution to the PD fluid. An average sized adult can tolerate 2L exchanges. In smaller patients and those with respiratory disease, the exchange volume should be reduced. In pediatric patients the exchange volume is 30ml/kg body weight [27].

Additives in peritoneal dialysis fluids

Some drugs such as electrolytes, anticoagulants, antibiotics *etc.* may be added to the PD fluid in certain specific conditions. Potassium (K^+) is lost during PD by diffusion and convection. Since commercial PD solutions do not contain K^+, a significant number of chronic PD patients either develop hypokalemia ($K^+ < 3.5$ mmol/L) or require K^+ supplementation to maintain normal serum K^+ levels. Hypokalemia reduces gastrointestinal motility and is a risk factor for peritonitis. Hypokalemia may cause serious cardiovascular instability and is a predictor of death in PD patients. In acute PD, each 2L exchange has the potential to remove up to 2 times the serum K^+ concentration. Hypokalemia might be prevented or corrected by adding K^+ to the dialysis solution (2- 4 mmol/L) [26, 28, 29].

Heparin is used to prevent clot formation. Usually, a dose of 250 - 500 units/litre is used. No systemic anticoagulation risk exists as there is no systemic absorption of heparin through peritoneum.

The glucose content of the PD fluid can worsen hyperglycemia. Insulin can be added to the PD fluid, and the dose is adjusted based on frequent blood glucose monitoring. Insulin should be skipped in last 2-3 exchanges to prevent post dialysis hypoglycemia.

Intraperitoneal administration of antibiotics is efficient and provides an alternative route for patients with poor vascular access and for those with peritonitis.

Adequacy of peritoneal dialysis

The most appropriate dose for PD in the management of patients with AKI is poorly defined. The dose and/or efficacy of PD are often assessed with a Kt/V urea measurement (urea clearance over time). In a prospective, randomised crossover study in India by Chitalia *et al*, using acute PD in the setting of hypercatabolic AKI using rigid catheters and either continuous equilibrated PD (CEPD) where long dwells of 4 hours with up to 2 litres of dialysate each or Tidal PD (TPD) with short dwells of 20 minutes each, it was seen that CEPD with 4 hourly exchanges achieved a weekly Kt/V of 1.8 and for tidal APD, it was 2.34. TPD was better than CEPD in terms of urea clearance [30]. In yet another RCT by Ponce *et al,* to assess dosing patterns of PD in critically ill AKI patients, randomized to receive higher or lower intensity PD therapy (prescribed weekly Kt/V of 5.6 vs. 3.5), it was found that the 2 groups had similar mortality rates after 30 days (55 vs. 53%, p = 0.83) and hence a weekly Kt/V of 3 was adequate [31].

According to the ISPD guidelines, PD for AKI recommendations, where resources permit, targeting a weekly Kt/V urea of 3.5 provides outcomes comparable to those of daily HD; targeting higher doses does not improve outcomes. This dose may not be necessary for many AKI patients and targeting a weekly Kt/V of 2.1 may be acceptable [26, 31].

Peritoneal dialysis outcomes in AKI

There are very few studies directly comparing PD with other RRT methods in AKI patients, and have conflicting reports with regard to efficacy and cost [31].

A systematic review published by Chion *et al,* concluded that currently there is no evidence to suggest significant differences in mortality between PD and extracorporeal blood purification in AKI, and there is need for good-quality evidence in this important area [25]. Relatively good outcomes have been reported by acute PD programmes in very low resource settings [32, 33, 34].

The study by Jacob George *et al*, from India where two groups of 25 patients each with AKI and multi organ involvement were randomised to receive continuous venovenous hemodiafiltration (CVVHDF) or to continuous peritoneal dialysis (CPD) found that there were no significant differences seen in correction of hyperkalemia, altered sensorium, or hemodynamic disturbance between the 2 groups and mortality was 84% in the CVVHD group and 72% in the CPD group respectively. It was concluded that the differences in metabolic and clinical outcomes between the groups was minimal [37].

In a study conducted in our institution by Sathyan. *et al*, (unpublished data) between 2007 - 2008 involving 151 patients with various causes for AKI where all the patients were initially started on PD and if there was no, or inadequate recovery of renal function after two sessions of PD or 6 days after institution of PD, they were converted to intermittent HD, the data showed that the patients with acute diarrheal

disease leading to AKI had better recovery with PD alone (66%) when compared to other causes such as sepsis (33%), snake bite (14%) (35). In another study by Balamurugan. S. *et al*, in 2010 – 2011 involving 108 patients with AKI, 58 % recovered with PD alone [36].

In a study from Africa by Arogundade *et al,* two groups of twenty patients with renal failure were managed with AIPD and HD and compared for effectiveness, costs and complications, it was found that both were comparably effective in the control of uraemia [33]. In yet another pilot study from Tanzania by Kilonzo *et al*, on 20 patients with AKI who were treated with PD, 16 patients recovered completely and only 4 patients died [34].

Dialysis adequacy should be assessed ideally by measuring Kt/V. Since it may not be feasible in many countries, adequacy will have to be assessed by clinical signs of fluid balance, normalization of potassium levels and acid base improvement [26].

Complications of peritoneal dialysis

Acute PD is associated with a number of potential complications. These include mechanical, infectious, or medical complications.

Catheter obstruction may be a result of fibrin blockage or displacement with or without omental wrapping of the catheter. Flushing the catheter with sterile saline may dislodge the fibrin blockage. Once flow is re-established, 500 – 1000 units of heparin may be added to each litre of PD fluid. Prophylactic heparin for all patients reduces the incidence of blockage. Other common causes of inadequate drainage are improper positioning of catheter, disruption of siphon effect, constipation and air in the peritoneal cavity or tubings. Displaced PD catheters may be manipulated with guide wire blindly or under fluoroscopic guidance after giving a laxative. This may increases the risk of perforation and peritonitis. If these methods fail, the catheter should be replaced using the original catheter track into the peritoneum, to reduce leakage. Peri-catheter leak is a common occurrence, which can be managed by reducing the exchange volume for the first 24 hours. In some cases, a purse-string suture may be necessary.

Perforation of bowel and bladder can occur during the insertion of the PD catheter, more commonly with rigid catheter. The diagnosis of the perforated organ may be evident immediately after the event or it may remain silent for some time, leading to other complications. Bowel injury can be avoided by priming the abdomen with fluid prior to catheter insertion. Bladder injury can be avoided by ensuring empty bladder before the procedure.

Mild abdominal pain or discomfort is common and is usually secondary to abdominal distension and can be minimized by reducing the exchange volume. Sometimes pain is experienced during inflow due to multiple factors such as low pH of PD fluid, low temperature, the jet flow from catheter tip. This pain may be

minimized by infusion of alkaline PD fluid with the addition of sodium bicarbonate and slower infusion rate [37].

Bleeding is frequently observed after catheter insertion and clears spontaneously after a few exchanges. Bleeding can result from laceration of anterior abdominal wall vessels (*i.e.*, inferior hypogastric artery) or less frequently, puncture of intra-abdominal vessels. The treatment of bleeding depends on its severity. Usually frequent exchanges and use of intra-peritoneal heparin to prevent clotting in the tubings is sufficient [37].

Peritonitis is seen in around 10% patients. It presents with abdominal pain, cloudy effluent. PD fluid leukocyte count of> 100 cells μL (or polymorphonuclear cells > 50%) after a 2-hour dwell is diagnostic. Antibiotic therapy should be initiated as soon as possible empirically to avoid serious consequences of peritonitis like sepsis and catheter removal [38].

Hypovolemia or Hypervolemia can occur due to the use of either hyperosmotic fluid or due to ultrafiltration failure respectively. These can be prevented by close monitoring and adjusting the prescription of dialysis.

Hypernatremia can occur with frequent hypertonic exchanges as the ultrafiltrate generated in PD is hypotonic and contains approximately 70 mmol/ L of Sodium. Hypernatremia can be prevented by intravenous replacement of hypotonic fluids. Hypoalbuminemia, hypokalemia and hyperglycemia can occur in PD, these conditions have already been dealt with.

Conclusions

Acute PD is a very simple, life saving and an acceptable form of RRT in the treatment of AKI. Recent publications have suggested that outcomes with PD are as good as with other extracorporeal RRTs. There are major advantages in using PD for the management of patients with AKI particularly in resource poor settings. There are a number studies from India and lot of unpublished data from the south Indian state of Tamil Nadu which has one of the best state provided Nephrology services which have good evidence to prove the efficacy of PD in managing AKI [35,36]. Though, we do need more studies to establish the right dose prescription, the concerns regarding inefficiency compared with other modalities and complications have been largely dispelled. PD was also chosen as the modality of choice for treating AKI by the International Society of Nephrology “0 by 25” initiative and this largely is being driven through the “Saving Young Lives Campaign”, where centres in developing countries in Africa and Asia are being supported in setting up acute PD programmes for the treatment of AKI [39]. The ISPD has firmly recommended that PD is a suitable modality for treating patients with AKI [26].

References

1. Philip, K., T. Li, E. A. Burdmann and R. L. Mehta, 2013: Acute kidney injury: Global health alert. *J. Nephropathol*., **2,** 90–97.

2. Lameire, N., W. Vanbiesen, and R. Vanholder, 2011: When to start dialysis in patients with acute kidney injury? When semantics and logic become entangled with expectations and beliefs. *Crit. Care,* **15,** 171.

3. Ponce, D., A. Balbi, and B. Cullis, 2017: Acute PD: Evidence, Guidelines, and Controversies. *Seminars Nephrol.*, **37,** 103–112.

4. Frank, H., A. Seligman, and J. Fine, 1946: Treatment of uraemia after acute renal failure by peritoneal irrigation. *JAMA,* **130,** 703-705.

5. Moraes, T. P., R. Pecoits-Filho, S. C. Ribeiro, M. Rigo, M. M. Silva, P. S. Teixeira, D. D. Pasgual, R. Feurbringer, and M. C. Riella, 2009: Peritoneal dialysis in Brazil: twenty-five years of experience in a single center. *Perit. Dial. Int.,* **29,** 492-498.

6. Mohandas, N., and D. Chellapandian, 2004: Value of intermittent peritoneal dialysis in rural setup. *Indian J Perit Dial.,* **6,** 19–20.

7. Kumar, V., R. Ramachandran, M. Rathi, H. S. Kohli, V. Sakhuja, and V. Jha, 2013: Peritoneal dialysis: the great savior during disasters. *Perit. Dial. Int.* **33,** 327–329.

8. Gabriel, D. P., J. T. Caramori, L. C. Martim, P. Barretti, and A. L. Balbi, 2008: High volume peritoneal dialysis vs daily haemodialysis: a randomized, controlled trial in patients with acute kidney injury. *Kid. Int. Suppl*., **73,** 87-93.

9. Morgera, S., M. Haase, T. Kuss, O. V. Hein, H. Z. Becker, C. Melzer, H. Krieg, B. Wegner, R. Bellomo, H. H. Neumayer, 2009: Pilot study on the effects of high cut off haemofiltration on the need for norepinephrine in septic patients with acute renal failure. *Crit Care Med.*, **34,** 2099-2104.

10. Naheed A., 2015: Peritoneal Dialysis in Renal Replacement Therapy for Patients with Acute Kidney Injury. *Int. J. Nephrol.* **2011,** 10.

11. Abraham, G., S. Varughese, M. Mathew, and M. Vijayan, 2015: A review of acute and chronic peritoneal dialysis in developing countries. *Clin. Kid. J*., **8,** 310–317.

12. Sever MS, Erek E, Vanholder R, B. Yurugen, G. Kantarci, M. Yavuz, H. Ergin, S. Bozfakioglu, S. Delmak, M. Y. Tulbek, H. Kiper, and N. Lameire, 2002: Renal replacement therapies in the aftermath of the catastrophic Marmara earthquake. *Kid. Int*., **62,** 2264–2271.

13. Sanchez, J. E., T. Ortega, C. Rodriguez, B. D. Molina, M. Martin, C. G. Cueto, P. Vidau, E. Gago, and F. Ortega, 2010: Efficacy of peritoneal ultrafiltration in the treatment of refractory congestive heart failure. *Nephrol. Dial. Transplant.* **25,** 605–610.

14. Mactier, R., 1992: Non-renal indications for peritoneal dialysis. Advances in peritoneal dialysis. *Conference on Peritoneal Dialysis,* **8,** 141–144.

15. Reuler, J. B., and R. A. Parker, 1979: Peritoneal dialysis in the management of hypothermia. *J. Am. Med. Ass.,* **240,** 2289–2290.

16. Asola, M., K. Virtanen, K. Nagren, S. Helin, M. Taittonen, H. Kasterinen, B. Anderstam, J. Knuuti, K. Metsarinne, and P. Nuutila, 2008: Amino-acid-based peritoneal dialysis solution improves amino-acid transport into skeletal muscle. *Kid. Int.,* **108,** 131–136.

17. Tjiong, H. L., T. Rietveld, J. L. Wattimena, J. W. V. Berg, D. Kahriman, J. V. Steen, W. C. Hop, R. Swart, and M. W. Fieren, 2007: Peritoneal dialysis with solutions containing amino acids plus glucose promotes protein synthesis during oral feeding. *Clin. J. Am. Soc. Nephrol.,* **2,** 74–80.

18. Gabriel, D. P., G. V. Nascimento, J. T. Caramori, L. C. Martim, P. Barretti, and A. L. Balbi, 2006: Peritoneal dialysis in acute renal failure. *Ren Fail*., **28,** 451-456.

19. Brown, S. T., D. J. Ahearn, and K. D. Nolph, 1973: Potassium removal with peritoneal dialysis. *Kid. Int.,* **4,** 67–69.

20. Ponce, D., M. B. Buffarah, C. Goes, and A. Balbi, 2015: Peritoneal dialysis in acute kidney injury: trends in the outcome across time periods. *PLoS One*., e0126436.

21. Ponce, D., M. N. Berbel, C. T. P. Almeida, C. R. Goes, and A. L. Balbi, 2012: High volume peritoneal dialysis in acute kidney injury: indications and limitations. *Clin. J. Am. Soc. Nephrol.,* **6,** 887-894.

22. Ilabaca-Avendano, M., G. Yarza-Solorzano, J. Rodriguez- Valenzuela, G. Arcinas-Fausto, V. Ramírez-Hernandez, D. A. Hernández-Hernández, and L. A. Jáuregui-Flores, 2008: Automated peritoneal dialysis as a life- saving therapy in an emergency room: report of four cases. *Kid. Int.,* **73,** 173-176.

23. Bargman, J. M., J. Bick, P. Cartier, M. K. Dasgupta, A. Fine, S. D. Lavoie, E. Spanner, and P. A. Taylor, 1999: Guidelines for adequacy and nutrition in peritoneal dialysis. Canadian Society of Nephrology. *J. Am. Soc. Nephrol.,* **10,** 311-321.

24. Góes, C. R., M. N Berbel, A. L. Balbi, and D. Ponce, 2013: Approach the metabolic implications of peritoneal dialysis in acute kidney injury. *Perit. Dial. Int.*, **34,** 631-636.

25. Chionh, C.Y., S. S. Soni, F. O. Finkelstein, C. Ronco, and D. N. Cruz, 2013: Use of peritoneal dialysis in AKI: a systematic review. *Clin. J. Am. Soc. Nephrol.,* **8,** 1649.

26. Cullis, B., M. Abdelraheem, G. Abrahams, A. Balbi, D. N. Cruz, Y. Frishberg, V. Koch, M. McCulloch, A. Numanoglu, P. Nourse, R. Pecoits-Filho, D. Ponce, B. Warady, K. Yeates, and F. O. Finkelstein, 2014: ISPD guidelines/Recommendations, Peritoneal dialysis for acute kidney injury. *Perit. Dial. Int.,* **34,** 494.

27. Ponce, D., Peritoneal dialysis for the treatment of acute kidney injury, in Handbook of Dialysis, J. T. Daugirdas, Philadelphia, PA: Lippincott Williams & Wilkins, pp- 451-463,.

28. Zanger, R., 2010: Hyponatremia and hypokalemia in patients on peritoneal dialysis. *Semin. Dial.*, **23,** 575–580.

29. Chuang, Y. W., K. H. Shu, T. M. Yu, C. H. Cheng, and C. H. Chen, 2009: Hypokalaemia: an independent risk factor of Enterobacteriaceae peritonitis in CAPD patients. *Nephrol. Dial. Transplant*. **24,** 1603–1608.

30. Chitalia, V. C., A.F. Almeida, H. Rai, M. Bapat, K. V. Chitalia, V. N., V. N. Acharya, and R. Khanna, 2002: Is peritoneal dialysis adequate for hypercatabolic acute renal failure in developing countries? *Kid. Int*., **61,** 747–757.

31. Ponce, D., M. N. Berbel, J. M. Abrão, C. R. Goes, and A. L. Balbi, 2013: A randomized clinical trial of high volume peritoneal dialysis versus extended daily hemodialysis for acute kidney injury patients. *Int. Urol. Nephrol*., **45,** 869–878.

32. George, .J, S. Varma, S. Kumar, J. Thomas, S. Gopi, and R. Pisharody, 2011: Comparing continuous venovenous hemodiafiltration and peritoneal dialysis in critically ill patients with acute kidney injury: a pilot study. *Perit. Dial. Int*., **31,** 422–429.

33. Arogundade, F. A., D. A. Ishola Jr., A. A. Sanusi, and A. Akinsola, 2005: An analysis of the effectiveness and benefits of peritoneal dialysis and hemodialysis using Nigerian-made PD fluids. *Afr. J. Med. Med. Sci.,* **34,** 227–233.

34. Kilonzo, K., S. Ghosh, S. Temu, V. Maro, J. Callegari, M. Carter, G. Handelman, F. O. Finkelstein, N. Levin, K. Yeates, 2012: Outcome of acute peritoneal dialysis in Northern Tanzania. *Perit. Dial. Int.,* **32,** 261–266.

35. Sathiyan, S., M. Jayakumar, and E. Fernando, Role of acute intermittent peritoneal dialysis for the treatment of acute kidney injury. Unpublished Data; Madras Medical College, Chennai.

36. Balamurugan S., R. Arul, T. K. Dinesh, J. Dhanapriya, Role Of Acute Intermittent Peritoneal Dialysis In Treating Acute Kidney Injury & Acute On CKD In A Tertiary Govt .Hospital. PDSI abstracts: IJPD 2011, p 43- 55.

37. Paul T. T., and K. S. Ramprasad, 1994: Acute Peritoneal Dialysis Using Stylet Catheter. *Saudi J. Kid. Dis. Transplant*., **5,** 184-189.

38. Li, P., C. Szeto, B. Piraino, J. Bernardini, A. Figueiredo, A. Gupta A, D. W. Johnson, E. J. Kuijper, W. C. Lye, W. Salzer, F. Schaefer, and D. G. Struijk, 2010: Peritoneal dialysis-related infections. *Perit. Dial. Int*., **30,** 393–423.

39. Finkelstein, F. O., W. E. Smoyer, M. Carter, A. Brusselmans, and J. Feehally, 2014: Peritoneal dialysis, acute kidney injury, and the Saving Young Lives program. *Perit. Dial. Int.,* **34,** 478–480.

Chapter 9

Peritoneal Dialysis Access

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Peritoneal Dialysis Access

Introduction

Globally, Peritoneal Dialysis (PD) has a chequered history as a modality of renal replacement therapy (RRT) for patients with End Stage Renal Disease (ESRD). While in the developing countries it is gaining slow foothold, it has fallen out of favour in the developed countries [1]. Part of the reason could be due to the reliance on surgeons for placement of PD catheters. Since it is an elective procedure, surgeons often regard it with at best peripheral interest resulting in increased wait times. This is a dampener on both the patient and the nephrologist. During the training period, the nephrology trainees gain the knowledge and skill necessary for introducing the stiff PD catheters for carrying out acute PD. Placement of permanent PD catheter is just another step in the learning curve. Multiple observations across centers have clearly shown that PD penetration increases if the nephrologist initiates the procedure of PD catheter insertion. That the results are non inferior to surgical placement is satisfying from patient point of view [2, 4].

PD catheter placement techniques which can be mastered by the Nephrologists in the increasing order of complexity are,

1. Blind seldinger technique.
2. Seldir fluoroscopic technique.
3. Peritoneoscopic placement.
4. Mini Lap.

Of these, the Seldinger fluoroscopic technique strikes the balance between safety and complexity and will be described in detail.

Patient Selection

It is crucial to select the ideal and appropriate cases during the early part of career as confidence is gathered so that more challenging and complex cases can be taken up later (**Table 1**).

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Table 1: Case Selection and Exclusion

Ideal case selection for initial series.
1.Adult patient
2.Non obese
3.Moderate Ascites
4. First time insertion
Contra Indications
1. Multiple laparotomy scars,
2. Hernia- (Surgical correction followed by catheter insertion is ideal)
3. Suspected adhesions due to previous peritonitis for which PD catheter was removed
4. Morbid obesity (cholecystectomy, Appendicectomy and Cesarean section scars are not contraindications)

It is important to examine the patient with his clothes on to know about his belt line. In those with high belt line the exit site should be below it while in those with low belt line the exit site should be above it. Indelible Marking pen can be used to identify the exit site. The site of deep cuff also should be marked. A bowel cleansing enema is administered the previous night since constipation has been shown to interfere with the PD exchanges. Secondly, it can increase microbial transmigration. Patient should fast at least 6 hours before the procedure. A single pre-operative prophylactic antibiotic is administered (IV Cefazoline1000 mg or Cefuroxime 1500 mg). Anxiolytic cum awake analgesia in the form of IV Midazolam and Fentanyl will be required. Bladder should be confirmed to be in the empty state or if in doubt should be catheterised prior to procedure.

Catheter selection

Double cuff swan neck catheters with straight intraabdominal course are commonly selected. However, coiled catheters and straight neck catheters are also in use. Coiled catheters have been designed with the hope that omental wrap will be less of a problem. But, comparative case series have shown that catheter migration is higher with latter than with swan neck catheters [5]. **Figure 1** shows the swan neck catheter along with Peel away sheath.

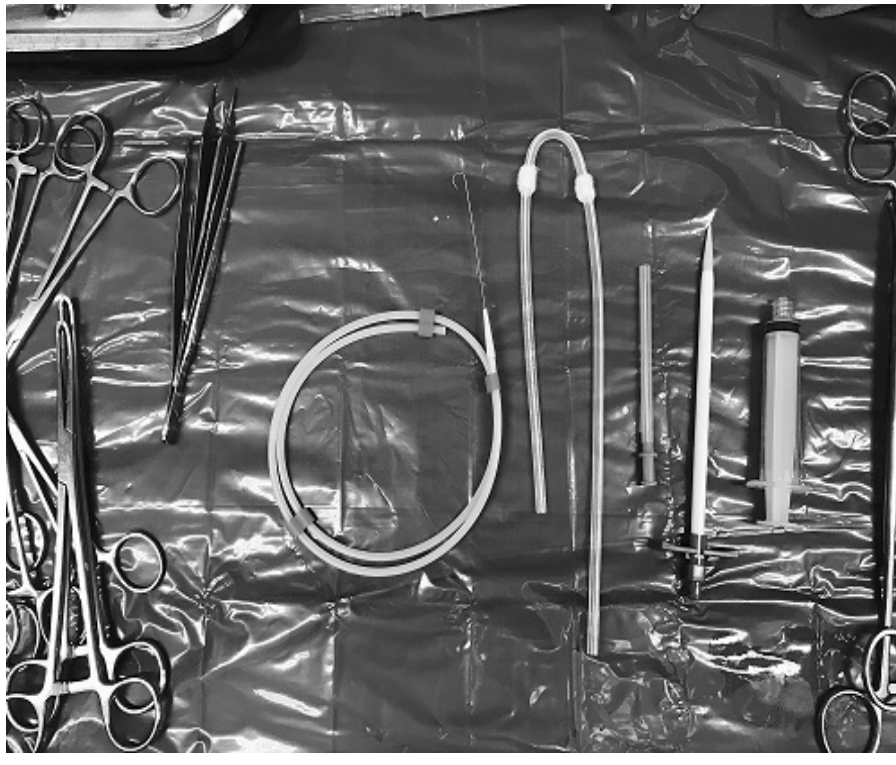

Figure 1: Guide wire, Swan Neck Catheter, Needle and Peel Away Sheath

As shown in **Figure 2** , the inner cuff is either placed on the linea alba which is relatively less vascular, or in either side in the lateral edge of rectus abdominis sheath away from the inferior epigastric artery. Some units routinely delineate the artery beforehand by a Doppler study.

Next, palpate pubic symphysis which is taken as the position where the tip of the catheter should lie [6]. If the catheter tip is placed deeper than this spot , then inflow pain and discomfort may develop [7].

Step by Step Explanation.

Step 1: Incision and blunt dissection to expose Linea alba/ Anterior Rectus sheath

Adequate skin preparation can be done either by 10% povidone Iodine or 2% Chlorhexidine. The catheter is placed in a sterile solution and air expressed from both cuffs; 2% Xylocaine is injected subcutaneously. Next , a 2-3 cm horizontal incision is made on the skin below the umbilicus. Blunt dissection is done to reach the linea alba which is a shiny white sheath.

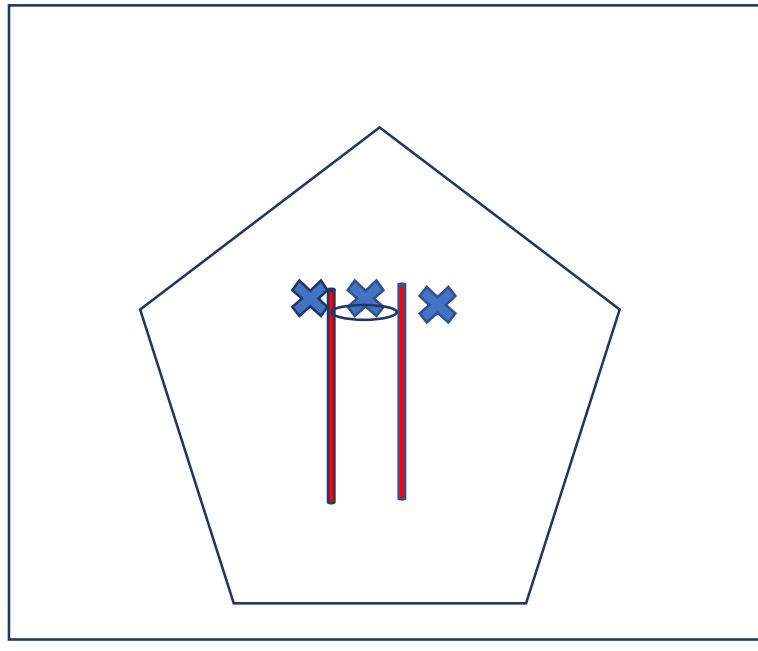

Figure 2: Site Selection on the Anterior Abdominal Wall. Inferior Epigastric Artery is shown in Red

Step 2: Puncture of anterior abdominal wall and entry into peritoneal cavity

Now, the anterior abdominal wall is punctured and peritoneal cavity is entered. This step is crucial from the point of view of successful placement of PD catheter while minimising trauma to intrabdominal structures. The veres needle used for laparoscopy is devised with built in safety mechanism in that the spring loaded device will automatically let the blunt tip come into the peritoneal cavity on the introduction, thus, reducing chances of bowel and blood vessel injury. The other alternative is the pediatric stiff PD catheter with stylet. Once the needle or PD catheter is introduced with a 45degree angle aiming at the symphysis Pubis, 5-8 ml of radiocontrast is injected to check the position. Pre peritoneal placement is characterised by non diffusion of the dye. Peritoneal placement results in free diffusion of the dye with faint delineation of the bowel as shown in **Figure 3**.

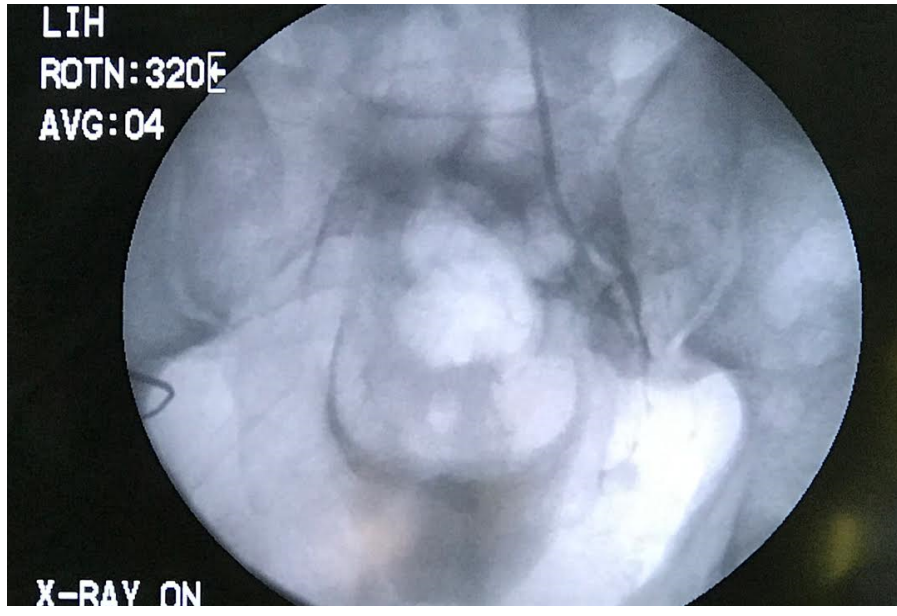

Figure 3: Fluoroscopic Assessment Shows Injected Dye in Peritoneal cavity which Collects in the Pouch of Douglas

Pre peritoneal placement is characterised by non diffusion of the dye. Once confirmed to be in the peritoneal cavity, 500 ml of sterile normal saline or PD fluid is infused into the peritoneum. This is another safety step which ensures that the bowel is not impaled when the plastic dilator and peel away sheath are introduced.

Step 3: Guidewire insertion followed by track dilatation and Peel away sheath insertion

Next, 0.035 inch J tipped guidewire is introduced through the needle and fluroscopically seen to enter the pelvis. The guidewire is advanced further till it curves up from the Pelvic floor due to the reflection of parietal peritoneum as seen in **Figure 4**. It is another point of reassurance that intraperitoneal plane is reached since the guidewire cannot cross the midline unless it is in the peritoneum.

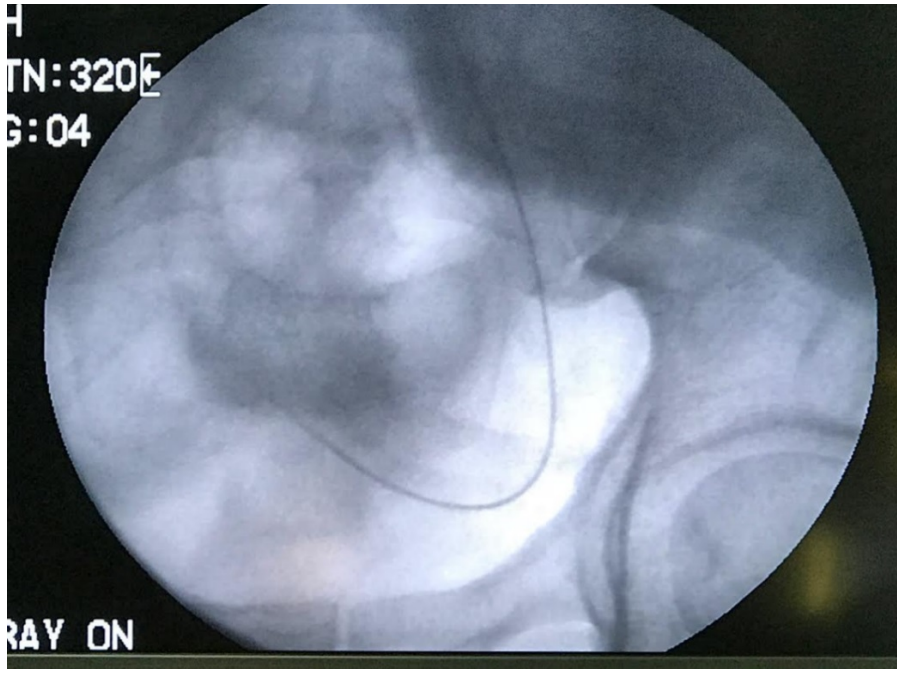

Figure 4: Guide Wire Arches over the Pelvic Foor Rflection and Crosses the Midline

Then 18F plastic dilator with peel away sheath assembly is threaded through the guidewire using seldinger technique. Fluoroscopy is employed at this step to ensure that the guidewire does not get kinked. Now, half a centimeter horizontal slit incision is made in the linea alba to allow the deep placement of inner cuff deep to it. The inner dilator is removed leaving the peel away sheath in place.

Step 4: Catheter placement through Peel away sheath

Next, the intraabdominal portion of PD catheter is introduced *via* the sheath so that the tip reaches the pelvis. The 2 radio opaque lines on the catheter is positioned on the anterior surface which will ensure that the catheter is not twisted along its longitudinal axis. Now, the assistant grasps the inner cuff with a non traumatic forceps as the operator peels away the sheath. Once the sheath is fully removed, the inner cuff is pushed through the slit with the help of a tissue holding forceps in the linea alba so that the inner cuff snugly fits within the anterior abdominal wall. Dye is injected now to ascertain the proper intraabdominal position of the catheter.

Step 5. Exit site creation

Next, the exit site is fashioned down and lateral to deep cuff by making a horizontal 1 cm incision and the catheter pulled out through it so that superficial

cuff lies at a distance of 2-3 cm from the exit site skin surface. The curvature of the catheter is ascertained by fluroscopy. Titanium adaptor is fitted in to the free end of the catheter and transfer set is connected. In and out exchanges are started. If exchanges are rapid, the main wound is sutured. The exit site is left unsutured. Sterile non-occlusive dressings are applied to the main wound and exit site. Depending upon the urgency of the situation , either low volume supine exchanges (500 ml) can start immediately or a week to 10 days can elapse for the break in period.

Complications

1. Pre-peritoneal placement of catheter. Tell tale signs of pain and discomfort for the patient with asymmetric swelling of anterior abdominal wall is present. It is confirmed by dye study with CT scan. The catheter is removed and reintroduced at a different site.
2. Needle stick injury can occur to the bowel or vascular structures intra-abdominally. An omental vessel can get impaled leading to intra-abdominal bleeding. Bleeding usually stops after a few rapid exchanges of PD fluid with added heparin. If the bleeding is exsanguinating then surgical intervention in the form of laparotomy to suture the bleeding vessel may be required.
3. Needle stick injury to the bowel is diagnosed by turbid and at times feculent exudate. The needle is withdrawn and the procedure is abandoned. Antibiotics are started and the patient is observed for peritonitis for 24 hours without oral intake. If the patient develops bowel leak and peritonitis surgical intervention is needed.
4. Leakage is common if exchanges are started within 24 – 48 hours of implantation. The patient is taken up for HD for 2 weeks and the wound is left undisturbed. After 2 weeks, low volume supine exchanges are started and gradually increased.
5. Catheter malpositioning can develop over the first two weeks or later. Most commonly due to omental wrap. This can be prevented by placing the tip of the catheter in the pelvic position which is free of omentum. If detected, the patient is treated conservatively as long as the exchanges are brisk. In case of a blocked catheter, 5000 IU of Urokinase is instilled into the catheter and allowed to dwell. After one hour, the exchanges are started. The procedure can be repeated twice. In case of recalcitrant migration with poor flow, surgical intervention is required. Omentectomy and catheter repositioning are carried out. Stiff Wire manipulation of the catheter is rarely successful and fraught with complications such as bowel injury and omental bleed.

Meenakshi Mission Hospital experience of Fluoroscopic PD catheter insertion

Over a 10 year period from 2006 to 2016, 256 PD catheters were inserted using the percutaneous Seldinger technique for initiation of CAPD [8]. There were 159 men and 97 womens. The mean age was 53$\pm$13 years. Children and those with high probability of intraabdominal peritoneal adhesions due to previous surgeries were excluded. The procedure had to be converted to open surgical placement in 9 cases

due to unsatisfactory catheter positioning. There were 5 major complications; 3 intestinal injuries, 1 bladder injury, and 1 Omental vessel haemorrhage. Of the intestinal perforations, 2 were managed conservatively while laparotomy and closure was performed in one. Bladder injury was managed by continuous bladder drainage. Omental bleeding was managed by laparotomy followed by suturing of the bleeding vessel with omentectomy. Overall, 8 instances of exit site leaks were observed, which resolved spontaneously when PD was stopped for 2 weeks and restarted. Patients were in the hospital for a mean period of 8 ± 3 days in the post operative period. Compared to 59 catheters inserted primarily by open surgical technique in the same period the following differences were noted. The incision size and post operative pain was less in the percutaneous insertion group. The break in period was earlier (4+ 1 day vs 10 + 3 days) in the percutaneous group. They were discharged earlier with considerable reduction in the hospital expenditure. Thus this procedure has many advantages over the surgical method and should be taken up by more number of Nephrologists across India.

Conclusion

PD catheter insertion can be successfully carried out by the nephrologists resulting in improved patient acceptance and PD penetration. Seldinger technique of insertion of PD catheter under the fluoroscopic guidance can be carried out in sterile side rooms of the nephrology wards with excellent short and long term results.

References

1. Jain, A. K., P. Blake, P. Cordy, and A. X. Garg, 2012: Global trends in rates of peritoneal dialysis. *J. Am. Soc. Nephrol.,* **23,** 533–544.

2. Alvarez, A. C., and L. Salman, 2009: Peritoneal Dialysis Catheter Insertion by Interventional Nephrologists. *Adv. Chronic Kid. Dis.,* **16,** 378–385.

3. Perl, J., A. Pierratos, G. Kandasamy, B. B. McCormick, R. R. Quinn, A. K. Jain, A. Huang, J. M. Paterson, and M. J. Oliver, 2014: Peritoneal dialysis catheter implantation by nephrologists is associated with higher rates of peritoneal dialysis utilization: a population-based study. *Nephrol. Dial. Transplant.,* **30,** 301–309.

4. Kumar S. K., A. R. Mahaldar, Y. S. Sooraj, M. Ramkrishnan, A. Kumar, and R. Ravichandran, 2008: Percutaneous CAPD catheter insertion by a nephrologist versus surgical placement: A comparative study. *Indian J. Nephrol.,* **18,** 5–8.

5. Strippoli, G. F., A. Tong, D. W. Johnson, F. P. Schena, and J. C. Craig, 2004: Catheter type, placement and insertion techniques for preventing peritonitis in peritoneal dialysis patients. *Cochrane Database Sys. Rev.,* CD004680.

6. Henderson, S., E. Brown, and J. Levy, 2009: Safety and efficacy of percutaneous insertion of peritoneal dialysis catheters under sedation and local anaesthetic. *Nephrol. Dial. Transplant.,* **24,** 3499–3504.

7. Abdel-Aal, A. K., P. Dybbro, P. Hathaway, S. Guest, M. Neuwirth, and V. Krishnamurthy, 2014: Best practices consensus protocol for peritoneal dialysis catheter placement by interventional radiologists. *Perit. Dial. Int.,* **34,** 481–493.

8. Kumar, S. K., M. Ramakrishnan, R. N. A. Kumar, A. K. Sah, and R. Ravichandran, 2010: Percutaneous CAPD Catheter Insertion by Nephrologist - Single Centre Experience over 4 Years. *Indian J. Perit. Dial.,* **18,** 15–18.

Chapter 10

Laparoscopic Peritoneal Dialysis Catheter Placement

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Laparoscopic Peritoneal Dialysis Catheter Placement

Peritoneal dialysis (PD) is widely being used as a primary mode of renal replacement therapy (RRT) [1, 2]. Access is provided with a PD catheter. Even though the requirement is high, there is decline in the use of PD due to a lack of expertise in insertion and management of PD catheters [3]. The role of surgeon is crucial in these patients, in not only providing access to the peritoneal cavity but also diagnosing and treating the catheter related problems [1]. Various techniques of catheter insertion both laparoscopic and open are described in literature. Major problem in patients on PD is catheter related, of which peritonitis and catheter dysfunction are most important. Catheter dysfunction can be due to intraperitoneal adhesions, catheter tip migration or omental wrapping. Various surgical techniques are being tried to minimise these catheter related complications. None has proven to be a safe technique in completely preventing the catheter dysfunction.

Laparoscopic PD catheter insertions were first described in early 1990s; since then it is being used in upto 50% of insertions. Advantage of laparoscopy is to facilitate additional techniques which help to minimize the catheter dysfunction. Laparoscopic approach allows complete visualisation of peritoneal cavity with identification of critical adhesions which can be lysed [4, 5]. Migration of catheter tip away from pelvis is another cause for dysfunction as catheter functions best in pelvis [6]. Fixation of catheter to parietal wall in lower abdomen has been shown to decrease catheter dysfunction [7-9]. But, studies have shown that this requires an extra port and there may be difficulty in removal of catheter [10]. Rectus sheath tunnelling was described to prevent catheter migration. This long tunnel has shown to prevent catheter migration, dialysate leak and also avoids an extra port [11, 12].

But rectal sheath tunnelling is a relatively complex procedure and also there is technical difficulty in catheter removal. Catheter dysfunction can occur also due to omental occlusion, which is more common in children [13]. Both omentectomy and omentopexy are described for prevention of catheter dysfunction. Laparoscopic omentopexy is preferred over omentectomy as this decreases the complexicity of procedure, procedure time, risk of bleeding and bowel injuries [14, 15]. Omentopexy involves fixing the omentum to the anterior abdominal wall away from the catheter site and pelvis. Most preferred site for omentopexy is parietal wall in left hypochondrium. Omentopexy is done either with a suture or a tacker. Advanced laparoscopic technique involves combination of adhesiolysis, suture fixation of the catheter to the parietal wall or rectus sheath tunneling, and Omentopexy in the left hypochondrium [16]. Multiple studies have shown lower catheter dysfunction rates with the advanced laparoscopy when compared to basic laparoscopy technique [17]. At Our institute, we insert PD catheter using advanced

V. R. Reddy

laparoscopic technique, *i.e.*, adhesiolysis, catheter fixation to parietal wall and omentopexy using only 2 ports instead of 3 ports in others.

Procedure: Procedure is performed under general anaesthesia. No bowel preparation required. Perioperative antibiotic prophylaxis is given. The patient is placed in supine position with operating surgeon on left and camera assistant on the right side and the monitor at the foot end of patient (**Figure 1**). Two ports are used, first 10mm port is placed in the infraumbilical region by open technique. Care should be taken to direct the port insertion into pelvis so that there is no acute kinking of catheter at the insertion site, which may lead to catheter migration. We had one patient with catheter migration twice due to directing the port insertion into upper abdomen leading to an acute kink and migration of the catheter. During second re-exploration for migration, we have noticed the kink and reinserted the port and catheter in the direction of pelvis. After primary inspection of peritoneal cavity, second 5mm port is placed in the right lumbar region. Adhesiolysis is done if there are bowel or omental adhesions in the pelvis (**Figure 2**). Omentum is held with grasper and checked to know if it is long enough to reach the pelvis. In few, especially after previous surgical procedure, omentum may be adherent to parietal wall in upper abdomen and may not reach the pelvis (**Figure 3**). If it is long and enough to reach the pelvic cavity, then omentopexy is planned. Omentopexy is done by placing a transparietal suture with 1-0 prolene in the left hypochondrium with the use of suture passer (**Figure 4**). After Omentopexy, a 1-0 prolene suture loop is taken using suture passer needle in the suprapubic region about 7-10cms below umbilicus for fixing catheter. Loop is taken before catheter insertion to avoid placing an extra port (**Figure 5**). Catheter is introduced through the umbilical port through the reducer. PD catheter is passed into the 10mm reducer retrograde as passing antegrade is not possible due to the cuff on the catheter (**Figure 6**). PD catheter with the reducer is introduced into the umbilical port. Catheter is advanced into pelvis passing through the preplaced polypropylene suture loop. Port with reducer is withdrawn slowly under vision leaving the catheter behind in place (**Figure 7**). Catheter is fixed by tying the preplaced prolene suture loop (**Figure 8, 9, 10**). Catheter is tunnelled in the subcutaneous plane for exit in the left lumbar region. All the patients undergo intraoperative catheter trial to document adequate inflow and outflow. After confirmation of flow, 5mm port is removed. Rectus sheath is closed around the PD catheter with interrupted 1-0 vicryl sutures. Skin is sutured with 2-0 Ethilon.

Using this technique, we have performed 120 CAPD catheter insertions during the last 3 years. Out of this, 102 (85%) were primary insertions and 18 (15%) were reinsertions or correction of catheter dysfunction following open insertion earlier. The mean age was 53.48 years. Overall, 86 (71.7%) were males and 34(28.3%) were females. Thirty-four (28.3%) patients had previous abdominal surgery; 16(13.3%) patients had previous abdominal surgery other than prior PD catheter insertion; 2 patients had prior renal transplant. Of the 18 redo patients, 6 were for catheter dysfunction and 12 were for reinsertion; 5 had catheter dysfunction due to omental and bowel wrapping with catheter migration and 1 patient had catheter

transacted with only inflow and no outflow. A total of 12 patients had PD catheter removed earlier for infection or dysfunction. The mean duration of procedure was 33 (21-55) min. Adhesiolysis was done in 28 (23.3%) patients and 103 (85.8%) patients had omentopexy done. Others had parietal adhesions precluding the need for omentopexy. In the post operative period, all the patients were started on enteral feeds on the same day and were discharged or transferred to the nephrology unit on the day 1. Five (4.1%) patients had dialysate leak in the immediate postoperative period; 3 patients had pericatheter fluid leak (at catheter exit site), 2 had leak at umbilical port site. In all the 5 patients, leak subsided on conservative management; 2 patients had catheter dysfunction. One was due to blood clot blocking catheter lumen in patient with extensive adhesiolysis, which needed relaparoscopy and catheter replacement. Another patient had slippage of catheter from the suture loop and migrated into upper abdomen which was replaced into pelvis and fixed with another suture. The same patient had catheter migrated into upper abdomen again in the immediate postoperative period. Relaparoscopy was done. On assessing the cause for recurrent catheter slippage, we have found that the entry of umbilical port and the catheter were directed into upper abdomen and then turned into pelvis. Hence, we have reintroduced the port in the direction of pelvis and reinserted the catheter. Later we have confirmed position of catheter with repeat X- Ray. No patient had catheter infection which required catheter removal in the immediate post operative period. Mean hospital stay was 2 days. There was no surgical mortality in our study.

Usually for advanced laparoscopic PD catheter insertion, a total of 3 ports are required. Third port is used for suturing in omentopexy and catheter fixation. Instead of laparoscopic suturing we use preplaced sutures for catheter fixation and omentopexy which precludes the use of 3rd port. We have compared the results of laparoscopic PD catheter insertion using rectus sheath tunnelling and suture fixation of catheter in **Table 1** (see inside of back cover page for the procedure). In our series, catheter dysfunction rates are 1.6%. When compared to catheter dysfunction rates with rectus sheath tunnelling in published series, the dysfunction rates with our technique are lower (1.6% *vs*.0-4.6%).

Table 1: Laparoscopic PD Catheter Insertion using Rectus Sheath Tunnelling and Suture Fixation of Catheter

Insertion technique	Series	No. of Patients	Prior surgery (%)	Catheter dysfunction (%)	Leak (%)
Adhesiolysis + Rectus sheath tunnelling + Omentopexy	Crabtree (2009) (18)	428	57	3.7	2.6
	Attaluri (2010) (19)	129	NA	4.6	0
	Ogunc (2005) (20)	44	20.5	0	0
Adhesiolysis + suture fixation of catheter + omentopexy	Bar-Zoar (2006) (21)	34	26	11.6	3
	Schmidt (2007) (22)	47	NA	6.4	12.8
	Haggerty(2007) (23)	33	60	6.5	NA
	Keshava(2009) (24)	175	NA	8.5	7.4
	Our Series(2015)	120	28.3	1.6	4.1

In conclusion, providing access for PD and minimizing catheter dysfunction are most important for success of peritoneal dialysis. Laparoscopic PD catheter insertion or reinsertion comprising of adhesiolysis, catheter fixation, and omentopexy is superior to open procedure in reducing the catheter dysfunction rates as laparoscopy addresses all the major causes of catheter dysfunction.

References

1. Haggerty, S., S. Roth, D. Walsh, D. Stefanidis, R. Price, R. D. Fanelli, T. Penner, W. Richardson, SAGES Guidelines Committee. Guidelines for Laparoscopic Peritoneal Dialysis Access Surgery
2. Mehrotra, R., D. Kermah, L. Fried, K. Kalantar-Zadeh, O. Khawar, K. Norris, and A. Nissenson, 2007: Chronic peritoneal dialysis in the United States: declining utilization despite improving outcomes. *J. Am. Soc. Nephrol.,* **18,** 2781-2788.
3. Shahbazi, N., and B. B. McCormick, 2011: Peritoneal dialysis catheter insertion strategies and maintenance of catheter function. *Semin. Nephrol.,* **31:** 138-151.
4. Kurihara, S., T. Akiba, M. Takeuchi, K. Nakajima, H. Inoue, and H. Yoneshima, 1995: Laparoscopic mesenterioadhesiotomy and Tenckhoff catheter placement in patients with predisposing abdominal surgery. *Artif. Organs,* **19:** 1248-1250.
5. Wang, J. Y., F. M. Chen, T. J. Huang, M. F. Hou, C. J. Huang, H. M. Chan, K. I. Cheng, H. C. Cheng, and J. S. Hsieh, 2005: Laparoscopic assisted placement of peritoneal dialysis catheters for selected patients with previous abdominal operation. *J. Invest. Surg.,* **18,** 59-62.
6. Cronen, P. W., J. P. Moss, T. Simpson, M. Rao, and L. Cowles, 1985: Tenckhoff catheter placement: surgical aspects. *Am. Surg.,* **51,** 627-629.
7. Harissis, H. V., C. S. Katsios, E. L. Koliousi, M. G. Ikonomou, K. C. Siamopoulos, M. Fatouros, and A. M. Kappas, 2006: A new simplified one port laparoscopic technique of peritoneal dialysis catheter placement with intra-abdominal fixation. *Am. J. Surg.,* **192,** 125-129.
8. Wang, J. Y., J. S. Hsieh, F. M. Chen, C. H. Chuan, H. M. Chan, and T. J. Huang, 1999: Secure placement of continuous ambulatory peritoneal dialysis catheters under laparoscopic assistance. *Am. Surg.,* **65,** 247-249.
9. Watson, D. I., D. Paterson, and K. Bannister, 1996: Secure placement of peritoneal dialysis catheters using a laparoscopic technique. *Surg. Laparosc. Endosc.,* **6,** 35-37.
10. Frost, J. H., and A. Bagul, 2012: A brief recap of tips and surgical manoeuvres to enhance optimal outcome of surgically placed peritoneal dialysis catheters. *Int. J. Nephrol.,* **19,** 251584
11. Schmidt, S. C., C. Pohle, J. M. Langrehr, G. Schumacher, D. Jacob, and P. Neuhaus, 2007: Laparoscopic-assisted placement of peritoneal dialysis catheters: implantation technique and results. *J. Laparoendosc. Adv. Surg. Tech. A.,* **17,** 596-599.
12. Keshvari, A., I. Najafi, M. Jafari-Javid, M. Yunesian, R. Chaman, and M. N. Taromlou, 2009: Laparoscopic peritoneal dialysis catheter implantation using a Tenckhoff trocar under local anesthesia with nitrous oxide gas insufflation. *Am. J. Surg.,* **197,** 8-13.
13. Harvey, E. A., 2001: Peritoneal access in children. *Perit. Dial. Int.,* **21,** 218-222.
14. Barone, G. W., M. L. Lightfoot, and B. L. Ketel, 2002: Technique for laparoscopy-assisted complicated peritoneal dialysis catheter placement. *J. Laparoendosc. Adv. Surg. Tech. A.,* **12,** 53-55.

15. Numanoglu, A., L. Rasche, M. A. Roth, M. I. McCulloch, and H. Rode, 2008: Laparoscopic insertion with tip suturing, omentectomy, and ovariopexy improves lifespan of peritoneal dialysis catheters in children. *J. Laparoendosc. Adv. Surg. Tech. A.,* **18,** 302-305.
16. Crabtree, J. H., and A. Fishman, 2005: A laparoscopic method for optimal peritoneal dialysis access. *Am. Surg.,* **71,** 135-143.
17. Attaluri, V., C. Lebeis, S. Brethauer, and S. Rosenblatt, 2010: Advanced laparoscopic techniques significantly improve function of peritoneal dialysis catheters. *J. Am. Coll. Surg.,* **211,** 699-704.
18. Crabtree, J. H., and R. J. Burchette, 2009: Effective use of laparoscopy for long-term peritoneal dialysis access. *Am. J. Surg.,* **198,** 135-141.
19. Attaluri, V., C. Lebeis, S. Brethauer, and S. Rosenblatt, 2010: Advanced laparoscopic techniques significantly improve function of peritoneal dialysis catheters. *J. Am. Coll. Surg.,* **211,** 699-704.
20. Ogunc, G., 2005: Minilaparoscopic extraperitoneal tunneling with omentopexy: a new technique for CAPD catheter placement. *Perit. Dial. Int.,* **25,** 551-555.
21. Bar-Zohar, D., B. Sagie, N. Lubezky, M. Blum, J. Klausner, and S. Abu-Abeid, 2006: Laparoscopic implantation of the Tenckhoff catheter for the treatment of end-stage renal failure and congestive heart failure: experience with the pelvic fixation technique. *Isr. Med. Assoc. J.,* **8,** 174-178.
22. Schmidt, S. C., C. Pohle, J. M. Langrehr, G. Schumacher, D. Jacob, and P. Neuhaus, 2007: Laparoscopic-assisted placement of peritoneal dialysis catheters: implantation Technique and results. *J. Laparoendosc. Adv. Surg. Tech. A.,* **17,** 596-599.
23. Haggerty, S. P., T. M. Zeni, M. Carder, and C. T. Frantzides, 2007: Laparoscopic peritoneal dialysis catheter insertion using a Quinton percutaneous insertion kit. *JSLS*, **11,** 208-214.
24. Keshvari, A., I. Najafi, M. Jafari-Javid, M. Yunesian, R. Chaman, and M. N. Taromlou, 2009: Laparoscopic peritoneal dialysis catheter implantation using a Tenckhoff trocar under local anesthesia with nitrous oxide gas insufflation. *Am. J. Surg.,* **197,** 8-13.

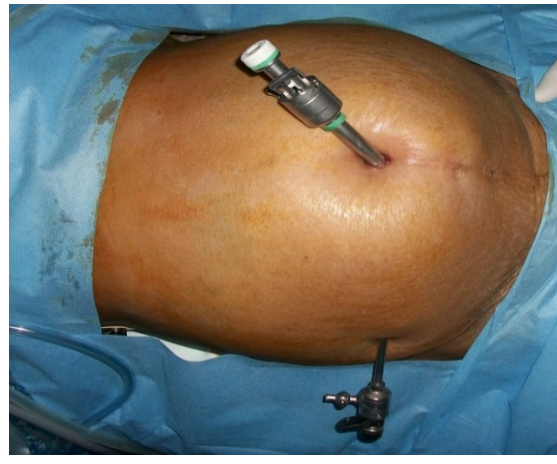

Figure 1: Port positions. 10mm port infraumbilical and 5mm port in Right Lumbar Region

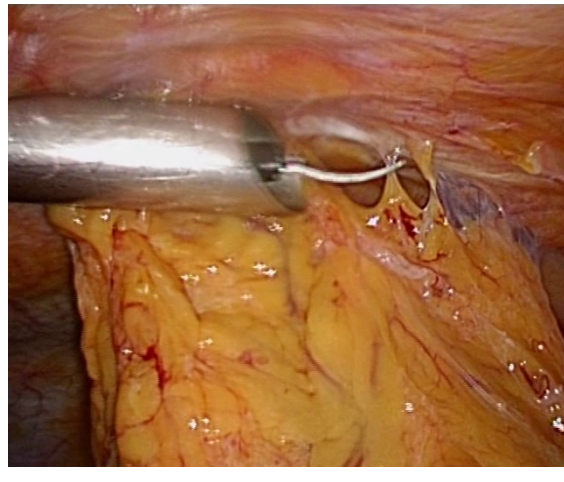

Figure 2: Releasing Omental Adhesions in Lower Abdomen and Pelvis

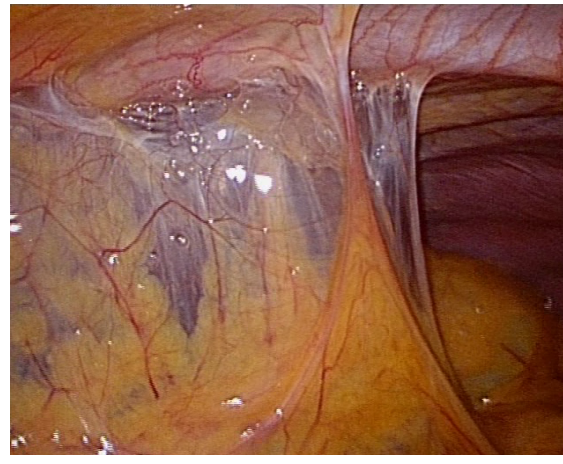

Figure 3: Omental Adhesions in Upper Abdomen Prevents Migration of Omentum into Pelvis– Precludes Omentopexy

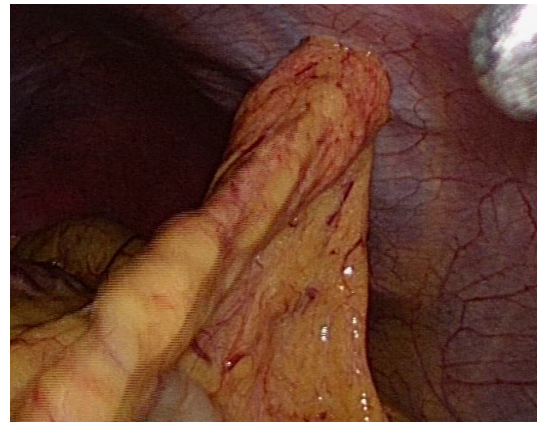

Figure 4. Omentopexy to Parietal Wall in Left Hypochondrium

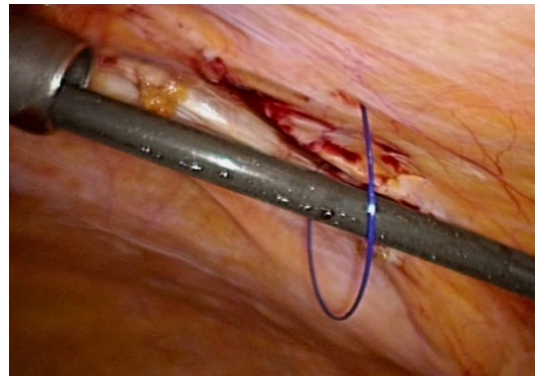

Figure 5. Preplaced Prolene Loop in the Lower Abdomen for Catheter Fixation.

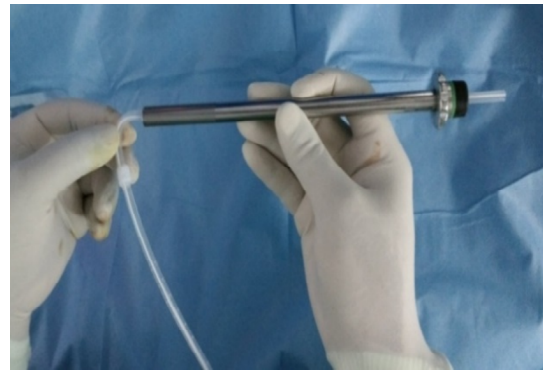

Figure 6. Retrograde Passage of Catheter into the Reducer

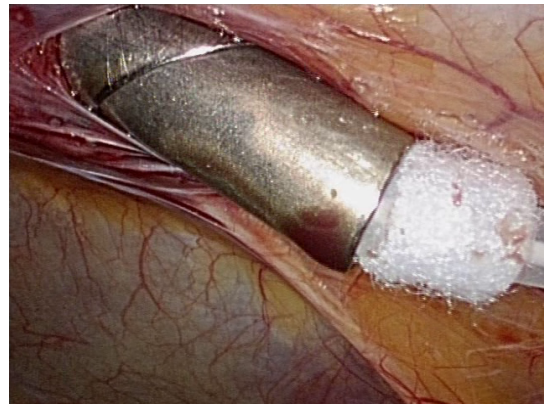

Figure 7. Port along with Reducer is Withdrawn Slowly Under Vision While Pushing the Catheter Into Pelvis

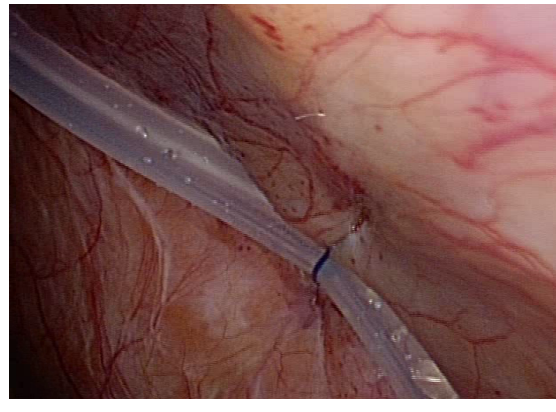

Figure 8. Catheter is Fixed by Tying the Preplaced Prolene Suture Loop

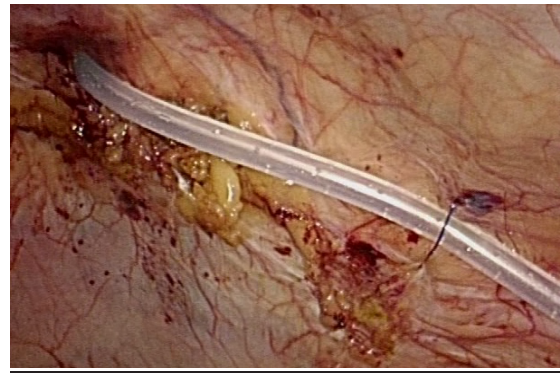

Figure 9: Final Appearance of Catheter in Peritoneal Cavity Fixed to Parietal Wall and Exit Near the Umbilicus Through the Port Site

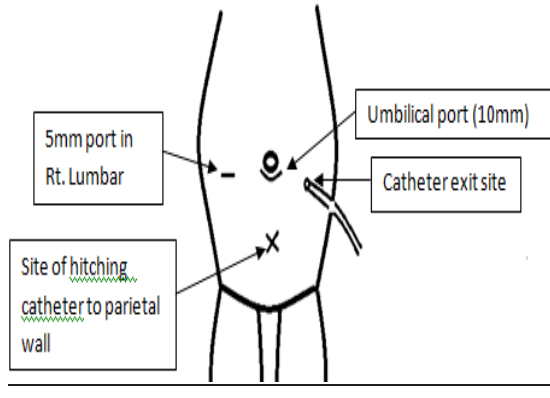

Figure 10: At the End of the Procedure

Chapter 11

Catheter-Tip Migration

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Catheter-Tip Migration

Peritoneal dialysis catheter migration refers to displacement of the peritoneal dialysis catheter from the pelvis to the upper abdomen. It often results in peritoneal dialysis failure and catheter removal.

With the Tenckhoff catheter, the recommendation is to create a subcutaneous catheter tunnel that is slightly arcuate (**Figure 1**) giving a caudal direction to both the external and internal segments. [1] The arcuate tunnel shape is preferred because it allowed an exit below the belt [1]. Frequently the external cuff eroded out of the subcutaneous tunnel because of the "shape memory" of the straight catheter, gradually converting an arcuate tunnel into a straight one [2].

The conversion of an arcuate tunnel into a straight one creates another complication. This conversion along with another force – the resilience of the catheter, leads to migration of tip of the catheter. The internal cuff acts like fulcrum on which the catheter tip moves into the upper abdomen. The swan neck catheter is designed to prevent the migration [2]

The other catheters specifically designed to reduce the migration include a straight catheter, with perpendicular silicone discs [Toronto Western Hospital (TWH) or Oreopoulos–Zellerman catheter] and the self-locating catheter, designed by Di Paolo, with twelve grams of tungsten inserted in the tip of the conventional Tenckhoff catheter to prevent the movement from pouch of Douglas [3, 4]. The discs in TWH catheter are designed to prevent omental wrapping and to keep the catheter placed low in the pelvis. The catheters with a coiled intraperitoneal segment have more intraperitoneal mass and may not migrate [5]. In addition, a one-stitch fixation of the catheter to the peritoneum and posterior sheath to prevent catheter tip migration had also been advocated [6]. The drawback of this procedure is when the removal of catheter is planned an elaborate surgery may be required. Another modification proposed is low site peritoneal catheter implantation. The catheter is inserted approximately 6 – 8 cm above the pubic symphysis instead of the conventional procedure of using umbilicus as the reference point. By the low-site implantation technique the catheter is much nearer and straighter to the pelvic cavity, thus preventing migration [7]. We, at our institute have modified the peritoneal dialysis catheter placement with hitching of peritoneal dialysis catheter to the anterior abdominal wall by a suture around it (see the chapter: Laparoscopic Peritoneal Dialysis Catheter Placement).

Ram

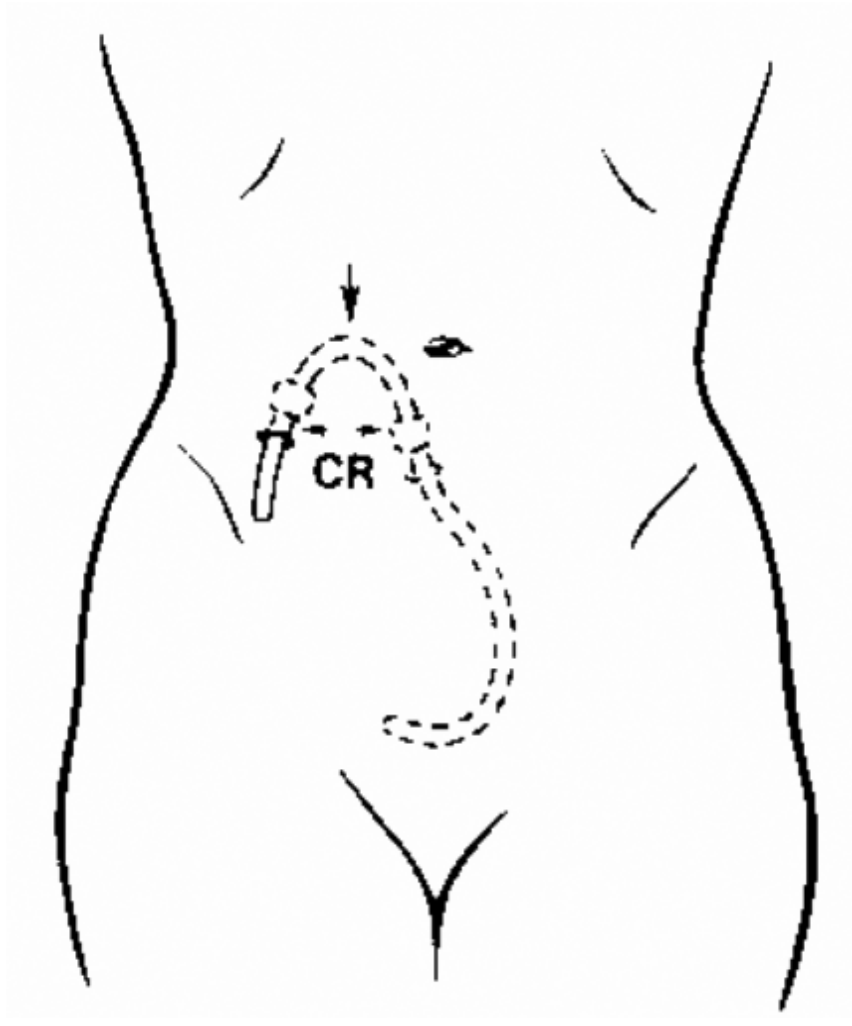

Figure 1: Arcuate Tunnel (arrow) in which a Peritoneal Dialysis Catheter has to be Placed. (Cr: catheter resilience)

If the tip translocates to the left upper abdomen the peristalsis of the descending colon may restore proper position of the tip (reversible catheter tip malposition); however, a tip translocated to the right upper abdomen usually does not return to the proper position because the forces of both catheter resilience and ascending colon peristalsis push the tip upwards (permanent catheter tip malposition) (**Figure 2**).

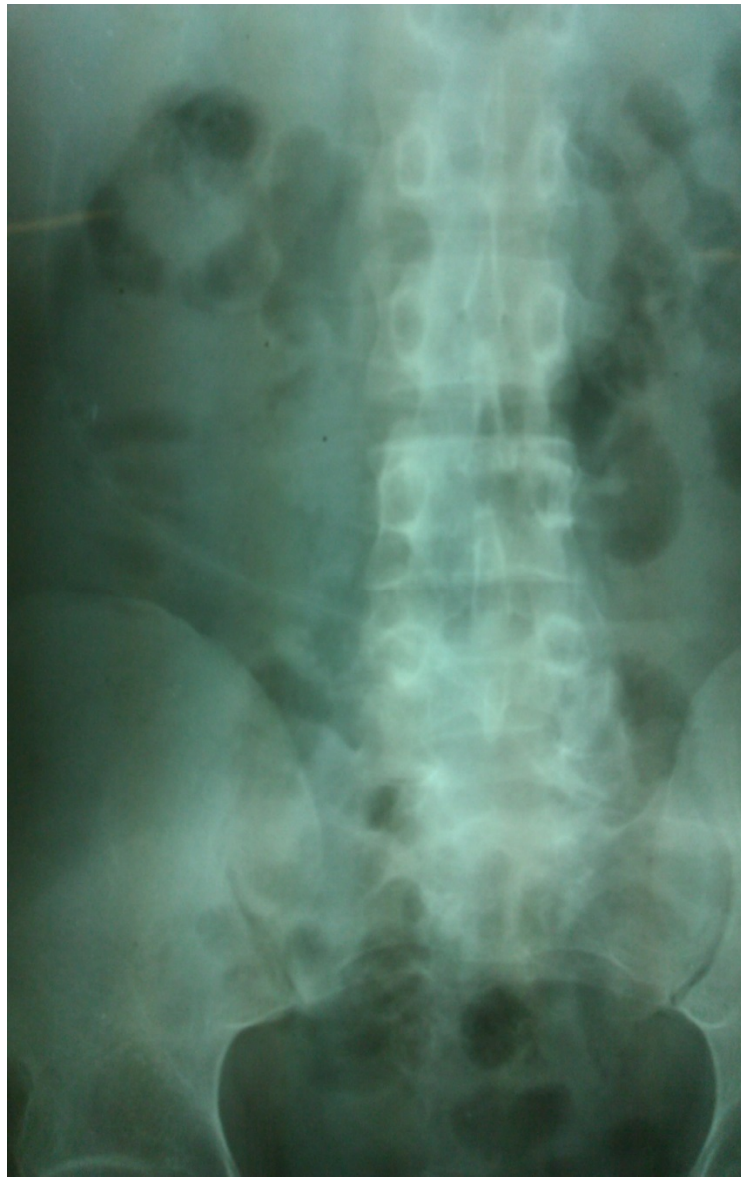

Figure 2: Permanent Catheter Tip Malposition

Our experience indicates that the dominant factor in catheter-tip position is the resilience force of the catheter. To avoid the unfavourable influence of resilience forces on the intra-abdominal catheter segment, the catheter needs to be moulded in the shape in which it is to be implanted in the tunnel.

The peritoneal catheter migration may occur between 12.7% and 35% of patients [8, 9]. The surgical revision of the catheter might be required in 90% of patients [10]. Several non-surgical correction measures have been tried [11-13]. One of these is a series of moves requiring skill and care for repositioning migrated peritoneal dialysis catheter [13]. We do not have any experience in these methods. We often use laxatives which sometimes repositions the catheter translocated to the left upper abdomen to the pelvis.

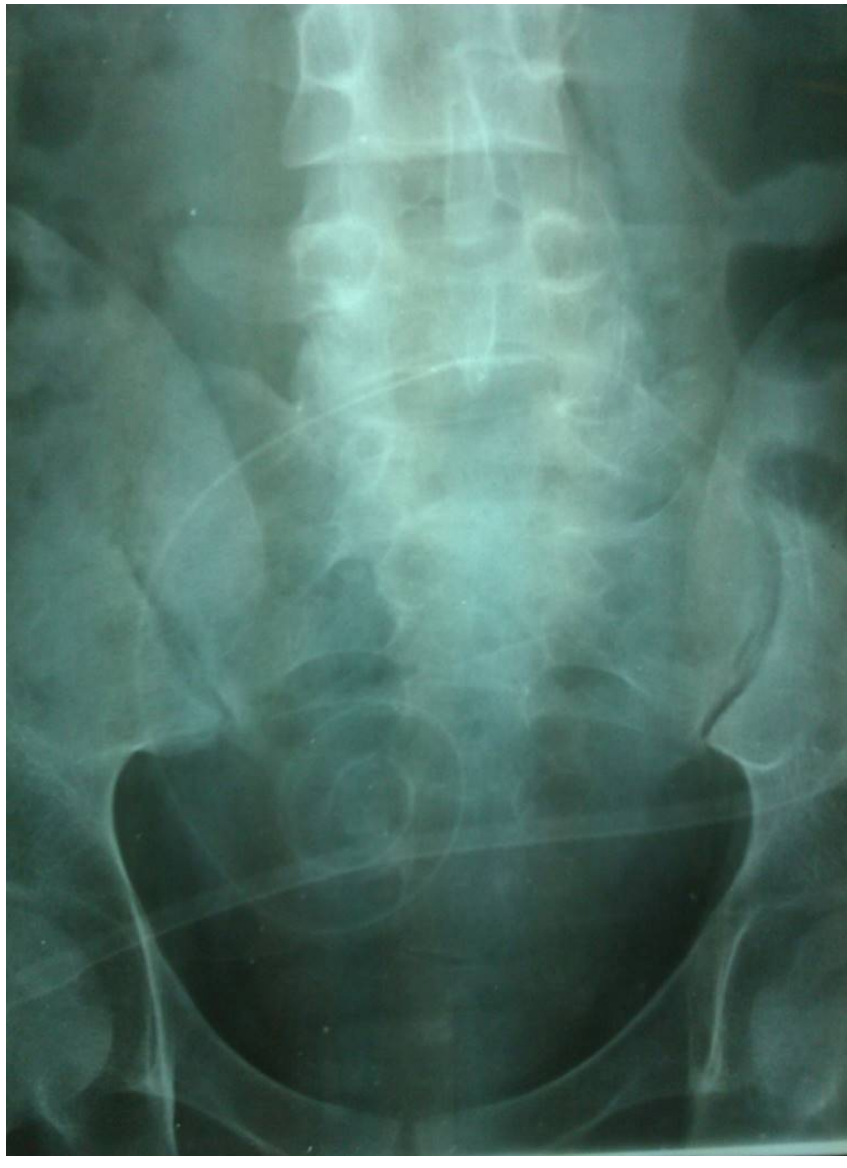

Figure 3: Catheters with a Coiled Intraperitoneal Segment have more Intraperitoneal Mass

References

1. Tenckhoff, H., and H. Schechter, 1968: A bacteriologically safe peritoneal access device. *Trans. Am .Soc. Artif. Intern. Organs,* **14,** 181-187.
2. Twardowski, Z. J., K. D. Nolph, R. Khanna, F. Barbara. B. F. Prowant, and L. P. Ryan, 1985: The need for a "swan neck" permanently bent, arcuate peritoneal dialysis catheter. *Perit. Dial. Bull.,* **5,** 219-223.
3. Oreopoulos, D. G., S. Izatt, G. Zellerman, S. Karanicolas, and R. E. Mathews, 1976: A prospective study of the effectiveness of three permanent peritoneal catheters. *Proc. Clin. Dial. Transplant. Forum.,* **6,** 96–100.
4. Dell'Aquila, R., S. Chiaramonte, M. P. Rodighiero, E. Spanó, P. Di Loreto, and C. O. Kohn, 2007: Rational choice of peritoneal dialysis catheter *Perit. Dial. Int.,* **27,** 119–125.
5. Swarnalatha, G., R. Ram, B. P. Santosh, V. Ramesh, and K. V. Dakshinamurty, 2011: Coiled catheter for recurrent migration. *NDT Plus,* **4,** 142-143.
6. Chen, W. M., and C. L. Cheng, 2007: A simple method to prevent peritoneal dialysis catheter tip migration. *Perit. Dial. Int.,* **27,** 554–556.
7. Zhang, L., J. Liu, J. Shu, J. Hu, X. Yu, and H. Mao, 2011: Low-site peritoneal catheter implantation decreases tip migration and omental wrapping *Perit. Dial. Int.,* **31,** 202-204.
8. Eklund, B. H., 1995: Surgical implantation of CAPD catheters: presentation of midline incision-lateral placement method and review of 110 procedures. *Nephrol. Dial. Transplant.,* **10,** 386–390.
9. Bay, W. H., G. J. Cerilli, V. Perrine, S. Powell, and L. Erlich, 1983: Analysis of a new technique to stabilize the chronic peritoneal dialysis catheter. *Am. J. Kid. Dis.,* **2,** 133–135.
10. Schleifer, C., H. Ziemek, B. Teehan, R. Benz, M. Sigler, and G. Gilgore, 1987: Migration of peritoneal catheters: personal experience and survey of 72 other units. *Perit. Dial. Int.,* **7,** 189–193.
11. Jwo, S. C., K. S. Chen, C. M. Lee, and C. Y. Huang, 2001: Correction of migrated peritoneal dialysis catheters using Lunderquist guidewire: a preliminary report. *Perit. Dial. Int.,* **21,** 621-623.
12. Terawaki, H., M. Nakayama, H. Nakano, T. Hasegawa, M. Ogura, and T. Hosoya, 2007: Transluminal replacement of displaced peritoneal catheter using a special “alpha-replacer” guidewire: effectiveness and limitations. *Perit. Dial. Int.,* **27,** 702–706.
13. Tu, W. T., Z. Su, and Y. S. Shan, 2009: An original non-traumatic maneuver for repositioning migrated peritoneal dialysis catheters. *Perit. Dial. Int.,* **29,** 325–329.

Chapter 12

Peritoneal Dialysis Solutions- Dextrose based

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Peritoneal Dialysis Solutions – Dextrose Based

Dialysis involves removal of solutes and water and correction of acid-base and electrolyte disorders. The backbone of peritoneal dialysis are various peritoneal dialysis (PD) solutions. Different PD solutions contain different osmotic agent, buffering agent and electrolytes. An ideal PD solution should have sustained and predictable solute clearance with minimal absorption of osmotic agent. It should provide deficient electrolytes and nutrients and correct acid-base problems. It should be free of pyrogens, micro-organisms and toxic metals [1].

Osmotic agent is an integral part of PD solution. There can be two different groups of PD solutions depending upon the osmotic agent used – high molecular weight solutions like glucose polymer, Icodextrin and low molecular weight solutions like dextrose or amino acids. The oldest commercially available solution is dextrose based and happens to be still the most widely used.

Dextrose Based Peritoneal Dialysis Solutions

Composition

Osmotic Agent: Dextrose is the most commonly used osmotic agent in PD solutions worldwide. It comes in different concentrations - 1.5, 2.5, and 4.25% (see composition in **Table 1**). Some countries also have 0.5%, which practically does not result in any ultrafiltration. The advantages of dextrose solutions are that it is cheap, safe and easily available.

Table 1: Composition of standard dextrose PD solution.

Volume (Liters)	**2, 2.5, 5 (variable in different countries)**
Sodium (meq/L)	132
Potassium (meq/L)	0 to 2 mostly 0
Dextrose (g/dl)	1.5, 2.5, 4.25
Calcium (meq/L)	2.5 to 3.5
Magnesium (meq/L)	0.5 to 1.5
Lactate (meq/L)	35 to 40
Osmolality (mOsm/kg)	346, 396, 485
Molecular Weight (Daltons)	182

Buffers: PD solution contains buffer which is the source of bicarbonate for correction of acidosis. It can be acetate, lactate or bicarbonate. The first two gets metabolised in the liver to bicarbonate. Dextrose solution contains lactate as buffer.

Electrolytes: PD solution also contains electrolytes like sodium, magnesium, calcium and chloride. The sodium concentration in PD solution varies from 130 to 137 mmol/L. The calcium concentration is either 1.75 mmol/L or 1.25 mmol/L (low calcium bath). Magnesium levels are 0.5 to 1.5 meq/L.

Physiology and Use

Solute removal with dextrose dialysate occurs by means of diffusion across the peritoneal membrane. In 4 hours dwell, urea is > 90 % equilibrated and creatinine is > 60 % equilibrated. Ultrafiltration with dextrose dialysate occurs across the small pores, also called the aquaporin 1 channels. Higher the concentration of dextrose, higher is the ultrafiltration. The ultrafiltration coefficient is maximum in the initial hour of dwell. This leads to 'sodium sieving' in the initial hours of dialysis. Measurement of dialysate sodium level at the first hour helps in determining the 'ultrafiltration failure'.

The peritoneal membranes are classified into 'fast' and 'slow' transporters based on D/P (dialysate to plasma creatinine) ratio in 4 hour dwell with 2.5% dextrose exchange – the standard PET. The test can also be conducted with 4.25% dextrose solution which is utilized for defining 'Ultrafiltration failure' and also the 'sodium sieving'.

Disadvantages

Despite being widely used, it is not the 'ideal' solution. It is rapidly absorbed resulting in short-lived ultrafiltration and positive balance, if left for longer. Its absorption and metabolism results in metabolic complications like hyperglycemia, hyperinsulinemia, hyperlipidemia and weight gain [2]. It is also considered bio-incompatible because of low pH and high glucose degradation products (GDPs) that affect peritoneal host defense mechanisms by inhibiting phagocytosis and bactericidal activity [3]. High concentration of dextrose and GDPs results in formation of advanced glycation end products (AGEs) which results in local peritoneal membrane damage and long term increase in peritoneal small solute transport rate (conversion to 'fast transporters') and 'ultrafiltration failure' [4, 5].

Structural and Functional Changes in Peritoneal Membrane Overtime

Data suggests that morphological changes in peritoneal membrane starts early in uremia. It includes sub-endothelial hyalinization of postcapillary venules and luminal narrowing with obliteration. The thickness of sebmesothelial collagenous compact zone also increases. All these changes are progressive as the duration of uremia and dialysis increases and is more prevalent in PD than in HD. It was hypothesized that conventional glucose based dialysate by virtue of low pH, lactate buffer, and GDP might be more damaging and biocompatible solution may be protective against structural damage to peritoneal membrane [6].

One of the Japanese study showed that the biocompatible PD solution minimizes the progression of peritoneal interstitial sclerosis and hyalinizing vascolopathy over 3 years [7]. However, another study from Hongkong refuted this finding and noted no difference in effects of long-term exposure to glucose based or biocompatible solutions [8]. More evidence is required to prove the advantage of biocompatible solution on structural changes in peritoneal membrane.

Despite all odds, dextrose based dialysate remains the most widely used PD solution worldwide. In cases of emergencies like pulmonary edema or hyperkalemia, frequent exchanges with dextrose dialysate may be lifesaving as against other PD solutions.

References

1. Vanholder, R. C., and N. H. Lameire, 1996: Osmotic agents in peritoneal dialysis. *Kid. Int. Suppl.,* **56,** 86-91.
2. Grodstein, G. P., M. J. Blumenkrantz, J. D. Kopple, J. K. Moran, and J. W. Coburn, 1981: Glucose absorption during continuous ambulatory peritoneal dialysis. *Kid. Int.,* **19,** 564-567.
3. Sitter, T., and M. Sauter, 2005: Impact of glucose in peritoneal dialysis: saint or sinner? *Perit. Dial. Int.,* **25,** 415-425.
4. Mortier, S., D. Faict, C. G. Schalkwijk, N. H. Lameire, and A. S. De Vriese, 2004: Long term exposure to new peritoneal dialysis solutions: effects on peritoneal membrane. *Kid. Int.,* **66,** 1257-1265.
5. Mortier, S., D. Faict, N. H. Lameire, and A. S. De Vriese, 2005: Benefits of switching from a conventional to a low GDP Bicarbonate / lactate buffered dialysis solution in a rat model. *Kid. Int.,* **67,** 1559-1565.
6. Williams, J. D., K. J. Craig, N. Topley, and G. T. Williams, 2003: Peritoneal dialysis: changes to the structure of the peritoneal membrane and potential for biocompatible solutions. *Kid. Int.,* **84,** 158-161.
7. Nobuhiro, A., I. Yoshitaka, T. Yutaka, K. Haruki and F. Toshiro, 2012: Peritoneal morphology after long-term peritoneal dialysis with biocompatible fluid: Recent clinical practice in Japan. *Perit. Dial. Int.,* **32,** 159-167.
8. Abdullah, K. A., A. S. Mohamed, S. A. Ibrahiem, A. Nadia, A. Bander, C. D. Jose, A. Abdalla, Z. Hazem, A. N. Mohammad, E. Ahmed, E. Tamer, and A. A. Fahed, 2016: Changes in peritoneal membrane with different peritoneal dialysis solutions: Is there a difference. *Hongkong J Nephrol.,* **19,** 7-18.

Chapter 13

Peritoneal Dialysis Solutions- Icodextrin

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Peritoneal Dialysis Solutions- Icodextrin

Development of Icodextrin

Even as early as the 1980s there was clear recognition for an alternative osmotic agent that would minimize metabolic derangements and provide the ultrafiltration profile to suit long dwell exchanges. A range of different macromolecules was evaluated based on the simplistic concept that large molecular weight (MW) agents are less readily absorbed through the peritoneum and are likely to produce sustained ultrafiltration while reducing metabolic complications. Early investigations clearly identified the problems associated with use of non-physiological hyperviscous macromolecules and defined the need for a neutral substance that is soluble, non-allergeic, and readily metabolized [1]. Glucose polymer (GP), derived from hydrolyzed cornstarch, seemed a natural contender. In Manchester, UK, considerable experience had been developed while investigating GP (Caloreen) as an intravenous high-energy nutrient source in the management of patients with renal and hepatic failure. The first formal Phase 1 study, using solutions containing 5% (52 mmol/L) and 10% (104 mmol/L) of this GP formulation over a 6-hour dwell, produced net ultrafiltration 1.5–2.5 times greater than the glucose solutions. However, the metabolism of GP was incomplete, resulting in an accumulation of maltose, with a peak serum level reaching 1148 mg/L with 5% GP solution, and this almost doubled with 10% solution [2]. The recognition that the direction of osmotic force across a solute-permeable membrane is governed by the differences in the size of the sum of the products of the reflection coefficients and molar concentrations of solutes rather than the traditional total osmolality gradient was the key to further development [3]. Therefore, it was theoretically possible that a "large" MW GP fraction at a low concentration could exert an osmotic effect across the peritoneum, provided it was largely impermeable, and might even reduce the systemic load of maltose.

The Caloreen was fractionated into two component parts using the conventional solvent-based fractionation process. The high MW fraction of GP was isolated, with 95% of the profile containing glucose chain length > 12 glucose units with Mw 16823 Da and Mn 5304 Da (Mn is number average MW and is the total weight of the sample divided by the number of molecules in the sample). A pilot study using a 5% GP solution (9.4 mmol/L) containing high MW fraction, with osmolality similar to uraemic serum, produced remarkably good ultrafiltration compared to glucose solutions over a 6-hour dwell [4]. However, two patients developed severe chemical peritonitis with polymer solution contaminated with pyrogens [5]. This was the first indication that GP probably exerted its effect by a mechanism resembling colloid osmosis, and demonstration of superior ultrafiltration with 5% iso-osmolar GP solution for dwells up to 12 hours. Furthermore, only 14% – 28% of polymer was absorbed transperitoneally, compared to 62% – 83% of glucose, during the exchanges [6]. This lower rate of absorption also led to an 80% reduction in systemic accumulation of maltose compared to the original formulation.

Using this process, the optimal GP fraction (Mw 22000 Da; Mn 7000 Da) for ultrafiltration that minimized maltose accumulation was subsequently used in all long-term studies. This fraction, originally referred to as "dextrin 20," was later renamed "icodextrin," from the Greek *icosa*, meaning twenty. In 1991, M L Laboratories, the original manufactures of icodextrin in collaboration with Mistry CD, Gokal R and Peers MA performed the first large, long term, randomised controlled study of icodextrin, the Midas Study [7]. Icodextrin received a product license in the UK in January 1993, European Marketing approval in March 1994, and, finally, USA marketing approval in 2002. Initially, M L Laboratories reached an agreement with Fresenius AG to launch the product in Europe and the USA, but that agreement was terminated in March 1996, and 2 months later M L Laboratories granted an exclusive worldwide license to Baxter Healthcare.

The MIDAS study

A randomised, controlled Multicenter Investigation of Icodextrin in Ambulatory peritoneal dialysis (MIDAS) was undertaken to evaluate the long-term safety and efficacy by comparing daily overnight (8 to 12 hour dwell) use of isosmolar icodextrin (282 mOsmol/kg) with conventional 1.36% (346 mOsmol/kg) and 3.86% (484 mOsmol/kg) glucose exchanges over six months. Two hundred and nine patients were randomised from 11 centers, with 106 allocated to receive icodextrin (D) and 103 to remain on glucose (control group; C); 138 patients completed the six month study (71 C, 67 D). The mean (± SEM) overnight ultrafiltration (UF) with D was 3.5 times greater than 1.36% glucose at eight hours [527±36 vs. 150±47 mL; 95% confidence interval (CI) for the difference +257 to +497 ml; P< 0.0001] and 5.5 times greater at 12 hours (561±44 vs. 101±48 ml, 95% CI for the difference +329 to +590; P< 0.0001) and no different from that of 3.86% glucose at 8 hours (510±48 vs. 448±60 ml, 95% CI for the difference —102 to +226 ml; P = 0.44) and at 12 hours (552±44 vs. 414±78 ml, 95% CI for the difference —47 to +325 ml; P = 0.06). The mean serum maltose increased from a pre-dialysis value of 0.04 g/liter to a steady state level of 1.20 g/liter within two weeks and remained stable throughout the study. This was not associated with any adverse clinical effects and the overall CAPD-related symptom score was significantly better for D than C [7].

Physical and chemical properties

Icodextrin is derived in a two-step process. Corn starch is converted to malto-dextrin by enzymatic hydrolysis. In the second step, malto-dextrin is converted to icodextrin by membrane fractionation [8]. The structure of icodextrin is similar to glycogen, consisting of polysaccharide polymers of D -glucopyranose linked by α -(1 → 4) and α -(1 → 6) glucosidic bonds (**Figure 1**) [9]. The structure of icodextrin differs from glycogen in that it has a lower percentage of α - (1 → 6) linkages (< 10%) and hence is less highly branched.

Its weight-average molecular weight is between 13,000 and 19,000 Da and its number-average molecular weight between 5,000 and 6,500 Da. The substance is a

white to off-white solid, and the solution is clear and colourless to pale yellow. It is absorbed from the peritoneal cavity mainly *via* the lymphatic circulation, and the amount absorbed ranges from 20 to 40% for an 8–16 hour dwell [9, 10].

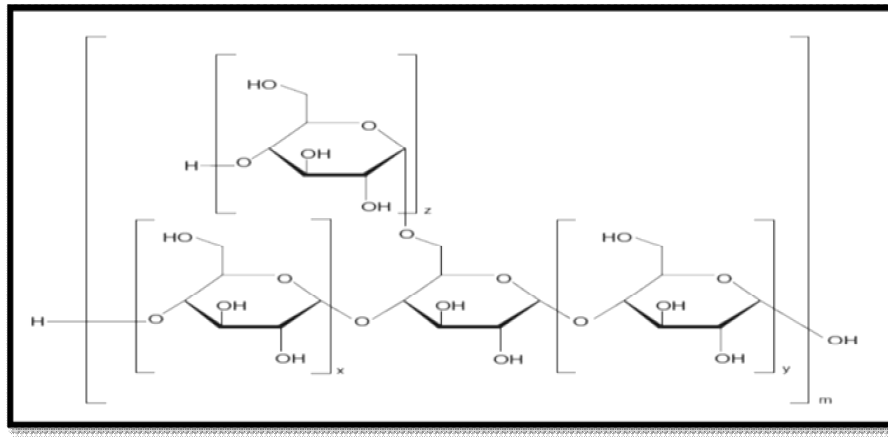

Figure 1: Structure of Icodextrin

Pharmacodynamic and Pharmacokinetic Profile

Glucose and other small molecules are absorbed from the peritoneal cavity primarily by diffusion across the peritoneal capillary endothelium. Diffusion is limited for icodextrin.

The absorption of icodextrin occurs primarily due to convective fluid movement out of the peritoneal cavity via the lymphatics [11]. Oncotic pressure created by icodextrin is relatively constant, and ultrafiltration (UF) is sustained throughout a long dwell [6, 7, 12, 13]. The rates of icodextrin absorption is 19.6 and 33.5% during 8 hour and 12 hour dwells, respectively [7, 11]. The rate of absorption is nearly constant during the dwell. The percentage of icodextrin absorbed is directly related to the length of the dwell, with peak plasma levels occurring at the 12-h dwell, indicating a relatively short transit time of icodextrin from lymphatic vessels or peritoneal tissues into blood.

Icodextrin elimination from plasma follows a one compartment model with first-order kinetics. It occurs both by renal excretion and by dialysis during subsequent exchanges. Circulating α- amylases hydrolyze icodextrin into glucose polymers such as maltose (DP2), maltotriose (DP3) and maltotetraose (DP4) [11]. These small oligosaccharides are the principal metabolites of icodextrin observed in blood following exposure to icodextrin [7, 12]. Maltose and other icodextrin metabolites are further metabolized to glucose by tissue maltases, excreted into the urine (in patients with residual renal function) or eliminated by peritoneal dialysis itself [11]. The relative contributions of each of these routes of elimination of icodextrin and its

metabolites are not known. Icodextrin and amylase-derived metabolites that are not eliminated renally or by dialysis ultimately undergo metabolism to glucose by intracellular enzymes, such as α -glucosidase (maltase), phosphorylase and debranching enzymes such as amylo-1,6-glucosidase. The steady-state levels of icodextrin and metabolites are constant for at least two years of administration with no evidence for long-term accumulation, and that, on discontinuation, blood icodextrin levels return to baseline values with a similar kinetic profile even after many months of administration [11, 14].

Mechanism of Action of Icodextrin

The differences in mechanism of actions of dextrose and icodextrin are given in the **Tables 1** and **2** and in **Figure 2**.

Table 1: Dextrose *versus* Icodextrin [15]

Dextrose	**Icodextrin**
Hypertonic in relation to the plasma	Isotonic in relation to the plasma
Since dextrose is hypertonic transport through the ultra-small pores is induced. There is sodium sieving.	Since the icodextrin solution is not hypertonic in relation to the plasma, no transport through ultra-small pores is induced. It removes fluid from the body by inducing water transport through small pores. Also there is solvent drag of small solutes. Less sodium sieving. Because of its low absorption from the dialysate, icodextrin maintains this gradient for several hours,
Removes fluid down an osmotic gradient	Macromolecules such as glucose polymers can induce transcapillary ultrafiltration even under isotonic conditions. The process of colloid osmosis is based on the principle that water is transported from the capillaries in the direction of relative excess of impermeable large solutes, rather than down an osmotic gradient

Table 2: Pores in Peritoneal Membrane

Pore and its size	**Mechanisms of transport**
Transcellularpores/ Ultra small pores /Aquaporins r < 0.8 nm 1-2% of total pore area	Greatest osmotic effect of glucose at this pore 40% of ultrafiltrate from this pore Solute free water is removed Causes sodium sieving
Small pore Present at the arteriolar end of capillaries r = 4.0 - 6.0 nm 90% of total pore area	Diffusive and convective transport of small solutes Also, 50% of glucose induced ultrafitration is affected at this pore Absorption of glucose is through this pore Icodextrin action is at the small pores
Large pore Venular end of capillaries R = > 20 nm <1% of total pore area	Macromolecules are removed through this pore Convection and restricted diffusion at this pore

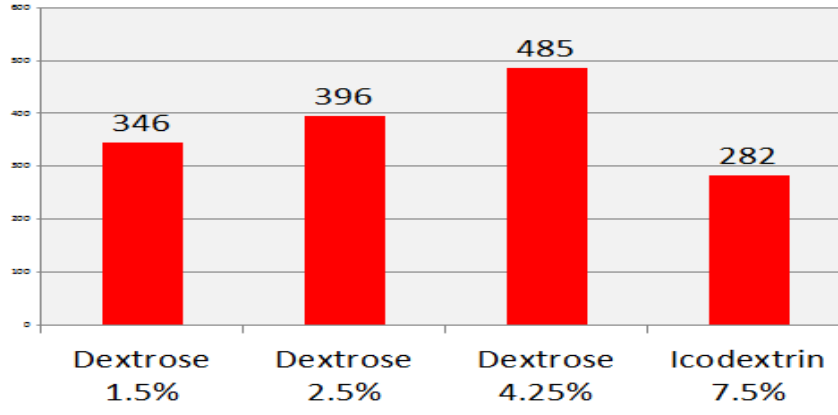

Figure2: Osmolality: Icodextrin *versus* Dextrose Solutions

Haemodynamic Effects

Ultrafiltration and Blood Pressure

With the enhanced UF provided by icodextrin, patients may be at risk for hypovolemia and even hypotension. While this pattern has been observed in several clinical trials, albeit of limited power, the effect on blood pressure remains mixed. **Table 3** presents studies of the impact of icodextrin on UF, blood pressure and residual kidney function.

In daily practice, ultrafiltration may not be so high as expected with icodextrin (**Figure 3**). The reasons appear to be:

1. Thought to be due to secondary to high lymphatic absorption of icodextrin and its metabolites negating the osmotic gradient that drives UF [16].
2. When icodextrin is initiated early in the course of PD therapy, impaired UF may be a manifestation of mechanical complications, such as catheter and non-catheter-related dialysate leaks. These complications are more common among patients new to PD and patients who used to be empty during the day. In other words, patients on icodextrin on the development of UFF, should undergo a complete work-up into all possible aetiologies [16].

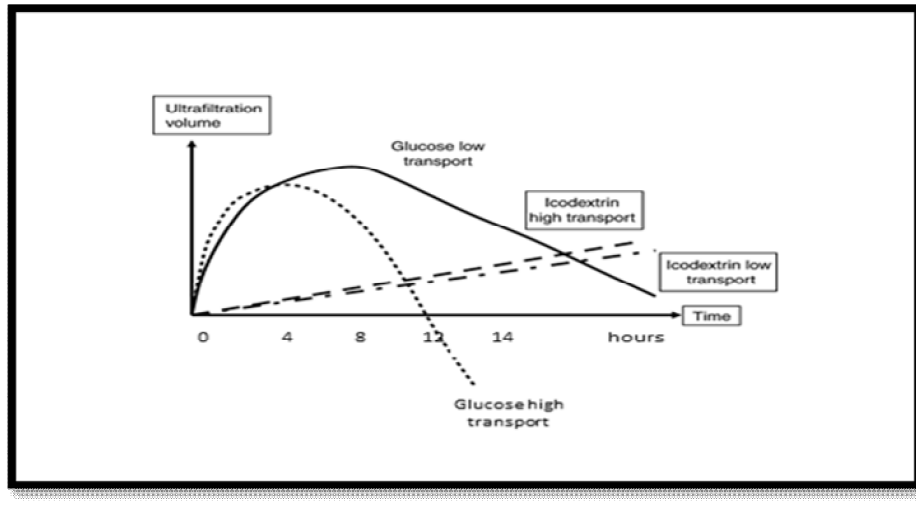

Figure 3: Ultrafiltration: Icodextrin *versus*

Table 3: Studies of the Impact of Icodextrin on UF, Blood Pressure and Residual Kidney Function**.**

	Follow-up and Study type	**No of patients and Modality**	**Comparison Group**	**Blood Pressure**	**Residual Kidney Function**
Mistry *et al.*, 1994 [32]	6-month Multicenter RCT	209 CAPD	1.36% and 3.86% In long dwell		
Wolfson *et al.*, 2002 [41]	4-week Multicenter RCT	175 CAPD	2.5% in Long dwell		
Plum *et al.*, 2002 [42]	12-week Multicenter RCT	39 APD	2.27% in Long dwell	Icodextrin: 138.2-146.7 mm hg Glucose: 136.8-127.0 mm hg	
Davies *et al.*, 2003 [21]	6-month Multicenter RCT	50 CAPD or APD *Urine output <_750* D/P cr_>0.6 hypertension	2.27% in long dwell	Icodextrin: BP drug increased 19% BP drug decreased 33% Glucose: BP increased 10% BP drug decreased 14%	Icodextrin: 291—280 ml Glucose: 251—131 ml

Finkelstein *et al.*, 2005 [20]	2-week Multicenter RCT	92 APD *D/P cr>0.70 *D/Po glucose <0.34	4.25% in long dwell	Icodextrin: 134.2—134.6 mm hg Glucose: 135.1—133.3 mm hg	
Rodriguez carmona *et al.*, 2007[26]	10-day Single-center RCT Crossover design	17 APD	2litres glucse based Dialysate in Nocturnal mixture (0.92g/dl)		Icodextrin: 500 ml Glucose: 600 ml
Paniagua *et al.*, 2009 [22]	1-year multicenter RCT	59 CAPD *DM nephropathy *high and high-average transport Status	2.5% in Long dwell	Icodextrin: 148—138.5 mm hg Glucose: 139.8—141.3mm hg P<0.01 between Groups for BP change	
Lin *et al.*, 2009 [48]	4-week multicenter RCT	201 CAPD	2.5% in Long dwell		
Takatori *et al.*, 2011 [18]	2-year multicenter RCT	41 CAPD or APD *DM nephropathy	1.5% or 2.5%	Icodextrin: 157.0—141.4mm hg BP drug increased 33% BP drug decreased 24% Glucose: 147.6—141.0mm hg BP drug increased 65% BP drug decreased 5%	Icodextrin: 1,149—395 ml Glucose: 1,086—508 ml

In the majority of patients with enhanced UF on icodextrin, there is a lack of consistency on blood pressure (BP) control. This may be related to the fact that the patients on PD may compensate for the increased UF with icodextrin by a simultaneous increase in fluid intake. This may limit the ability to detect true blood pressure improvements. In the few studies in which investigators coupled enhanced UF with dietary restrictions, improved BP control has been observed with the use of icodextrin [17, 18]. Our institute's practice is to introduce icodextrin till the first

peritoneal equilibration test. Typically till 4–6 weeks after PD initiation. This allows us to better understand the expected UF based on the availability of membrane characteristics and UF capacity. To avoid hypotension we take precautions like

1. A close monitor of UF.
2. In particularly frail and vulnerable patients or patients in whom the prescription was adjusted to address adequacy instead of UF, icodextrin may be prescribed incrementally starting with either lower dwell volumes (<1 liter) or administered on alternating days until the patient response to the enhanced UF is better appreciated.
3. We avoid the addition of new antihypertensive medications or hypertonic glucose-based solutions.

Loss of Residual Renal Function

An additional concern with the enhanced UF achieved with icodextrin is that volume depletion will lead to a decrease in residual renal function (RRF). This finding has been noted in a number of observational studies, but the results have been mixed in randomised controlled trials.

The effect of icodextrin on RRF is difficult to quantify. The reasons are

1. The natural course of PD patients is to lose RRF over time regardless of the PD solution used.
2. Also, any peritoneal membrane changes will influence RRF.

The range of effects of icodextrin on RRF is from a modest increase in RRF to a slight decrease in RRF. It is reassuring that there is no drastic decline in RRF. But the lack of evidence at this point in time suggests that RRF should be monitored at regular intervals in patients that begin an icodextrin regimen. Overall, there is currently insufficient evidence to recommend stopping an icodextrin PD regimen based solely upon declining RRF. However, during periods in which patients may be particularly susceptibleto RRF decline (i.e. radiocontrast procedures), it is prudent to hold icodextrin temporarily to mitigate the risk of extracellular fluid volume contraction [19].

Metabolic Effects

Glycaemic profile

Following intraperitoneal instillation of glucose-based solutions, glucose is rapidly absorbed by diffusion across paracellular pathways and appears immediately in the circulation. The concentrations of glucose in the dialysis solution (ranging from 1360 mg/dL to 3860 mg/dL) far exceed circulating concentrations of glucose even in poorly controlled diabetic patients and the transport is predominantly unidirectional from the peritoneal cavity to the circulation. This influx of glucose is also dependent on the transport characteristics of the patient's peritoneal membrane (**Figure 4**).

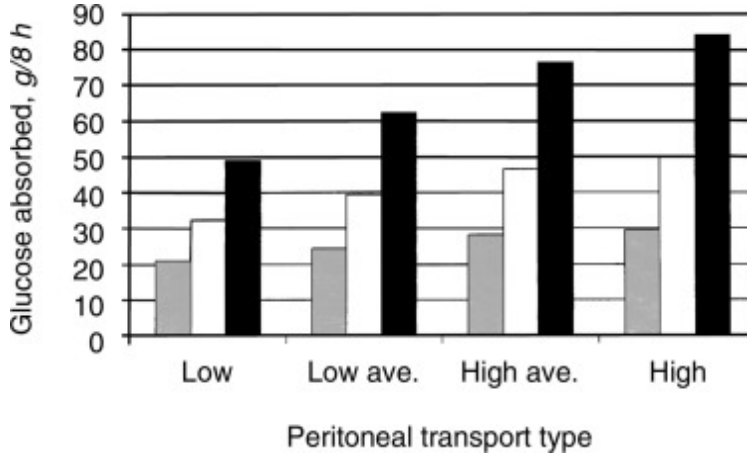

Figure 4: Absorption of glucose during 8 hour dwell based on transporter status.

The expected amounts of glucose absorbed at various tonicities of dialysis solution dextrose derived from validated computer modeling are shown [22]. Symbols are: (■) 1.50%; (□) 2.50%; (▪) 4.25%

Gordstein calculated that the net glucose absorption averaged 182 ± 61 g/day in 19 studies with a dialysate dextrose concentration of 1.5 or 4.25 g/dL. The glucose absorption in CAPD can be calculated in accordance with the formula of Grodstein *et al*, [20].

$$GU = [11.3 \times (G - 10.9)] \times V$$

Where GU is the glucose uptake, G the mean glucose concentration in the dialysis fluid, and V is the volume of dialysis fluid. Because of the differences of dialysis fluid administration periods between CAPD and IPD, glucose absorption was calculated in relation to the glucose concentration instead of the period of time.

The hyperglycaemia due to intraperitoneal glucose administration was associated with an acute hyperinsulinemic response. Insulin levels increased from 76 ± 9 pmol/L to a peak of 308 ± 82 pmol/L at two hours and decreased to near baseline by four hours [21].

In contrast to the acute hyperglycaemia and hyperinsulinemia associated with glucose-based solutions, icodextrin does not lead to hyperglycaemia or hyperinsulinemia following its intraperitoneal administration. Further, the metabolism of the carbohydrate polymers to glucose has a latency period caused by

multiple metabolic steps: extracellular metabolism of large carbohydrate moieties to oligosaccharides with smaller degrees of polymerization (maltose, maltotriose, etc.), uptake of small oligosaccharides into cells; and finally release of glucose within cells by intracellular maltases. During the transit of icodextrin from the peritoneal cavity to its site of final intracellular metabolism, very little glucose is produced in the extracellular compartment [22].

Maltose Accumulation

Even though only a fraction of the icodextrin glucose polymer load is absorbed, the metabolism of icodextrin is incomplete. The absorbed polymer is rapidly hydrolyzed by amylase to oligosaccharides and eventually to maltose. Further, metabolism is limited by the absence of maltase activity in the human circulation [23].

In the MIDAS study the mean level of icodextrin and its metabolites increased from a baseline value of 0.35 g/L to a steady-state level of 4.87 g/L [7]. The serum maltose followed an identical pattern and rose from 0.04 g/L to a steady-state level of 1.20 g/L. This increase occurred within 2 weeks of icodextrin administration, and steady-state levels were maintained throughout the 6-month study duration. These metabolites were not associated with any adverse clinical effects.

In another study, in patients who received icodextrin for more than 2 years, a small group was further studied to investigate the effect on icodextrin and maltose metabolite levels upon cessation of icodextrin treatment [11]. The levels fell to pre-treatment values within 2 weeks. Upon recommencing icodextrin after a 3-week period of non-use, the icodextrin and maltose metabolite levels rose to the initial treatment phase and reached a plateau within 2 weeks. The authors argue that these icodextrin kinetics suggest that there can be no capacity-limited compartment for icodextrin metabolites. Therefore, deposition of icodextrin in tissues is unlikely.

Insulin Requirements and Hypoglycemia

Dextrose-based PD regimens typically result in a daily absorption of 150–300 g of glucose, and the caloric load from an icodextrin exchange is less than a 2.5% dextrose exchange [22].

Hence the insulin requirement may reduce. Small and non-randomised trials have demonstrated mixed results on the effect of icodextrin on glycemic control. Three long-term randomised controlled trials have been performed [24, 25, 26].

Based on these three studies, there is an insufficient data to support proactive reductions in insulin requirements for patients started on icodextrin. However, we would recommend that all diabetic patients be advised to monitor more closely for hypoglycemia upon initiation of icodextrin.

The method used to monitor blood sugar while on icodextrin is important. Non-glucose sugars like icodextrin metabolites are measured by many glucometers and

strips as 'glucose,' resulting in falsely elevated readings. All of the icodextrin metabolites affected glucose measurements in the two glucose dehydrogenase/pyrroloquinoline quinone systems by >10% and the combined effect of the three metabolites of icodextrin was additive (**Table 4**). Interference was still present in the two glucose dehydrogenase/NAD glucometers, but was less pronounced and the interferences by the combination of metabolites were also reduced. Amongst these meters, the glucose dehydrogenase/ NAD 5-s machine was less affected. Significantly, meters which used the glucoseoxidase enzyme were least affected by icodextrin metabolite interference.

Table 4: Interference of Icodextrin Metabolites with Glucose Meters (From Highest to Lowest Interference)

Enzyme/cofactor System	**Analyser**
GDH/PQQ	Accu-Chek Performa
GDH/PQQ	Accu-Chek Advantage–II
GDH/NAD	OptiumXceed (20-s strips);
GDH/NAD	OptiumXceed (5-s strips),
GO/NAD	StatStrip
GO/H2O2	Radiometer

ADP, adenine diphosphate; G6PD, glucose 6 phosphate dehydrogenase; GDH, glucose dehydrogenase; GO, glucose oxidase; H2O2, hydrogen peroxide; HK, hexokinase; NAD, nicotine adenine dinucleotide; NADP, nicotine adenine dinucleotide phosphate; PQQ, pyrroloquinoline quinone [27]. To prevent maltose interference systems that utilize a glucose-specific method should be used, such as hexokinase, are to be utilized [22].

1 Use of these glucometers in patients with icodextrin has the risk of administration of inappropriate excessive insulin by healthcare professionals who mistakenly interpret the glucometer findings in patients on icodextrin as hyperglycemia. From 1997 to 2009, the United States Food and Drug Administration (FDA) received 13 reports of death due to non-specific test strips with documentation of interference from maltose and other non-glucose sugars. Of these 13 patients, 10 were on PD using icodextrin [28].

The period when icodextrin is discontinued is another sensitive period for patients on PD. Since maltose metabolites with icodextrin do not return to baseline until 2 weeks after cessation, glucometers that non-specific place peritoneal patients at risk of iatrogenic hypoglycaemia for weeks after their last exposure to icodextrin [29].

To avoid devastating consequences including severe hypoglycemia, coma, or death related to the icodextrin-glucometer interaction, hospital protocols should require that all peritoneal dialysis patients' blood glucose are measured in central biochemistry laboratories [28]. By setting the guidance that in all patient on PD, glucose determinations are done in this manner, it precludes any confusion in patient history regarding the timing and type of prescriptive peritoneal dialysis fluids used [29].Since manufacturers of glucometers may change assay methods, it is not possible in this article to provide a comprehensive list of the products that has interfere with icodextrin. We suggest that clinicians refer to the product labelling included in test strip packages.

Baxter Healthcare has established a risk management programme that includes electronic web-based safety tools (www.glucosesafety.com) [29]. A list of all devices and test strip products that are glucose-specific, and those that are not, is available on this website.

Amylase Interpretation

An apparent decrease in serum amylase activity has been reported in multiple studies of icodextrin [14, 65, 78]. Levels of serum amylase activity declined 70 to 90% within one week of icodextrin administration and remained low (but stable) during administration. Upon discontinuation of icodextrin administration, serum amylase activity returned to baseline levels. In combined data from comparative trials, icodextrin treatment was associated with consistently lower plasma amylase levels compared with 2.5% dextrose and the difference between treatment groups was statistically significant at each study visit ($P< 0.001$).

Icodextrin is a β-glucose polymer consisting mainly of α1, 4-linkages. Amylase breaks α1, 4-linkages. Since most methods for determining amylase in routine clinical practice are based on the consumption of substrate, spuriously low concentrations of serum amylase may be Measured [19].

Although the interaction has not been associated with any clinical adverse events, this laboratory interference should be taken into account when attempting to diagnose or monitor pancreatitis in patients using icodextrin. It is recommended that serum amylase should not be used in the diagnosis or monitoring of pancreatitis in patients using icodextrin. Determination of serum lipase activity does not appear to be influenced by the presence of icodextrin and therefore may be an adequate method to diagnose pancreatitis [19].

Alkaline Phosphatase

A small increase in mean serum alkaline phosphatase (ALP) has been reported in some studies of icodextrin [14]. In combined comparative studies of icodextrin versus 2.5% dextrose, mean ALP levels increased significantly (mean increase 17.3 U/L), but remained within normal limits at all time-points and did not show evidence of a progressive increase over a 12-month study period. ALP levels

returned to baseline coincident with the return of icodextrin and metabolite blood levels to pretreatment values, suggesting that elevations were neither permanent nor related to significant alterations in the liver function. On a proportional basis, however, the percentage increase in intestinal ALP appeared greater than for the bone or liver isoforms. Although this may be related to the fact that the intestinal isoform represents a smaller proportion of total ALP, it is possible that the intestinal ALP isoforms may be affected differently by icodextrin.

The proposed mechanism for the small increase in ALP during icodextrin treatment is a partial inhibition of ALP clearance due to competition between ALP and icodextrin for hepatocyte asialoglycoprotein receptors. Clearance of ALP is mediated by the presence of carbohydrate on the protein, and interference of ALP clearance has been reported due to other carbohydrates [22]. Differences in the carbohydrate composition of the intestinal isoform, which is much more heavily asialoglycated, may account for the greater impact on clearance of this isoform. Increases in ALP were not associated with any clinical symptoms, adverse events or abnormalities in any other liver function tests.

Hyponatraemia

Decreases in serum sodium and chloride have been observed in multiple studies of icodextrin, including controlled clinical trials [7, 17, 62]. In trials comparing icodextrin and 2.5% dextrose, mean values for serum sodium were within normal limits (normal range: 135 to 148 mEq/L) in both the treatment groups at each evaluation point, but were consistently near the lower limit of normal in the icodextrin group.

Serum sodium levels decreased early after the initiation of icodextrin, were stable over time, and rapidly returned to baseline values after discontinuation of treatment [22]. The greatest mean change from baseline with icodextrin was -3.6 mmol/L. Serum chloride typically followed a similar pattern.

The decline in serum sodium and chloride associated with icodextrin therapy is caused mainly by a dilutional effect resulting from blood levels of icodextrin metabolites, particularly maltose and maltotriose. The presence of osmotically active particles in the vascular compartment is sufficient to cause a slight shift in water from the interstitial and cellular compartments to the vascular compartment, resulting in the dilutional hyponatremia (sometimes called hypertonic hyponatremia). This dilutional hyponatremic effect is similar to that due to hyperglycemia or the presence of mannitol-like solutes in blood.

The decline in serum sodium and chloride is generally modest and rarely results in adverse event reports of hyponatremia. However, Gradden *et al,* [32] have recently reported neurological complications secondary to hyponatremia in two diabetic patients using icodextrin [33]. Both of these patients presented with hyperglycemia (glucose> 900 mg/dL), hyponatremia (sodium <121 mEq/L) and neurological problems, specifically seizures in one patient and markedly depressed

consciousness level in the other. Following these events, the authors examined sodium levels in their entire group of patients on peritoneal dialysis. Sodium levels prior to initiation of icodextrin were significantly lower in diabetic patients than in non-diabetic patients ($P< 0.005$), although the absolute level remained within the normal range in both groups (136 to 145 mmol/L). Sodium levels after initiation of icodextrin were significantly lower than pre-icodextrin levels in both diabetic ($P< 0.05$) and non-diabetic patients ($P< 0.05$), but fell below the lower limit of the normal range only in diabetic patients, suggesting that the effects of hyperglycemia and icodextrin are additive. Therefore, use of icodextrin may produce clinically relevant symptoms if, as in their two cases, the hyponatremia is compounded by other factors, such as poor blood sugar control.

Adverse Events

Rash due to icodextrin may be attributable to its structural similarity to dextran, which can be responsible for a variety of allergic reactions including anaphylactoid reactions [34]. The two polymers differ only in their linkage of glucose molecules, α-1, 4 for icodextrin and α-1,6 for dextran. Although the epitope for the dextran allergic reaction has not been identified, there have been studies that have confirmed the immunogenicity of dextrans and the formation of immunocomplexes with skin localization [35]. It is plausible that either the same or a similar epitope may also be responsible for the hypersensitivity reaction seen with icodextrin. In addition, icodextrin is derived from cornstarch, and so it should not be used in patients with a documented corn allergy.

In 1997 Wilkie *et al*, and Lam-Po-Tang *et al*, reported the first cases of hypersensitivity reactions in response to icodextrin dialysis [36, 37]. The skin rash associated with icodextrin often is described as a mild or moderate psoriasiform macular rash that includes peeling of the skin over the palms of the hands and soles of the feet. However, generalized and pustular rashes have also been reported [38, 39]. When a rash occurs, it generally develops early in therapy, is self-limited, and resolves without consequences after discontinuation of icodextrin.

From a single-centre in the United Kingdom in October 1998/1999, there were 102 patients exposed to icodextrin, which was maintained for 6 months or more in 80 patients. The prevalence of skin reactions in their center was 15% [39]. Reported skin reactions in the patients exposed to icodextrin were of two types – blistering and exfoliative. Acute blistering reactions occurred on sun-exposed areas (hands, face, and neck) and tended to occur at 3 and 6 months after commencement of icodextrin. Patients responded to icodextrin withdrawal, taking approximately 6–7 weeks to resolve completely.

Baxter Healthcare global surveillance programme database in August 1999 revealed an incidence of 108 skin reactions in over 4,000 patients, resulting in a rate of about 2.5%. In most cases, the symptoms were mild and over 50% of the 108 reported patients were maintained on icodextrin therapy [40].

However, the recent IMPENDIA-EDEN trial found that a skin rash developed in 12 patients (1%) in the icodextrin group [26]. One explanation for these lower rates are improvements in the quality of icodextrin preparation, especially since peptidoglycan were removed in 2007.

Therefore, the current evidence suggests that icodextrin skin reactions limited to the palms and soles do not necessitate icodextrin withdrawal, but careful medical attention to monitor for progression is needed. When a rash does occur, it generally develops early in therapy. Rashes have been reported even after prolonged icodextrin exposure; however, the high-risk period appears to be the first 14 days of icodextrin initiation. Immediate icodextrin withdrawal should be considered when diffuse or pustular rash develops. With a pustular rash, rechallenging patients with icodextrin after 6 months may be attempted, since the source of the immunogenic response may have waned. Patients are often unwilling to try icodextrin for a second time though, and risk suffering another rash. Icodextrin rashes of all types should be recorded and reported to enable post-marketing surveillance [19].

Sterile peritonitis

During 1999-2003 several reports of sterile chemical peritonitis have been attributed to icodextrin prescription [41-47]. Patients with icodextrin-associated sterile peritonitis present with abdominal discomfort and cloudy dialysates. No associated rash, fever or other hypersensitivity manifestations are present. Many patients have noticed that dialysates were mainly cloudy under icodextrin and that they progressively cleared under glucose-based solutions [48, 53]. Cell count in the dialysate varies from 100 to 3500 white blood cells/µl [48]. It shows a predominance of mononuclear cells (macrophages and/or monocytes), although neutrophils and lymphocytes have also been identified [46]. An excess of eosinophils has also been reported in some patients [48, 51]. Most importantly, all dialysate cultures remain sterile, even in enriched media [46-49, 53]. Usually, icodextrin has to be discontinued to clear the dialysates, although we have observed that symptoms may progressively subside in a few cases despite maintenance of icodextrin prescription [48]. In addition, re-challenge often results in re-appearance of cloudy dialysates within a few days [41, 42, 46-48].The delay between initiation of icodextrin and the first symptoms ranges from a few hours, i.e. the first exchange, to several months.(41-43, 45, 48) Finally, the symptoms may also occur in the resolution phase of an infectious peritonitis [44, 45, 50].

Williams and Foggensteiner, initially reported the occurrence of these symptoms in 20% (3/15) of their patients exposed to single exchanges of icodextrin in an early-start dialysis programme [46]. Subsequently, the same group extended their series with an incidence of 46% (12/26 patients). Goffin reported nine in 104 patients (8.7%), whereas MacGinley *et al,* reported a prevalence of 4.3% (6/141 patients) [47-49].

At admission, the vast majority of patients has been initially diagnosed as having an infectious peritonitis and was given empirical antibiotics. Catheter removal has even been performed in a few patients in whom a diagnosis of relapsing peritonitis was made [46, 53].

Evidence suggests that sterile chemical peritonitis secondary to icodextrin is not a benign event. Several manifestations of acute peritoneal inflammation have been demonstrated on the peritoneal biopsy from a patient with a typical symptomatology [52].

According to Baxter Healthcare's pharmacovigilance programme,sterile peritonitis secondary to icodextrin was reported in less than 1% of patients before January 2001, with prevalence reaching more than 10% during the first 6 months of 2002 [51]. The Baxter Healthcare, attributed this complication to peptidoglycan contamination of the dialysate by the Gram-positive bacteria, *Alicyclobacillus acidocaldarius*.Peptidoglycans are major components of the Gram-positive cell wall; like endotoxins, peptidoglycans have many biological activities including the ability to release pro-inflammatory cytokines from mononuclear cells [54]. This latter point is thus likely to explain both the occurrence of cloudy dialysate effluents observed under icodextrin and the presence of the mononuclear cell infiltration within the peritoneal membrane [55]. Since June 2002, icodextrin batches are guaranteed to contain <7.4 ng/ml of peptidoglycan, but they are not guaranteed to be free of peptidoglycan [50]. It is therefore possible that a very low concentration of peptidoglycan still may be able induce an immunologic response in sensitized patients. Nonetheless, the improved preparation of icodextrin has had an effect on lowering the rates of sterile peritonitis.

The clinical practice guidelines on icodextrin peritonitis include

1. To delay icodextrin in incident PD patients for 4–6 weeks so that sterile peritonitis is not confused with eosinophilic peritonitis, which occurs early after PD initiation regardless of PD solution.

2. If sterile peritonitis with icodextrin is diagnosed, for mild reactions, icodextrin could be continued, with the hope of a progressive reduction in symptoms.

3. Withdrawal of icodextrin is usually necessary in cases of severe reactions [4]. The dialysate usually clears within 24–48 h of icodextrin cessation [56]. If the PD effluent becomes clear, then icodextrin should not be reintroduced unless under close supervision. If the cloudy fluid recurs with icodextrin rechallenge, then the patient should not be prescribed icodextrin in the future. In severe cases of sterile peritonitis, a rechallenge of icodextrin could be hazardous and should not be attempted [19, 56]. However, even if clinically tolerable, the long-term consequences for the peritoneal membrane of recurrent chemical peritonitis and lowgrade mononuclear inflammation remain unknown.

Antibiotic Compatibility

Table 5 summarizes the antimicrobial stability data of icodextrin in polyolefin and polyvinyl chloride (PVC) containers [57-61]. Stability data for solution in nonPVC containers may not be applicable to containers made of PVC, since some medications may adsorb to the PVC container material [57].The dosage of each antibiotic in the above studies followed the recommended treatment dose. Drugs were considered stable if their concentration exceeded 90% of the original, which is a percentage used in previous studies.

Table 5: Antibiotic Stability in Icodextrin Transporters [62]

Drug	**Concentration, Mg/l**	**Drug stability in PVC containers**	**Drug stability in polyolefin containers**
Vancomycin	1,000	7days at 4°C 7days at 24°C 1day at 37°C	1 day at 25°C
Cefazolin	500[a] 750[b]	30 days at 4°C 7 days at 25°C 1 day at 38°C	1 day at 25°C
Ceftazidime	500	7 days at 4°C 2 days at 25°C 8h at 37°C	
Cefepime	500	7 days at 4°C 2 days at 20°C 4h at 37°C	
Tobramycin	40[a] 60[b]	14 days at 4°C 7 days at 25°C 1 day at 37°C	1 day at 25°C
Gentamicin	60		1 day at 25°C
Netilmicin	60		1 day at 25°C

The Place of Icodextrin in Modern Peritoneal Dialysis and Future

The use of icodextrin for the long dwell both in continuous ambulatory peritoneal dialysis and automated peritoneal dialysis (APD) is well established because of its superior ultrafiltration profile and reduced exposure to glucose and glucose degradation products. Icodextrin is also very suitable for patients, particularly high or high-average, with persistent symptoms of over hydration -a scenario possibly exacerbated by difficulties in managing fluid intake and/or declining residual renal function (**Table 6**).

The results of a recently published European-wide prospective study indicate that icodextrin can be used to successfully maintain anuric patients on APD [63]. Another recent European-based (Spanish) multicentre trial, found that patients who used icodextrin at some stage during a median follow-up period of 14.5 months had a one-third (32%) lower risk of transferring to HD due to technique failure compared with non-icodextrin users [64].

It should, however, be appreciated that plasma sodium levels are on average 3 mmol/L lower compared to dextrose solutions and glucometer determinations will have to be checked for interference of maltose. When these precautions are taken

into account, icodextrin is currently the preferred osmotic agent for the long dialysis dwells. Mixing icodextrin with other osmotic agents, for instance, a small amount of glucose, has been investigated [65-67]. But, this solution has not been taken into production. More recently, an experimental solution consisting of 6.8% icodextrin, 2.86% glucose, and a sodium concentration of 121 mmol/L reported superior ultrafiltration and sodium removal during a 15-h dwell, but its applicability is not known [68]. The use of icodextrin in a glucose and amino acids mixture has been investigated in short APD dwells and was associated with only moderate increases in plasma levels of icodextrin metabolites, while leading to a marked reduction in the absorption of glucose [69]. However, this approach is also experimental.

Another novel prescription is two icodextrin bags during a 24-hour period. This can be done with or without continued dextrose-based cycler therapy at night. This is following the reassuring data that the, deposition of icodextrin and metabolites in tissues is unlikely.

Table 6: Established and potential clinical benefits of icodextrin

Increased ultrafiltration, particularly in high transporters Improved glycemic control in diabetic patients
Improved lipid profiles [70,71]
Improvements in left ventricular geometry 72,73]
Enhanced phosphate removal(74]
? Preserved peritoneal membrane function [75]
? Increased technique survival [76,77]

References

1. Mistry, C. D., and R. Gokal, 1991: New osmotic agents for peritoneal dialysis: where weareand where we're going. *Semin. Dial.,* **4,** 9–12.
2. Mistry, C. D., R. Gokal, and N. P. Mallick, 1986: Glucose polymer as an osmotic agent in continuous peritoneal dialysis (CAPD). *Frontiers in Peritoneal Dialysis.* Maher, J. F., and Winchester, J. F., Eds. New York: Field, Rich and Associates. 241–248.
3. Staverman, P. J., 1951: The theory of measurement of osmotic pressure. Recl. Trav. Chim., **70,** 344–352.
4. Mistry, C. D., N. P. Mallick, and R. Gokal, 1985: The advantage of glucose polymer (Mw 20,000) as an osmotic agent in CAPD. *Proc. EDTA ERA*, **22,** 415–420.
5. Mistry, C. D., 1989: Glucose polymer as an osmotic agent in continuous peritoneal dialysis [Thesis]. London: University of London.

6. Mistry, C. D., N. P. Mallick, and R. Gokal, 1987: Ultrafiltration with isosmotic solution during long peritoneal dialysis exchanges. *Lancet*, 178–182.

7. Mistry, C. D., R. Gokal, and M. A. Peers, 1994: A randomized multicenter clinical trial comparing isosmolar dextrin 20 with hyperosmolar glucose solutions in continuousambulatory peritoneal dialysis (CAPD): a sixmonth study. *Kid. Int.,* **46,** 496–503.

8. Alsop, R. M., 1994: History, chemical and pharmaceutical development of icodextrin. *Perit. Dial. Int.,* **14,** 5–12.

9. Moberly, J. B., S. Mujais, T. Gehr, S. Sprague, A. Kucharski, R. Reynolds, F. Ogrinc, L. Martis, and M. Wolfson, 2002: Pharmacokinetics of icodextrin in peritoneal dialysis patients. *Kid. Int.,* **62,** 23-33.

10. Garcia-Lopez, E., and B. Lindholm, 2009: Icodextrin metabolites in peritoneal dialysis. *Perit. Dial. Int.,* **29,** 370-376.

11. Davies, D. S., 1993: Kinetics of icodextrin. *Perit. Dial. Int.,* **14,** 45-50.

12. HoDacPannekeet, M. M., N. Schouten, M. J. Langendijk, J. K. Hiralall, D. R. de Waart, D. G. Struijk, and R. T. Krediet, 1996: Peritoneal transport characteristics with glucose polymer based dialysate. *Kid. Int.,* **50,** 979 -986.

13. Rippe, B., and L. Levin, 2000: Computer simulations of ultrafiltration profiles for an icodextrin-based peritoneal fluid in CAPD. *Kid. Int.,* **57,** 2546-2556.

14. Plum, J., S. Gentile, Verger C, R. Brunkhorst, U. Bahner, B. Faller, J. Peeters, P. Freida, D. G. Struijk, R. T. Krediet, and B. Grabensee, 2002: Efficacy and safety of a 7.5% icodextrin peritoneal dialysis solution in patients treated with automated peritoneal dialysis. *Am. J. Kid. Dis.,* **39,** 862-871.

15. Pecoits-Filho, R., S. Mujais, and B. Lindholm, 2002: Future of icodextrin as an osmotic agent in peritoneal dialysis. *Kid. Int.,* **81,** 80-87.

16. Mujais, S., K. Nolph, R. Gokal, P. Blake, J. Burkart, G. Coles, Y. Kawaguchi, H. Kawanishi, S. Korbet, R. Krediet, B. Lindholm, D. Oreopoulos, B. Rippe, and R. Selgas 2000: Evaluation and management of ultrafiltration problems in peritoneal dialysis. *Perit. Dial. Int.,* **20,** 5–21.

17. Woodrow, G., B. Oldroyd, G. Stables, J. Gibson, J. H. Turney, and A. M. Brownjohn, 2000: Effects of icodextrin in automated peritoneal dialysis on blood pressure and bioelectrical impedance analysis. *Nephrol. Dial. Transplant,* **15,** 862–866.

18. Günal, A. I., S. Duman, M. Özkahya, H. Töz, G. Asçi, F. Akçiçek, and A. Basçi, 2001: Strict volume control normalizes hypertension in peritoneal dialysis patients. *Am. J. Kid. Dis.*, **37,** 588– 593.

19. Silver, S. A., Z. Harel, and J. Perl, 2014: Practical considerations when prescribing icodextrin: A narrative review. *Am. J. Nephrol.*, **39,** 515-527.

20**.** Grodstein, G. P., M. J. Blumenkrantz, J. D. Kopple, J. K. Moran, and J. W. Coburn, 1981: Glucose absorption during continuous ambulatory peritoneal dialysis. *Kid Int.,* **19,** 564-567.

21. Delarue, J., and C. Maingourd, 2001: Acute metabolic effects of dialysis fluids during CAPD. *Am. J. Kid. Dis.,* **37,** 103–107.

22. Gokal, R., J. Moberly, B. Lindholm, and S. Mujais, 2002: Metabolic and laboratory effects of icodextrin. *Kid. Int.,* **81,** 62–71.

23. Weser, E., and M. Sleisenger, 1967: Metabolism of circulating disaccharides in man and the rat. *J. Clin. Inves.,* **46,** 499-505.

24. Paniagua, R., M. D. Ventura, M. Avila-Diaz, A. Cisneros, M. Vicente-Martinez, M. D. Furlong, Z. Garcia-Gonzalez, D Villanueva, O. Orihuela, M. D. Prado-Uribe, G. Alcantara, and D. Amato, 2009: Icodextrin improves metabolic and fluid management in high and high-average transport diabetic patients. Perit. Dial. Int., **29,** 422–432.

25. Takatori, Y., S. Akagi, H. Sugiyama, J. Inoue, S. Kojo, H. Morinaga, K. Nakao, J. Wada, and H. Makino 2011: Icodextrin increases technique survival rate in peritoneal dialysis patients with diabetic nephropathy by improving body fluid management: a randomized controlled trial. *Clin. J. Am. Soc. Nephrol.,* **6,** 1337–1344.

26. Li, P. K., B. F. Culleton, A. Ariza, J. Y. Do, D. W. Johnson, M. Sanabria, T. R. Shockley, K. Story, A. Vatazin, M. Verrelli, A. W. Yu, and J. M. Bargman, 2013:

Randomized, controlled trial of glucose-sparing peritoneal dialysis in diabetic patients. *J. Am. Soc. Nephrol.,* **24,** 1889–1900.

27. Perera, N. J., P. M. Stewart, P. F. Williams, E. L. Chua, D. K. Yue, and S. M. Twigg, 2011: The danger of using inappropriate point-of care glucose metersin patients on icodextrin dialysis. *Diabet. Med.,* **28,** 1272-1276.

28. Firanek, C. A. , D. T. Jacob, and J. A. Sloand, 2014: Avoidable iatrogenic hypoglycemia in patients on peritoneal dialysis: the risks of nonspecific glucose monitoring devices and drug-device interaction. *J. Patient Saf.,* **10,** 218-221.

29. Sloand, J. A., 2012: Dialysis patient safety: safeguards to prevent iatrogenic hypoglycemia in patients receiving icodextrin. *Am. J. Kid. Dis.,* **60,** 514–516.

30. Kim, S.H., M. Goto, and T. Akaike, 2001: Specific binding of glucose-derivatized polymers to the asialoglycoprotein receptor of mouse primary hepatocytes. *J. Biol. Chem.,* **276,** 35312–35319.

31. Blom, E., M. M. Ali, B. Mortensen, and N. E. Huseby, 1998: Elimination of alkaline phosphatases from circulation by the galactose receptor. Different isoforms are cleared at various.rates. *Clin. Chim. Acta,* **270,** 125–137.

32. Gradden, C.W., R. Ahmad, and G. M. Bell, 2001: Peritoneal dialysis: New developments and new problems**.** *Diabet. Med.,* **18,** 360–363.

33. Posthuma, N., P. M. ter Wee, A. J. M. Donker, P. L. Oe, W. van Dorp, E. M. Peers, and H. A. Verbrugh, 1997: Serum disaccharides and osmolality in CCPD patients using icodextrin or glucose as daytime dwell**.** *Perit. Dial. Int.,* **17:** 602–607.

34. Furhoff, A. R., 1977: Anaphylactoid reaction to dextran—a report of 133 cases. *Acta. Anaesthesiol. Scand.,* **21,** 161–167.

35. Valance, A., B. Lebrun-Vignes, V. Descamps, G. Queffeulou, and B. Crickx, 2001: Icodextrin cutaneous hypersensitivity: report of 3 psoriasiform cases. *Arch. Dermatol.,* **137,** 309-310.

36. Wilkie, M. E., M. J. Plant, L. Edwards, and C. B. Brown, 1997: Icodextrin 7.5% dialysate solution (glucose polymer) in patients with ultrafiltration failure: extension of CAPD technique survival. *Perit. Dial. Int.,* **17,** 84-86.

37. Lam-Po-Tang, M. K. L., M. R. Bending, and J. T. C. Kwan, 1997: Icodextrin hypersensitivity in a CAPD patient. *Perit. Dial. Int.,* **17,** 82–84.

38. Valance, A., B. Lebrun-Vignes, V. Descamps, G. Queffeulou, and B. Crickx, 2001: Icodextrin cutaneous hypersensitivity: report of 3 psoriasiform cases. Arch Dermatol 2001; **137,** 309-310.

39. Goldsmith, D., S. Jayawardene, N. Sabharwal, and K. Cooney, 2000: Allergic reactions to the polymeric glucose-based peritoneal dialysis fluid icodextrin in patients with renal failure. *Lancet,* **355,** 897.

40. Filho, J. C. D. 2000: Allergic reactions to icodextrin in patients with renal failure. *Lancet,* **355,** 1364–1365.

41. Pinerolo, M. C., M. T. Porri, and G. D'Amico, 1999: Recurrent sterile peritonitis at onset of treatment with icodextrin solution. *Perit. Dial. Int.,* **19,** 491–492.

42. Del Rosso, G., L. Di Liberato, A. Perilli, P. Cappelli, and M. Bonomini, 2000: A new form of acute adverse reaction to icodextrin in a peritoneal dialysis patient. *Nephrol. Dial. Transplant.,* **15,** 927–929.

43. Heering, P., M. Brause, J. Plum, and B. Grabensee, 2001: Peritoneal reaction to icodextrin in a female patient on CAPD. Perit. Dial. Int., **21,** 321–322.

44. Reichel, W., B. Schulze, J. Dietze, and W. Mende, 2001: A case of sterile peritonitis associated with icodextrin solution. *Perit. Dial. Int.,* **21:** 414–419.

45. Goffin, E., and J. M. Scheiff, 2001: Transient sterile chemical peritonitis in a CAPD patient using icodextrin. *Perit. Dial. Int.,* **22,** 90–91.

46. Williams, P. F., and L. Foggensteiner, 2002: Sterile/allergic peritonitis with icodextrin in CAPD patients. *Perit. Dial. Int.,* **22,** 89–90.

47. MacGinley, R., K. Cooney, G. Alexander, S. M. Cohen, and D. J. A. Goldsmith, 2002: Relapsing culture-negative peritonitis in peritoneal dialysis patients exposed to icodextrin solution. *Am. J. Kid. Dis.,* **40,** 1030–1035.

48. Tintillier, M., J. M. Pochet, J. L. Christophe, J. M. Scheiff, and E. Goffin, 2002: Transient sterile chemical peritonitis with icodextrin: clinical presentation, prevalence, and literature review. *Perit. Dial. Int.,* **22:** 534–537.

49. Foggensteiner, L., J. Baylis, H. Moss, and P. Williams, 2002: Timely initiation of dialysis—single-exchange experience in 39 patients starting peritoneal dialysis. *Perit. Dial. Int.,* **22,** 471–47. Enia, G., A. Mandalari, G. Ventura, D. Pustorino, and V. Panuccio, 2003: Sterile icodextrin-associated peritonitis may induce hypersensitivity and recurrent peritonitis on re-challenge. *Nephrol. Dial. Transplant.,* **18,** 626.

51. Toure, F., M. Mohadjer, S. Lavaud, 2002: Clinical and biological presentation of icodextrin induced peritonitis: study of five cases and comparison with bacterial peritonitis. *J. Am. Soc. Nephrol.,* **43**, 18.

52. Goffin, E., M. Tintillier, J. P. Cosyns, and O. Devuyst, 2002: Sterile chemical peritonitis secondary to icodextrin: immunohistopathological description. *Perit. Dial. Int.,* **22,** 723–726.

53. Boer, W. H., P. F. Vos, and M. W. J. A. Fieren, 2003: Culture-negative peritonitis associated with the use of icodextrin-containing dialysate in twelve patients treated with peritoneal dialysis. *Perit. Dial. Int.,* **23,** 33–38.

54. Van Heijenoort, J., 2001: Formation of the glycan chains in the synthesis of bacterial peptidoglycan. *Glycobiol.,* **11,** 25–36.

55. Nakagawa, Y., H. Maeda, and T. Murai, 2002: Evaluation of the in vitro pyrogen test system based on proinflammatory cytokine release from human monocytes: comparison with a human whole blood culture test system and with the rabbit pyrogen test. *Clin. Diag. Lab. Immunol.,* **9,** 588–597.

56. Gokal, R., 2002: Icodextrin-associated sterile peritonitis. *Perit. Dial. Int.,* **22,** 445–448.

57. Voges, M., D. Faict, G. Lechien, and M. Taminne, 2004: Stability of drug additives in peritoneal dialysis solutions in a new container. *Perit. Dial. Int.,* **24,** 590–595.

58. Nornoo, A. O., and R. J. Elwell, 2006: Stability of vancomycin in icodextrin peritoneal dialysis solution. *Ann. Pharmacother.,* **40,** 1950–1954.

59. Pallotta, K. E., R. J. Elwell, A. O. Nornoo, and H. J. Manley, 2009: Stability of tobramycin and ceftazidimein icodextrin peritoneal dialysis solution. *Perit. Dial. Int.,* **29,** 52–57.

60. Robinson, R. F., R. S. Morosco, C. V. Smith, and J. D. Mahan, 2006: Stability of cefazolin sodium in four heparinized and non-heparinized dialysate solutions at 38 degrees celsius. *Perit. Dial. Int.,* **26,** 593–597.

61. Elwell, R. J., L. R. Volino, and R. F. Frye, 2004: Stability of cefepime in icodextrin peritoneal dialysis solution. *Ann. Pharmacother.,* **38,** 2041–2044.

62. Krediet, R., and S. Mujais, 2002: Use of icodextrin in high transport ultrafiltration failure. *Kid. Int.,* **62,** 53-61.

63. Riegel, W., E. A. Brown, S. J. Davies, P. Rutherford, F. Meeus, M. Borras, J. C. Divino Filho, E. Vonesh, and M. Van Bree, 2003: Can anuric patients besuccessfully treated by APD? Results of EAPOS (European APD Outcome Study) [abstract no. W698]. *Nephrol. Dial. Transplant.,* **18,**

64. DivinoFilho, J. C., 2003: A multicenter analysis shows that Extraneal may contribute to better technique and patient survival [abstract]. *Perit. Dial. Int.,* **23,** 19.

65. Mistry, C. D., and R. Gokal, 1993: Single daily overnight (12- h dwell) use of 7.5% glucose polymer + 0.35% glucose solution: 3 months study. *Nephrol. Dial. Transplant.,* **8,** 443–447.

66. Jenkins, S. B., and M. E. Wilkie, 2003: An exploratory study of a novel peritoneal combination dialysate (1.36% glucose/7.5% icodextrin), demonstrating improved ultrafiltration compared to either component studied alone. *Perit. Dial. Int.,* **23,** 475–480.

67. Dallas, F., S. B. Jenkins, and M. E. Wilkie, 2004: Enhanced ultrafiltration using 7.5% icodextrin 1.36% glucose combination dialysate: a pilot study. *Perit. Dial. Int.,* **24,** 542–546.

68. Freida, P., M. Galach, J. C. Divino Filho, A. Werynski, and B. Lindholm, 2007: Combination of crystalloid (glucose) and colloid (icodextrin) osmotic agents markedly enhances peritoneal fluid and solute transport during the long PD dwell. *Perit. Dial. Int.,* **27,** 267–276.

69. Rodriguez-Carmona, A., M. Perez Fontan, E. Garcia Lopez, T. Garcia Falcon, and H. Diaz Cambre, 2007: Use of icodextrin during nocturnal automated peritoneal dialysis allows sustained ultrafiltration while reducing the peritoneal glucose load: a randomized crossover study. *Perit. Dial. Int.,* **27,** 260–266.

70. Li, P. K., B. F. Culleton, A. Ariza, J. Y. Do, D. W. Johnson, M. Sanabria, T. R. Shockley, K. Story, A. Vatazin, M. Verrelli, A. W. Yu, and J. M. Bargman, 2013: Randomized, controlled trial of glucose-sparing peritoneal dialysis in diabetic patients. *J. Am. Soc. Nephrol.,* **24,** 1889–1900.

71. Bredie, S. J., F. H. Bosch, P. N. Demacker, A. F. Stalenhoef, and R. van Leusen, 2001: Effects of peritoneal dialysis with an overnight icodextrin dwell on parameters of glucose and lipid metabolism. *Perit. Dial. Int.,* **21,** 275–281.

72. Paniagua, R., O. Orihuela, M. D. Ventura, M. Avila- Diaz, A. Cisneros, M. Vicente-Martinez, M. D. Furlong, Z. Garcia-Gonzalez, D. Villanueva, M. D. Prado-Uribe, G. Alcantara, and D. Amato, 2008: Echocardiographic, electrocardiographic and blood pressure changes induced by icodextrin solution in diabetic patients on peritoneal dialysis. *Kid. Int.,* **108,** 125–130.

73. Konings, C. J., J. P. Kooman, M. Schonck, U. Gladziwa, J. Wirtz, A. W. van den Wall Bake, P. G. Gerlag, S. J. Hoorntje, J. Wolters, F. M. van der Sande, and K. M. Leunissen, 2003: Effect of icodextrin on volume status, blood pressure and echo-cardiographic parameters: A randomized study. *Kid. Int.,* **63,** 1556–1563.

74. Hiramatsu, T., T. Hayasaki, A. Hobo, S. Furuta, K. Kabu, Y. Tonozuka, and Y. Iida, 2013: Icodextrin eliminates phosphate and ameliorates cardiac hypertrophy and valvular calcification in patients with end-stage renal disease and diabetes mellitus undergoing peritoneal dialysis. *Adv. Perit. Dial.,* **29,** 9–13.

75. Martikainen, T. A., A. M. Teppo, C. Gronhagen-Riska, and A. V. Ekstrand, 2005: Glucose-free dialysis solutions: inductors of inflammation or preservers of peritoneal membrane? *Perit. Dial. Int.,* **25,** 453–460.

76. Takatori, Y., S. Akagi, H. Sugiyama, J. Inoue, S.Kojo, H. Morinaga, K. Nakao, J. Wada, and H. Makino, 2011: Icodextrin increases technique survival rate in peritoneal dialysis patients with diabetic nephropathy by improving body fluid management: a randomized controlled trial. *Clin. J. Am. Soc. Nephrol.,* **6,** 1337–1344.

77. Han, S. H., S. V. Ahn, J. Y. Yun, A. Tranaeus, and D. S. Han, 2012: Effects of icodextrin on patient survival and technique success in patients undergoing peritoneal dialysis. *Nephrol. Dial. Transplant.,* **27,** 2044–2050.

78. Grzegorzewska, A. E., D. Antczak-Jedrzejczak, and I. Mariak, 2000: Polyglucose dialysis solution influences serum activity of amylase and of lipase differently. *Adv. Perit. Dial.,* **16,** 113–118.

Chapter 14

Peritoneal Dialysis Solutions- Biocompatible Solutions

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Peritoneal Dialysis Solutions - Biocompatible Solutions

Introduction

The non-physiologic role that the peritoneal membrane is pushed to play in the peritoneal dialysis (PD) has consequences which ultimately turn detrimental to the further performance of the procedure. During the course of PD in a patient, it is not infrequent that the transport status of a patient progressively increases necessitating the use of higher concentrations of dextrose. From 3 % at the end of one year, the risk of ultrafiltration loss increases to 30% by six years [1]. Exposure to increasing concentrations of dextrose only makes the problem worse.

Peritoneal biopsies and autopsies, also to be mentioned are the animal models, clearly demonstrate the morphological changes that accompany such clinical observations. These changes include the progressive loss of mesothelial cells, thickening of the sub mesothelial layer, thickening of the basement membranes and the increase in effective surface area by progressive neovascularisation.

The vessels are characteristically affected by a hyalinising vasculopathy that eventually obliterates them [2]. What are the factors that induce these changes in the peritoneum? The answer is in the physical and chemical abuse that the peritoneum has to face and its reaction to it.

Manufacturing of PD fluids in a sterile fashion that would remain stable over long shelf lives needs heat sterilization, pH optimization and composition modification. Instead of direct addition of bicarbonate to the fluid that would precipitate with calcium ions, it is added in the form of lactate (stable, easy and safe to use with proven record as ringer's lactate) during the manufacturing process and storage. A low pH is needed to prevent the sugar from caramelizing during heat sterilization. These factors lead to the production of a fluid that was hyper-osmotic, acidic and contained glucose degradation products. Infusion of such fluids can result in pain. The loss of glucose osmotic gradient over long dwell times makes it a poor ultrafiltration agent. In the long run, both the peritoneum and the systemic metabolism are subject to the adverse effects of excess glucose. The newer fluids that came to be manufactured with these specific considerations are referred to as biocompatible PD fluids.

Understanding biocompatibility

Markers of biocompatibility **(Table 1):** While the ultimate test of biocompatibility is the long term stability of peritoneal membrane function and technique survival, short term indices of *in-vivo* human nd animal as well as *ex-vivo* cell culture studies of human and rodent mesothelial cells, leucocytes, endothelial cells and fibroblasts

can be used as surrogates. Morphological variations, measures of interleukins, prostaglandins, fibrogenic mediators and coagulant factors produced by mesothelial cells, leucocyte proliferative, phagocytic ability, respiratory burst with superoxide generation are the factors that establish the pathogenic role of acute and long term exposure to PD fluids as well as serve as models for testing newer fluids.

Table 1: Markers of biocompatibility [3].

Types	Names
Inflammation markers	Interleukins (IL-6)
	Prostaglandins (PGE2, PGI2)
	Adhesion molecules
Tissue repair and remodelling	Matrix metalloproteinases
	TGFβ
	Hyaluronan
Mesothelial cells	CA125
	Effluent cell count, morphology and proliferation potential
	Cell culture - induction of tPA, PGE2
Neutrophils (from peripheral blood)	Phagocytic ability
Macrophages (from effluent)	Respiratory burst

Glucose and glucose degradation products

The changes in the peritoneal structure during long-term PD closely resemble those seen in the diabetes. High levels of glucose promote the non-enzymatic binding to the mesothelial proteins and lipids leading to the formation of advanced glycation end products (AGEs). An accumulation of AGEs through cross-linking further leads to oxygen free radical generation. They also play a role in the increased generation of VEGF and TGFβ. Demonstration of accumulation of AGEs and their interactions with receptor was consistently associated with the development of peritoneal fibrosis, neo vascularisation, vascular sclerosis and the clinical sequel of high solute transport [4]. Elevated levels of plasma extracellular newly identified receptor for AGE seen in patients on PD is associated with pro-inflammatory milieu and accelerated carotid atherosclerosis [5]. High levels of glucose induce the damage in peritoneal fluid noted as inflammation, neo-angiogenesis, fibrosis, apoptosis and

necrosis through osmotic stress, generation of advanced glycation end products, polyols, glucose degradation products and subsequent generation of chemokines including fibrogenic mediators.

Heat sterilization leads to the formation of molecules described as glucose degradation products (GDP) [6]. These include formaldehyde, acetaldehyde, furaldehyde, glyoxal, methylglyoxal, 5-hydroxymethyl-furfural (5-HMF), 3, 4-dideoxyglucosone-3-ene (3, 4-DGE) and 3 deoxyglucosone (3-DG). Among these, 3 DG and 3, 4-dideoxyglucosone-3-ene (3, 4-DGE) are the most studied and considered to be the most potent toxin. GDP also lead to an enhanced AGE production. Local effects on the peritoneal membrane include reduced mesothelial cell growth and viability [7]. They also lead to a reduced neutrophilic phagocytic ability and respiratory burst compromising mesothelial immune functions. Systemic absorption of GDPs can lead to renal epithelial cell apoptosis with resultant rapid loss of residual renal function (RRF) [8]. The hypothesis of reduced GDP fluids preserving peritoneal membrane and RRF has been tested in many animal studies and clinical trials [9].

pH

Animal models of PD exposed to conventional fluids with high GDP (**Table 2**), filter purified fluid with low GDP and neutral pH fluid showed a deleterious inflammatory effect on the mesothelium by the glucose, GDP and lactate but the role of pH (beyond that caused by lactate itself) was unconvincing [10]. However, others have shown the worsening of intracellular acidosis in intra-peritoneal neutrophils impairing their function that was corrected by a change in the pH of the fluid [11]. Increase in the pH of the newer fluids has not always been successful in reducing infusion pain or even less in terms of reduction in peritoneal infections [12]. Non-dextrose PD fluids (**Table 3**) overcome the disadvantages of glucose absorption.

Table 2: Conventional PD Fluids

Osmotic agent	**Dextrose** **1.5%, 2.5%, 4.25%**
Osmolarity (mosm/l)	344- 386
pH	5.4-5.8
Glucose degradation products	350
3-DG (micromol/l)	167
3,4-DGE (micromol/l) (Variable concentration depending on manufacturer and dextrose content)	11

Table 3: Non Dextrose PD Fluids

Fluid	**pH**	**Buffer**	**GDP µmol/l**	**Osmotic agent**
Icodextrin	5.8	Lactate	45	7.5% Poly glucose Approx. 20 kDa
Amino acid	6.6	Lactate	-	1.1 %Amino acid Both essential and non essential

Icodextrin

Though it is an acidic fluid and uses lactate as the buffer, poly-glucose containing icodextrin based fluid potentially overcomes the disadvantages of glucose absorption, glucose degradation products and advanced glycation end products, with resultant peritoneal and systemic metabolic complications accompanying dextrose containing PD fluids [3]. Neutral pH icodextrin based PD fluids are under development [13]. Improved ex vivo phagocytic function of effluent leucocytes was noted, though there was no improvement in the mesothelial mass biomarker CA-125. The use of icodextrin almost always combined with dextrose containing fluids makes studies of biocompatibility difficult to interpret [14].

The preserved isotonic colloid osmosis across the small pores over prolonged dwell durations with no sodium sieving, in comparison to the diminishing hyperosmotic crystalloid osmosis of glucose, makes icodextrin a suitable candidate for the long dwells. Recommended icodextrin dwell times for CADP and CCPD longest dwells of the day are 6-12 hours and 14-16 hours, respectively. Icodextrin has an ultrafiltration capacity that is comparable to the 4.25% dextrose fluid (on 8 hour dwells and even better ultrafiltration volumes at 12 hour dwell times or compared to lower dextrose fluids) [15].

Despite absorption of significant amounts of the osmotic agent over 12 hours, only mild elevations of maltose concentrations are noted in the serum with no attributable adverse effects due to its accumulation. Mild hyponatremia and over estimating interference with glucose measurement by monitors that use glucose dehydrogenase pyrroloquinolinequinone (GDH-PQQ) or glucose-dye-oxidoreductase–based methods are due to the maltose in blood. Only glucose specific monitors should be used for patients using icodextrin to avoid unnecessary treatment of spurious hyperglycemia that may result in irreversible neurological sequel.

Skin rash that occurs in 10% of the patients usually involves the palms and soles, are mild to moderate in severity and rarely a mild desquamation. Its incidence decreases over the duration of use with only 2.6% affected at 1 year. No association was noted with the accumulation of systemically absorbed oligosaccharides [16].

The recent meta-analysis from Cochrane concludes that it is useful in improving ultrafiltration and volume control with no effect on residual urine produced [12]. No improvements in technique or patient survival have been reported [17]. Based on these meta-analyses, the ISPD recommends the use of icodextrin for a better volume control in high transporters. Icodextrin is also recommended in the diabetic patients for a better glycemic control [18].

Amino acid PD fluids

A bag of 1.1% 2l amino acid PD fluid used in one exchange a day would provide 22g of amino acids (2/3rd essential and 1/3rd non essential) which is approximately 25 % of the daily requirement and generate an ultrafiltration equal to that of a 2l 1.5% dextrose PD fluid. In malnourished patients, the use of amino acid PD fluid for one of the exchanges improves the biochemical and anthropometric measures of nutrition with some degree of protection against peritonitis, hospitalisation and worsening of solute transport.

Nutrineal (Baxter) in one exchange with icodextrin (Extraneal, Baxter) and Physioneal (Baxter) for other exchanges, as a regimen (NEPP regimen) with low glucose and GDP, was shown to preserve mesothelial cell mass but was associated with an increased VEGF in the peritoneal effluent. Further studies are needed to establish its role as a biocompatible fluid [19].

The osmolarity of this solution is 365 mosm/l compared to the 345 mosm/l of the 1.5 % dextrose solution. In the absence of glucose, the question of glucose degradation products doesn't arise but the pH of the solution is still an un-physiologic 6.6 contributed by the use of lactate buffer. Increases in serum urea concentration, worsening of acidosis, hyperhomocystenemia (due to the methionine content) and worsening hypokalemia (zero potassium content) should raise caution in patients with predisposing factors.

Newer PD fluids

The major path that has been adopted by the manufacturers in creating newer fluids is to design processes to maintain as normal a pH as possible with the use of multi compartmental bags with some or all of buffer as bicarbonate. The buffer compartment is mixed with the glucose compartment immediately prior to infusion. This allows heat sterilization at an optimal pH that would prevent glucose degradation product generation. The fluids are available at concentrations of dextrose similar to conventional PD fluids and can be used for both manual and automated peritoneal dialysis. The pH of these fluids ranges from 6.3-7.4 with low glucose degradation products atleast of 40- 75 µmol/l compared to approximately 350 µmol/l. The osmotic agent used is dextrose and are all hyperosmotic (**Table 4**).

Table 4: Dextrose Containing Newer Peritoneal Dialysis Fluids

Fluid	pH	Buffer	GDP µmol/l	Osmotic agent
Trio Gambro	6.3	Lactate	65	Dextrose
Physioneal	7.4	Bicarbonate+lactate	253	Dextrose
Balance	7.0	Lactate	42	Dextrose
Bicavera	7.4	Bicarbonate	42	Dextrose
DelflexNpH	7.0	Lactate+bicarbonate	70	Dextrose
T				

Physioneal

Physioneal (from Baxter) is a neutral pH PD fluid. The buffer is a combination of lactate and bicarbonate (10 or 15 mmol/l and 25 mmol /l respectively). It is manufactured as a two chamber bag with chamber A containing glucose in concentrations of 1.5%, 2.5% and 4.25% with osmolarities from 344, 395 and 483 mosm/l at a pH of 2.1 along with calcium and magnesium salts and chamber B containing the buffer at a ph 9.0 with lactate and bicarbonate buffer in it. The two solutions are mixed immediately prior to the infusion after breaking open the inter-chamber long seal. All additives are to be added to the chamber A, the acidic

glucose compartment. The volume of the chambers is in the ratio of 3:1. At least, 1.6 l of a bag should be instilled during each infusion to avoid accidental infusion of only the buffer chamber and the consequent alkalosis. Despite the efforts the glucose degradation product concentration of the fluid is still high at 253 µmol/l /l.

Balance

Balance (from Fresenius) is a double chamber bag PD fluid with one glucose and electrolyte chamber and another buffer chamber; both in equal volumes. The buffer solution is similar to the conventional dextrose PD fluid that is lactate to a post mixture concentration of 35mmol/l. The pH and GDP content of the fluid are 7.0 and 42 µmol/l respectively. Both the chambers have to be mixed prior to intra-peritoneal infusion within 24 hours.

Bicavera

Bicavera (from Fresenius) is the only fluid with only bicarbonate as the buffer solution. Similar to the other newer fluids, it is also manufactured as a double chamber bag with one chamber containing glucose along with calcium and magnesium chloride separate from the other chamber with bicarbonate preventing the precipitation of these salts. The pH after mixing of the fluid in the two chambers is 7.4. With the continued use of glucose as the osmotic agent, GDP persist at a low level of 42µmol/l.

Gambrosol Trio

Gambrosol Trio (from Gambro) is manufactured as a tri-compartmental bag with two smaller compartments of 50 % glucose solution and the third larger compartment with electrolytes sodium, calcium, magnesium, chloride and lactate. Mixing one, two or both the smaller compartments to the larger chamber results in low, medium and high osmolar fluids for intra-peritoneal infusion. The pH of the solution after mixing is 6.3 with low GDP concentrations.

Delflex Neutral pH

The newest entrant into the list (from Fresenius) is still based on glucose as the osmotic agent, along with other electrolytes (sodium, calcium, magnesium and chloride) in a main bag and the buffer solution as lactate (31.5mmoml/l) with bicarbonate (3.5 mmol/l) in a “mini bag”. It is designed with an interlock system between the compartments that would prevent the accidental infusion of the contents of only one bag without mixing the contents. It is the only US FDA approved neutral pH PD fluid. The pH after the mixing of the two chambers is 7.0± 0.4. The GDP levels in the fluid are 55, 70 and 95µmol/l/l depending on the glucose content of 1.5%, 2.5% and 4.25 %, respectively.

Recent Trials

The BalANZ trial reported in 2012 is the single largest trial till date comparing neutral pH, low GDP peritoneal dialysis fluid (Balance) to conventional (stay safe) PD fluid. Adult patients recently initiated on continuous ambulatory peritoneal dialysis with significant residual renal function (RRF) (measured glomerular filtration rate of ≥5ml/min/1.73 sqm and urine output of ≥400ml/day) were included and followed over a period of two years. Despite early (at 3 and 6 months) increased urine output with decreased peritoneal ultrafiltration volumes, over 2 years the rate of GFR decline though numerically lower was not statistically different in the intervention compared to the conventional PD fluid group. However, time to anuria was longer in the Balance arm. Number of peritonitis episodes was significantly lower in the intervention arm reasoned to be behind the longer time to anuria apart from the avoidance of lower GDPs in the newer fluid. Overall glucose exposure, icodextrin use, extra peritoneal infections, technique survival and patient survival were not different in both the arms of the study [20].

The recently reported Trio trial comparing biocompatible PD solution (Gambrosol Trio) to standard PD fluid (Dianeal) showed contrasting results with slower rates of GFR decline but higher peritonitis episodes in the intervention arm. The differences in the results were attributed to the measurement frequency of residual renal function and the different connectologies of the manufacturers. This study used bioimpedance analysis to assess volume status and showed no difference in fluid status despite the higher rate of icodextrin use and APD prescription in the standard treatment arm. Body fat mass was higher in the biocompatible fluid arm. D/P creatinine ratios were similar between the groups [21].

In 2016, the Cochrane database published a review of trials comparing neutral pH, low GDP fluid to standard PD fluid and summarized the better preservation of residual renal function, urine volume with greater benefit noted through longer use of the solutions (*i.e*, longer than 12 months) and lower infusion pain with moderate to high quality evidence. Peritonitis rates and technique survival were not found to be different in the groups [12].

Based on this review, the international society of peritoneal dialysis (ISPD) in its guidelines on management of cardiovascular risk factors suggested the use of biocompatible neutral pH, low GDP fluids for better preservation of RRF when used for longer than 12 months [18].

To conclude, the expectation that biocompatible fluids are the solution to problems of better preservation of renal and peritoneal membrane function remains unfulfilled, though they are used commonly for indications of infusion pain, where available (not marketed yet in India). Further innovation and research are needed to overcome the hurdles, but steady progress seems to be made.

References

1.Heimburger, O., J. Waniewski, A. Werynski, A. Tranaeus, and B. Lindholm, 1990: Peritoneal transport in CAPD patients with permanent loss of ultrafiltration capacity. *Kid. Int.,* **38,** 495-506.

2.Devuyst, R. W., and N. Topley, 2009: Long-Term Peritoneal Dialysis Patients Changes in Membrane Structure and Function. *Textbook of Peritoneal Dialysis*. R. Khanna, Eds. Nolph and Gokal's, Springer.

3.Cooker, L. A., C. J. Holmes, and C. M. Hoff, 2002: Biocompatibility of icodextrin. *Kid. Int.,* **62,** 34-45.

4.De Vriese, A. S., S. Mortier, and N. H. Lameire, 2001: What happens to the peritoneal membrane in long-term peritoneal dialysis? Peritoneal dialysis international. *J. Int. Soc. Perit. Dial.,* **21,** 9-18.

5.Kim, J. K., S. Park, M. J. Lee, Y. R. Song, S. H. Han, S. G. Kim, S. W. Kang, K. H. Choi, H. J. Kim, and T. H. Yoo, 2012: Plasma levels of soluble receptor for advanced glycation end products (sRAGE) and proinflammatory ligand for RAGE (EN-RAGE) are associated with carotid atherosclerosis in patients with peritoneal dialysis. *Atherosclerosis*, **220,** 208-214.

6.Schalkwijk, C., N. Posthuma, H. ten Brink, P. ter Wee, and T. Teerlink, 1999: Induction of 1,2-dicarbonyl compounds, intermediates in the formation of advanced glycation end-products, during heat-sterilization of glucose-based peritoneal dialysis fluids. *Perit. Dial. Int.,* **19,** 325-333.

7.Witowski, J., K. Korybalska, J. Wisniewska, A. Breborowicz, G. M. Gahl, U. Frei, J. P. Deetjen, and A. Jorres, 2000: Effect of glucose degradation products on human peritoneal mesothelial cell function. Journal of the American Society of Nephrology : *JASN,* **11,** 729-739.

8.Justo, P., A. B. Sanz, J. Egido, and A. Ortiz, 2005: 3,4-Dideoxyglucosone-3-ene induces apoptosis in renal tubular epithelial cells. *Diabetes*, **54,** 2424-2429.

9.Johnson, D. W., Y. Cho, and F. G. Brown, 2012: Trials (and tribulations) of biocompatible peritoneal dialysis fluids. Peritoneal dialysis international. *J. Int. Soc. Perit. Dial.,* **32,** 247-251.

10.Zareie, M., L. H. Hekking, A. G. Welten, B. A. J. Driesprong, I. L. S. Eestermans, D. Faict, A. Leysennes, C. G. Schalkwijk, R. H. J. Beelen, P. M. ter Wee, and J. van den Born, 2003: Contribution of lactate buffer, glucose and glucose degradation products to peritoneal injury in vivo. *Nephrol. Dial. Transplant.,* **18,** 2629-2637.

11.Dobos, G. J., J. Bohler, X. J. Zhou, A. Martin, N. Johannes, K. Eckhard, P. J. Schollmeyer, and N. D. Vaziri, 1994: Persistent inhibition of neutrophil function by glucose based dialysis solutions. *ASAIO J.,* **40,** 435-439.

12.Cho, Y., D. W. Johnson, J. C. Craig, G. F. Strippoli, S. V. Badve, and K. J. Wiggins, 2014: Biocompatible dialysis fluids for peritoneal dialysis. *The Cochrane database of systematic reviews,* CD007554.

13.Yamaguchi, N., K. Miyamoto, T. Murata, E. Ishikawa, and T. Horiuchi, 2016: Newly Developed Neutralized pH Icodextrin Dialysis Fluid: Nonclinical Evaluation. *Artif. Organs*, **40,** 158-166.

14.Feriani, RTK. M., 2009: New Peritoneal Dialysis Solutions and Solutions on the Horizon. *Textbook of Peritoneal Dialysis.* R. Khanna, RTK, Ed. Nolph and Gokal's.

15.Mistry, C. D., R. Gokal, and E. Peers, 1994: A randomized multicenter clinical trial comparing isosmolar icodextrin with hyperosmolar glucose solutions in CAPD. MIDAS Study Group. Multicenter Investigation of Icodextrin in Ambulatory Peritoneal Dialysis. *Kid. Int.,* **46,** 496-503.

16.Wolfson, M., F. Ogrinc, and S. Mujais, 2002: Review of clinical trial experience with icodextrin. *Kid. Int.,* **62,** 46-52.

17.Qi, H., C. Xu, H. Yan, and J. Ma, 2011: Comparison of icodextrin and glucose solutions for long dwell exchange in peritoneal dialysis: a meta-analysis of randomized controlled trials. *J. Int. Soc. Perit. Dial.,* **31,** 179-188.

18. Wang, A. Y. M., K. S. Brimble, G. Brunier, S. G. Holt, V. Jha, D. W. Johnson, S. W. Kang, J. P. Kooman, M. Lambie, C. McIntyre, R. Mehrotra, and R. P. Filho, 2015: ISPD Cardiovascular and Metabolic Guidelines in Adult Peritoneal Dialysis Patients Part I – Assessment and Management of Various Cardiovascular Risk Factors. *Perit. Dial. Int.,* **35,** 379-387.

19.le Poole, C. Y., A. G. Welten, P. M. ter Wee, N. J. Paauw, A. N. Djorai, R. M. Valentijn, R. H. J. Beelen, J. van den Born, and F. J. van Ittersum, 2012: A peritoneal dialysis regimen low in glucose and glucose degradation products results in increased cancer antigen 125 and peritoneal activation. *J. Int. Soc. Perit. Dial.,* **32,** 305-315.

20.Johnson, D. W., F. G. Brown, M. Clarke, N. Boudville, T. J. Elias, M. W. Y. Foo, B. Jones, H. Kulkarni, R. Langham, D. Ranganathan, J. Schollam, M. Suranyi, S. H. Tang, and D. Voss, 2012: Effects of Biocompatible versus Standard Fluid on Peritoneal Dialysis Outcomes. *J. Am. Soc. Nephrol.,* **23,** 1097-1107.

21.Sikaneta, T., G. Wu, M. Abdolell, A. Ng, S. Mahdevi, A. Svendrovaski, T. Tu, T. Mercer, M. Tong, D. Oreopilous, and P. Tam, 2016: The Trio Trial - A Randomized Controlled Clinical Trial Evaluating the Effect of a Biocompatible

Peritoneal Dialysis Solution on Residual Renal Function. *J. Int. Soc. Perit. Dial.*, **36,** 526-532.

Chapter 15

Peritoneal Dialysis Solutions – Amino Acid Based

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Peritoneal Dialysis Solutions - Amino Acid Based

Introduction

The loss of amino acids (AAs) and proteins into dialysate is substantial to contribute for the nutritional derangements in patients on peritoneal dialysis (PD) [1, 2] Patients on PD are reported to lose 3–4g/day of AAs and 4–15g/ day of proteins [3] In 1960s, the first article to supplement PDs solutions with AAs to mitigate the obligate AAs and protein losses with dialysate was published. Later, Oreopoulos *et al*. in 1980 proposed an AAs solution in PD both for nutritional supplementation and as an alternative to glucose as the osmotic agent. In the subsequent years, the experiments with an AA solution in a uremic rabbit model and in patients on PD [4- 6] brought to the fore the advantages of substituting glucose in the solution and improving nutritional support.

Physiological Advantages of Amino Acid Solutions

Though, the molecular weights of AAs used in PD, range from 75 to 214 Daltons, the AA mixtures have an average molecular weight of approximately 100 Daltons, [7] This is because of the presence of a higher proportion of small-molecular-weight compounds in the AA mixtures. This is lower than that of the glucose. In spite of this, the absorption rate of AAs is not significantly faster than that of glucose. Since, at the fresh dialysis solution pH, some AAs are electrically charged, the hydration shell increases the relative Einstein-Stokes radius of the molecules. Einstein-Stokes radius of a solute is the radius of a hard sphere that diffuses at the same rate as that of solute. It is closely related to solute mobility, factoring in not only size but also the solvent effects. A smaller ion with stronger hydration, for example, may have a greater Einstein-Stokes radius than a larger ion with a weaker hydration. This is because the smaller ion drags a greater number of water molecules with it as it moves through the solution. [8]. As a consequence, diffusion coefficients are smaller in comparison to uncharged molecules with equivalent molecular weight, and absorption velocity is reduced.

Osmotic efficacy

The results of studies are contradictory with AA solutions.

Studies which showed benefit with AA solutions

1. A 2% AA solution was compared to a 4.25% glucose solution: It was an acute study on 6 hour exchanges [6]. The two solutions induced equivalent amounts of ultrafiltration, similar amounts of urea, creatinine, and potassium removal. At the end of the exchange, 90% of the administered AAs were absorbed.

2. Ultrafiltration achieved with a 1% AA solution (osmolality 364 mmOsm/kg) was intermediate between that of 1.5% (osmolality 346 mmOsm/kg) and 2.5% (396 mmOsm/kg) standard glucose solution [9]
3. Statistically not different, but, excess ultrafiltrate volumes were reported when a 1% AA solution was compared with a 1.5% glucose solution [10]

- Studies which showed lack of definite benefit with AA solutions

1. A comparison between a 4.25% glucose (478 mmOsm/kg) and a 2.76% AA (501 mmOsm/kg) solution showed that intraperitoneal volume profiles were equal during the first 180min of dwell. At the end of the 6-h dwell time there was a non significant decrease in net ultrafiltration with amino acid solution [11].
2. Young *et al*, studied ultrafiltration and D/P ratios of several proteins in an 8 hour dwell time exchange using a 1% AA solution in comparison with 1.5% glucose standard solution [12]. The results were:
(i) Volumes of dialysate at the end of the exchanges were significantly less after amino acid exchanges.
(ii) The absorption of amino acids from the amino acid exchange increased during the study: 16.4 g at 4 weeks and 17.1 g after 12 weeks.
(iii) Total protein and prealbumin loss into dialysate increased by about 20%.
(iv) The loss of protein in dialysate was reversed when exchanges standard glucose solutions were resumed [12].The increase of the peritoneal permeability for proteins (and also for creatinine) during the use of AA based solution was attributed to an activation of the complement by the AAs or their metabolites to produce C5a. [13, 14]
3. AA dialysis solution 1.1% (Nutrineal) contains L-arginine, a substrate for nitric oxide (NO) synthesis [15]. NO causes vasodilation in many organs. To investigate the effects of AA dialysis solution on peritoneal permeability and perfusion, standard peritoneal permeability analyses were performed. The results were
(i) The mass transfer area coefficients of low-molecular-weight solutes (creatinine, urea, and urate) were significantly greater with AA solution compared to the glucose solution.
(ii) The clearances of the macromolecules, like albumin and IgG were also greater but not significantly.
(iii) Even though the transcapillary ultrafiltration rate was higher during the amino acid treatment, no significant difference in net ultrafiltration was found.
(iv) A vasodilatory effect of the AA solution showed as increased peritoneal blood flow and the effective peritoneal surface area. This study also demonstrated that these effects were not due to nitric oxide activity (L-arginine contained in the amino acid solution could serve as a substrate for nitric oxide synthesis) nor to the peritoneal release of prostaglandins.

Despite the contradictory results of kinetic studies, in clinical practice 1.1% AA solutions deliver ultrafiltration and small molecule clearances equivalent to those achieved with1.5 % glucose solutions. The differences in these studies are probably

due to the difference in concentration and composition of amino acids in the employed solutions.

Nutritional efficacy

Different amino acid composition solutions were used. In the commercially available solutions total amino acid concentration was increased to 1.1% in order to provide the same osmotic effect as that of 1.5% standard glucose solution. Essential AA concentrations, lactate concentration were increased (from 35 to 40 mmol/L).

Studies

1. A short term crossover multicentre study in patients on continuous ambulatory peritoneal dialysis (CAPD) with signs of protein malnutrition has been performed [16]. The nitrogen balance, serum transferrin, and total protein increased in 19 malnourished patients after using one or two 1.1% AA solution for 20 days. Protein anabolism was positive, as directly determined from 15N-glycine studies and indirectly from the plasma phosphate and potassium decrease. After commencing intraperitonealamino acidtherapy, nitrogen balance became significantly positive, there was a significant increase in net protein anabolism, the fasting morning plasmaamino acidpattern became more normal, and serum total protein and transferrin concentrations rose. Serum triglycerides and HDL cholesterol also increased. PlasmatotalCO_2 significantly decreased, showing a tendency toward a metabolic acidosis mainly in patients treated with two exchanges per day of this solution.
2. Fifteen patients on CAPD were studied in a non-randomized prospective 3-month study [17] Each patient received 2 litres of optimised 1.1%AAsolutionfor the second exchange of the day with a dwell time of 5-6 hours. After 3 months of intraperitonealAAs, serum albumin levels significantly increased from 32.7 ±2.3 to 35.1 ±2.2 g/l (mean ± SD; $P< 0.01$). This occurred in parallel with a significant increase in the transferrin levels from 2.21 ±0.26 to 2.39 ± 0.27 g/l ($P< 0.05$). As expected, urea levels rose from 23.7 ± 6.8 to 29.9 +/- 9.4 mmol/l. interestingly bicarbonate levels did not change (25.5 ± 4.2 *versus* 25.2 ± 3.3 mmol/l).
3. A prospective randomised study compared the nutritional effects of the 1.1% AA solution with the conventional glucose solution in 54 malnourished patients [18]. After an initial significant increase in serum albumin, transferrin, prealbumin, and total protein; after 3 months of treatment, these parameters did not achieve the statistical significance as compared with those of the 51 patients in the control group. However, in the tertile with the lowest albumin levels at the baseline, serum albumin and prealbumin remained significantly increased. In the tertile with the highest albumin levels at the baseline, the mid-arm muscle circumference increased significantly after 3 months of treatment. In the whole population treated with the AA solution, circulating insulin-like growth factor 1 (IGF-1) increased, while it slightly decreased in the control group.
4. During a dwell of 4 – 6 hours, about 80%, on average, of the amount of AAs in 1.1% AA solution is absorbed, that is, about 18 g with a dwell volume of 2 L [19].

This is much greater than the peritoneal loss of AA after 6 hours dwell time with conventional glucose solutions (0.7± 0.1g of total AA) [20].
5. Skeletal muscle AA uptake was increased after 6 weeks use of this AA solution [21].
6. In an acute study using the 3H-phenylalanine kinetics as an indicator, muscle protein synthesis increased by 20% [22].
7. Other studies could not demonstrate an improvement in nutritional parameters in well-nourished patients on CAPD treated with 1.1% AA solution [23, 24]
8. The longest experience with AA solution was a 3-year, randomised, prospective, controlled study of AA dialysate in malnourished Chinese patients on CAPD [25] Sixty patients were assigned randomly to either replace 1 exchange daily with AA dialysate (n = 30) or to continue with dextrose dialysate (n = 30). The results were
(i) Biochemical nutritional parameters including albumin and cholesterol decreased in the dextrose group but remained stable or increased in the AA group. The composite nutritional index did not differ between the 2 groups throughout the study period.
(ii) Normalised protein equivalent of nitrogen appearance and dietary protein intake showed a sustained increase only in the AA group.
(iii) The nutritional benefit of AAs appeared more prominent in women.
(iv) The two groups had similar total Kt/V (urea) and daily ultrafiltration volume, mortality, hospitalization duration, serial C-reactive protein levels, and drop-out rates during the study.
9. In malnourished Korean peritoneal dialysis patients, 31 out of the 43 malnourished patients (72%) showed nutritional benefit based on the change of lean body mass. But, no significant change in serum albumin levels was noted [26].

It is of utmost importance that intraperitoneal administration of the AAs is accompanied by a simultaneous intake of the calories. This has been shown convincingly by Delarue *et al*, who compared the effects of intraperitoneal AAs with or without simultaneously consuming a meal composed of carbohydrates and lipids in patients on CAPD [27]. While the AAs stimulated protein synthesis, the oral calories were found to induce inhibition of protein degradation, thereby reinforcing the positive effects of the AAs on protein balance. In that study, oral energy and absorbed intraperitoneal amino acids were given in a proportion of approximately 200 kcal/g nitrogen. The normal Western diet contains energy and proteins in a proportion of 150 – 200 kcal/g nitrogen. In everyday practice, however, poor appetite can prevent malnourished patients from ingesting enough calories simultaneously with intraperitoneal AAs, which may limit the usefulness of AA solutions to the typical target group.

Dialysate as Food

Anorexia in patients on PD may not allow ingestion of enough calories for optimal utilization of AA solutions. The hypothesis, therefore is, in patients on nocturnal automated peritoneal dialysis (APD), a dialysis solution containing a mixture of AAs and glucose as a part of a regular dialysis schedule could improve protein

metabolism. Standard AA and glucose-containing dialysis solutions were mixed using an automated cycler during a nocturnal APD. In a randomised crossover study, it was found that the mixture of AAs and glucose induced an acute anabolic effect on the protein metabolism; that is, the negative protein balance that is a physiological feature of the fasting state became significantly less negative [20]. This beneficial effect resulted from the combined effect of stimulation of protein synthesis and inhibition of protein degradation. AAs were given in a fixed amount of 27 g (1 bag of 2.5 L 1.1% solution), of which about 40% – 50% was absorbed [27, 28].

The protein gain was estimated to be 13 g of protein per night, which corresponds to roughly 65 g of beef. The proportion of energy and protein given with the dialysis solution varied between 160 and 300 kcal/g nitrogen; in the normal Western diet, this ratio is approximately 150 – 200 kcal/g nitrogen. Whole body turnover, degradation, oxidation, and synthesis of proteins were determined with the precursor ([13C] leucine) method [27, 28]. This metabolic response to intraperitoneal AAs is similar to that of ingesting food ("dialysate as food"). It should be emphasised that it involves acute changes for the duration of the administration of the AA and glucose mixture.

A study was conducted in malnourished patients on PD taking liquid food during the day [29]. The findings of this study supported to the notion that the body handles intraperitoneal and oral AAs in the similar fashion. Even in the fed state, the AA solutions turned out to give an extra stimulus to protein synthesis. When intake of calories is deficient a "two-compartment bag" system with glucose and AAs could provide enough calories for the optimal utilisation of AAs [30].

Other Benefits of Amino Acid Solutions

A non-glucose AA solution has positive effects on the fat metabolism. Plasma cholesterol level and triglyceride level decreased during the use of AA solution for 3 months 6 months, or 3 years [24, 25, 31]. Another 6-month study showed a significant decrease in the total body fat mass during the use of an AA solution, whereas it increased during the use of glucose solutions [32].

Guidelines

The following guidelines should be considered when prescribing AA PD solutions [33]. They are indicated for use only in malnourished or diabetic patients and/or those with recurrent peritonitis. A 1.1 % AA solution consisting of predominantly essential AAs (required by the patients on dialysis) should be used. Sufficient concurrent alternative caloric intake should be guaranteed.

Adverse Events

1. Increase in plasma urea levels is one expected consequence of an increased nitrogen load and due to oxidization of some of the amino acids supplied. In a study

with one AA bag per day, urea levels rose by 28% on average, from 140 to 180 mg/dL in the second month [31]. Thereafter, they slowly decreased. In another study, which used 2 bags per day, plasma urea increased by 46%, reaching 240 mg/dL in one patient [34]. This increased level of azotemia may cause loss of appetite, nausea, and vomiting, mainly with higher concentrations or multiple exchanges. Patients treated with one 1.1% AA exchange usually tolerate it well. Two exchanges should be delivered only to patients with very low protein intake; in these cases, a proportional increase in dialysis dose should be considered.

2. With the use of AA solutions, in particular when 2 bags per day were exchanged metabolic acidosis is reported [35]. It bothers a nephrologist, since acidosis stimulates protein degradation and it is commonly advised to use no more than one bag of 1.1% AA solution per day [36]. Acidosis is caused by metabolism of the sulphur-containing AA methionine and the cationic AAs arginine and lysine–HCl present in the dialysis solution [35, 37]. Dialysate buffer concentrations of 40 mmol/L, can preserve the acid–base homeostasis [38].

3. Dialysate Protein Losses

Several authors have reported that AA solutions induced an increased loss of both macromolecules, such as albumin and IgG, and small molecular weight substances (vide supra) [12]. The increased losses were accompanied by an increased release of prostanoids and proinflammatory cytokines into the peritoneal cavity consistent with an increase in peritoneal blood flow and effective peritoneal surface [39, 40]. In other studies, however, no consistent increase in protein losses or release of prostanoids was found [41].

Conclusions

1. AA solutions can improve the nutritional state of patients on PD with low dietary protein intake.

2. Administration of intraperitoneal AA solutions should be accompanied by a simultaneous intake of food containing sufficient calories.

3. In a subgroup of anorectic patients on PD, dialysates composed of a mixture of AAs and glucose in appropriate proportions can serve as a source of both proteins and calories.

4. In patients on APD, a dialysis solution containing such a mixture as a part of a regular nightly dialysis schedule brings about an acute improvement in the whole body protein metabolism, similar to food. Mixing standard AA and glucose solutions by the cycler can be easily performed in the home situation.

5. Using dialysis solutions with a buffer content of 40mmol/L can preserve acid base homeostasis. 1.1 % AA solutions deliver both ultrafiltration and small molecule clearances equivalent to those achieved with 1.5 % glucose solutions.

6. About 18 g of AAs that is 80% of AAs solution is absorbed in 4 to 6 hours of dwell.

Nutrineal (Baxter Corporation- Product monograph dated July 30, 2012) is a sterile, nonpyrogenic solution of essential, nonessential amino acids and electrolytes (**Table 1**).

Table 1: Composition of Nutrineal

Each 100 mL of Nutrineal contains	
Essential Amino Acids	
Histidine, USP	71.4 mg
Isoleucine, USP	84.9 mg
Leucine, USP	101.9 mg
Lysine (added as Lysine-HCl), USP	95.5 mg
Methionine, USP	84.9 mg
Phenylalanine, USP	57 mg
Threonine, USP	64.5 mg
Tryptophan, USP	27 mg
Valine, USP	139.3 mg
Nonessential Amino Acids	
Alanine, USP	95.1 mg
Arginine, USP	107.1 mg
Glycine, USP	50.9 mg
Proline, USP	59.5 mg
Serine, USP	50.9 mg
Tyrosine, USP	30 mg
Electrolytes	
Calcium Chloride Dihydrate, USP	18.3 mg
Magnesium Chloride Hexahydrate, USP	5.08 mg
Sodium Chloride, USP	538 mg
Sodium Lactate	448 mg
Excipients	
Water for Injection, USP	qs

Hydrochloric acid (for pH adjustment)	qs
Concentration of ions	
Amino Acids	87 mmol/L
Sodium	132 mmol/L
Calcium	1.25 mmol/L
Magnesium	0.25 mmol/L
Chloride	105 mmol/L*
Lactate	40 mmol/L

*Includes additional contributions from lysine hydrochloride and hydrochloric acid used for pH adjustment. pH (adjusted with hydrochloric acid to 6.8)

Calculated osmolarity: approximately 6.6(5.7: 365 mOsm/L).

Nutrineal is available in TWIN BAG® containers holding 2000 mL or 2500 mL and single bag containers holding 2500 mL.

References

1. Kopple, J. D., M. J. Blumenkrantz, M. R. Jones, J. K. Moran, and J. W. Coburn JW, 1982: Plasma amino acid levels and amino acid losses during continuous ambulatory peritoneal dialysis. *Am. J. Clin. Nutr.*, **36,** 395–402.

2. Lindholm, B., and J. Bergstrom, 1992: Nutritional aspects on peritoneal dialysis. *Kid. Int.,* **42,** 165–171.

3. Blumenkrantz, M. J., G. M. Gahl, J. D. Kopple, A. V. Kamdar, M. R. Jones, M. Kessel, and J. W. Coburn, 1981: Protein losses during peritoneal dialysis. *Kid. Int.,* **19,** 593–602.

4. Oreopoulos, D. G., P. Crassweller, and A. Katirtzoglou, 1980: Amino acids as an osmotic agent (instead of glucose) in continuous ambulatory peritoneal dialysis. In: Legrain M, editor. Continuous Ambulatory Peritoneal Dialysis. Amsterdam: *Excerpta Medica,* 335–340.

5. Oreopoulos, D. G., E. Marliss, G. H. Anderson, A. Oren, N. Dombros, P. Williams, R. Khanna, H. Rodella, and L. Brandes, 1983: Nutritional aspects of CAPD and the potential use of amino acid containing dialysis solutions. *Perit. Dial. Bull.,* **3,** 10–15.

6. Williams, P. F., E. B. Marliss, G. H. Anderson, A. Oren, A. N. Stein, R. Khanna, J. Petitt, L. Brandes, H. Rodella, L. Mupas, and N. Dombros, 1982: Amino acid absorption following intraperitoneal administration in CAPD patients. *Perit. Dial. Bull.,* **2,** 124–130.

7. Twardowski, Z. J., R. Khanna, and K. D. Nolph, 1986: Osmotic agents and ultrafiltration in peritoneal dialysis. *Nephron.,* **42,** 93–101.

8. Atkins, P., and P. De Julio, 2006: Physical Chemistry (8th edition.). Oxford: Oxford UP. P.766

9. Oren, A., G. Wu, G. H. Anderson, E. Marliss, R. Khanna, J. Pettit, L. Mupas, H. Rodella, L. Brandes, D. A. Roncari, and G. Kakis, 1983: Effective use of amino acid dialysate over four weeks in CAPD patients. *Perit. Dial. Bull.,* **3,** 66–73.

10. Goodship, T. H. J., S. Lloyd, P. W. McKenzie, M. Earnshaw, I. Smeaton, K. Bartlett, M. K. Ward, and R. Wilkinson, 1987: Short-term studies on the use of amino acids as an osmotic agent in continuous ambulatory peritoneal dialysis. *Clin. Sci.,* **73,** 471–478.

11. Lindholm, B., A. Werynsky, and J. Bergstrom, 1988: Peritoneal dialysis with amino acid solutions: fluid and solute transport kinetics. *Artif. Organs,* **12,** 2–10.

12. Young, G. A., J. B. Dibble, A. E. Taylor, S. Kendall, and A. M. Brownjohn, 1989: A longitudinal study of the effects of amino acid-based CAPD fluid on amino acid retention and protein losses. *Nephrol. Dial. Transplant.,* **4,** 900–905.

13. Young, G. A., S. Kendall, and A. M. Brownjohn, 1993: Complement activation during CAPD and the generation of prostaglandin E2. *Nephrol. Dial. Transplant.,* **8,** 1372–1375.

14. Steinhauer, H. B., I. Lubrich-Birker, R. Kluthe, G. Baumann, and P. Schollmeyer, 1992: Effects of amino acid based dialysis solution on peritoneal permeability and prostanoid generation in patients undergoing continuous ambulatory peritoneal dialysis. *Am. J. Nephrol.,* **12,** 61–67.

15. Douma, C. E., D. R. de Waart, D. G. Struijk, and R. T. Krediet, 1996: Effect of amino acid based dialysate on peritoneal blood flow and permeability in stable CAPD patients: a potential role for nitric oxide? *Clin. Nephrol.,* **45,** 295–302.

16. Kopple, J. D., D. Bernard, J. Messana, R. Swartz, J. Bergström, B. Lindholm, V. Lim, G. Brunori, M Leiserowitz, D. M. Bier, and L. D. Stegink, 1995: Treatment of malnourished CAPD patients with an amino acid based dialysate. *Kid. Int.,* **47,** 1148–1157.

17. Faller, B., M. Aparicio, D. Faict, C. De Vos, V. De Precigout, N. Larroumet, R. Guiberteau, M. Jones, and F. Peluso, 1995: Clinical evaluation of an optimized 1.1% amino acid solution for peritoneal dialysis. *Nephrol. Dial. Transplant.*, **10,** 1432–1437.

18. Jones, M. R., T. Hagen, E. Vonesh, J. Moran, 1995: Use of a 1.1% amino acid solution to treat malnutrition in peritoneal dialysis patients (abstract). *J. Am. Soc. Nephrol.,* **6,** 580.

19. Tiiong, H. L., R. Swart, J. W. van den Berg, and M. W. Fieren, 2009: Amino Acid based peritoneal dialysis solutions for malnutrition: New perspectives. *Perit. Dial. Int.,* **29,** 384-393.

20. Park, M. S., O. Heimburger, J. Bergstrom, J. Waniewski, A. Werynski, and B. Lindholm, 1993: Peritoenal transport during dialysis with amino acid-based solutions. *Perit. Dial. Int.,* **13,** 280–288.

21. Makku, A., V. Kirsi, N. Kjell, S. Helin, J. Knuuti, P. Nuutila, and K. Metsärinne, 2002: Amino acid based peritoneal dialysis solution improves amino acid transport into skeletal muscle. *J. Am. Soc. Nephrol.,* **13,** 205A.

22. Garibotto, G., A. Sofia, A. Canepa, S. Saffioti, P. Sacco, M. R. Sala, L. Dertenois, N. Pastorino, G. Deferrari, and R. Russo, 2001: Acute effects of peritoneal dialysis with dialysates containing dextrose or dextrose and amino acids on muscle protein turnover. *J. Am. Soc. Nephrol.,* **12,** 557–567.

23. Grzegorzewska, A. E., I. Mariak, A. Dobrowolska-Zachwieja, and L. Szajdak, 1999: Effects of amino acid dialysis solution on the nutrition of continuous ambulatory peritoneal dialysis patients. *Perit. Dial. Int.,* **19,** 462–470.

24. Misra, M., D. Reaveley, J. Ashwaorth, B. Muller, M. Seed, and E. A. Brown, 1997: Six-month prospective cross-over study to determine the effects of 1.1% amino acid dialysate in lipid metabolism in patients on continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **17,** 279–286.

25 Li, F. K., L. Y. Chan, and J. C. Woo, 2003: A3-year, prospective, randomized, controlled study on amino acid dialysis inpatients on CAPD. *Am. J. Kid. Dis.,* **42,** 173–183.

26. Park, M. S., S. R. Choi, Y. S. Song, S. Y. Yoon, S. Y. Lee, and D. S. Han, 2006: New insight of amino acid-based dialysis solutions. *Kid. Int.,* **70,** 110–114.

27. Delarue, J., C. Maingourd, M. Objois, M. Pinault, R. Cohen, and C. Couet, 1999: Effects of an amino acid dialysate on leucine metabolism in continuous ambulatory peritoneal dialysis patients. *Kid. Int.,* **56,** 1934–1943.

28. Tjiong, H. L., J. W. Van den Berg, J. L. Wattimena, T. Rietveld, L. J. Van Dijk, and A. M. Van der Wiel, 2005: Combined amino acid and glucose dialysate improves protein anabolism in renal failure patients on automated peritoneal dialysis. *J. Am. Soc. Nephrol.,* **16,** 1486–1493.

29. Canepa, A., A. Carrea, S. Menoni, E. Verrina, A. Trivelli, and R. Gusmano, 2001: Acute effects of simultaneous intraperitoneal infusion of glucose and amino acids. *Kid. Int.,* **59,** 1967–1973.

30. Tjiong, H. L., T. Rietveld, J. L. Wattimena, J. W. van den Berg, D. Kahriman, and J. van der Steen, 2007: Peritoneal dialysis with solutions containing amino acids plus glucose promotes protein synthesis during oral feeding. *Clin. J. Am. Soc. Nephrol.,* **2,** 74–80.

31. Bruno, M., C. Bagnis, M. Marangella, L. Rovera, A. Cantaluppi, and F. Linari, 1989: CAPD with an amino acid dialysis solution: A long-term, cross-over study. *Kid. Int.,* **35,** 1189–1194.

32. Maurer, O., H. Saxenhofer, and P. Jaeger, 1996: Six-month overnight administration of intraperitoneal amino acids not improved lean mass. *Clin. Nephrol.,* **45,** 303–309.

33. Faller, B. 1996: Amino acid-based peritoneal dialysis solutions. Kid. Int. Suppl., **56,** 81.

34. Bruno, M., C. Bagnis, D. Cosseddu, A. Tricerri, L. Rovera, and F. Linari, 1992: CAPD con aminoacid: Due mesi a scambialterni in 5 pazienti [Abstract]. *G. Ital. Nephrol.,* **2,** 92.

35. Kopple, J. D., D. Bernard, J. Messana, R. Swartz, J. Bergström, and B. Lindholm, 1995: Treatment of malnourished CAPD patients with an amino acid based dialysate. *Kid. Int.,* **47,** 1148–1157.

36. European Best Practice Guideline Working Group on Peritoneal Dialysis. Peritoneal dialysis solutions. *Nephrol. Dial. Transplant.,* 2005; **20,** 16–20.

37. Arfeen, S., T. H. J Goodship, A. Kirkwood, and M. K. Ward, 1990: The nutritional/metabolic and hormonal effects of 8 weeks of continuous ambulatory peritoneal dialysis with a 1% amino acid solution. *Clin. Nephrol.,* **33,** 192–199.

38. Tjiong, H. L., R. Swart, J. W. van den Berg, and M. W. Fieren, 2009: Amino Acid based peritoneal dialysis solutions for malnutrition: new perspectives. *Perit. Dial. Int.,* **29,** 384-393.

39. Rippe, B., and D. Venturoli, 2007: Peritoneal transport kinetics with amino acid-based and glucose-based peritoneal dialysis solutions. *Perit. Dial. Int.,* **27**, 518–522.

40. Plum, J., A. Fussholler, G. Schoenicke, T. Busch, C. Erren, and C. Fieseler, 1997: In vivo and in vitro effects of amino-acidbased and bicarbonate-buffered peritoneal dialysis solutions with regard to peritoneal transport and cytokines/ prostanoids dialysate concentrations. *Nephrol. Dial. Transplant.,* **12**, 1652–1660.

41. Olszowska, A., J. Waniewski, A. Werynski, B. Anderstam, B. Lindholm, and Z. Wankowicz, 2007: Peritoneal transport in peritoneal dialysis patients using glucose-based and amino acid based solutions. *Perit. Dial. Int.,* **27**, 544–553.

Chapter 16

Automated Peritoneal Dialysis

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Automated Peritoneal Dialysis

Introduction

Peritoneal dialysis (PD) that is performed using a cycler to fill the peritoneal cavity is called Automated Peritoneal Dialysis (APD). The volume and the duration of the exchanges can be adjusted on the cycler, as per the prescription. It is usually done at night to facilitate better social functioning during the day and is particularly apt in working men and women and school going children. APD is also suitable in neonates.

Types of APD

Nocturnal intermittent PD (NIPD) - only exchanges at night, the peritoneum is dry during the day

Continuous cyclic PD (CCPD) – there is a day time fill in addition to the night time exchanges

Where is APD indicated?

1. Inability to obtain adequate ultra filtration and solute clearance by continuous ambulatory peritoneal dialysis (CAPD).
2. Necessity to avoid high intra peritoneal pressures.
3. Patient preference.

What are the advantages of APD?

Use in children: APD has been particularly useful in children. In a study in Mexican children where 458 children were treated over a period of three years, APD was associated with better ultra filtration, lesser requirement for anti-hypertensive, decreased incidences of peritonitis rates and hospitalization [1]. It was also noted that there was an increased school attendance from 62% on CAPD to 82% on APD.

Better quality of life: In APD, the time spent on the performing the dialysis is the least when compared to hemodialysis (HD) or CAPD .Hemodialysis requires 18 hours therapy time along with travel time per week, while CAPD requires 18 hours per week at home, when using 4 exchanges and 14 hours when using 3 exchanges, APD on the other hand requires about 20 -30 minutes at night and 5-10 minutes in the mornings, if a midday exchange is added then another additional 30 mins per day, thus only 4.5 -9 hours per week is required. The free time can be used for recreational activities, work and family. It has been noted in a multicentre trial from Netherlands with 37 patients on APD and 59 patients on CAPD, that ocial activity and mental quality of life were better in patients on APD [2].

Better Compliance to Therapy: Patients on APD are more complaint due to lesser connections. Studies have estimated that CCPD patients are 80% complaint when

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compared to patients on CAPD, compliance rates with 4 exchanges and 5 exchanges are 53% and 40%, respectively [3].

Is there a decreased rate of peritonitis when using APD?

APD has been associated with a decreased rate of peritonitis in a majority of studies [4], with nine studies showing lesser rate of peritonitis in APD, though two studies showed increased rate when compared to CAPD, while two showed no significant difference between the two modalities. In an Indian study, CAPD was associated with higher rates of peritonitis when compared to APD [5].

However, there is no change in the exit sites infection rates among CAPD and APD patients, other complications like catheter leaks, umbilical and inguinal hernias and hydrothorax , also occur in both APD and CAPD and there is no significant difference in their incidences [6].

Is Patient Survival and Technique Survival Better with APD?

In a study of more than 4000 patients on PD in Australia and New Zealand over a period of 5 years, there was no difference in the patient survival, between CAPD and APD groups [7]. The same study also did not show any difference between technique survival between APD and CAPD. The Indian study also did not show any increase in technique survival on APD [5].

However, a Mexican study showed better technique survival with APD [8]. This was reinforced by a study in the USA, and also in the Chinese population [9, 10].

What are the Disadvantages of APD?

Decline in residual renal functions (RRF): APD has been traditionally associated with a more progressive loss of residual renal functions (RRF) than CAPD [11, 12]. However, there are several studies which show that RRF decline is not significantly different from that of CAPD. A study with 1032 PD patients, did not show any difference in RRF decline [13] .In another study with 70 CAPD patients and 114 CCPD patients ,the median slope of GFR loss for the entire group was 0.17 mL/min/month and there was no significant difference between the two [14]. Similar trends were noted in an Indian study [5].

Effect on Sodium Removal

The extracellular removal of sodium is less than the water in APD due to sodium sieving with shorter dwell. It has been seen that mean sodium removal per liter of ultra filtrate is 74 mmols in APD, and 121.2 mmols in CAPD (depending on the dwell time and prescription). Thus, rapid exchanges on cycler, will result in lower sodium removal, the result is that the patient will wake up thirsty and hence, there is an increased consumption of fluids resulting in an increased volume overload [15]. Increased loss of protein: APD is associated with somewhat higher 24-hour dialysate protein loss when compared to CAPD patients [16].

Adequacy of APD

The minimum delivered dose of total small-solute clearance is peritoneal KT/V urea of ≥1.7 per week. If the patient has residual urine > 100 ml, then it is considered as a part of the patient's total weekly solute clearance.

As the diffusion of creatinine is slower than that of urea in with short exchanges, in slow transport patients, it will result in disproportionately low peritoneal creatinine clearance. Thus, additional target of 45 L/week (in APD) have been recommended, though the current KDOQI guidelines do not have the creatinine clearance recommendations.

Minimum target for peritoneal net UF in anuric patients is 1.0 L/day; as recommended by the European best practice guidelines.

The recommendations by the various societies are tabulated below: (**Table 1**)

Table 1: Recommendations in Various Guidelines

	Weekly total Kt/V	**Weekly total Creatinine clearance**	**Continuous treatment**	**UF (per day)**
KDOQI(2006) [17]	≥1.7	NR	Yes	NR
ISPD (2006) [18]	≥1.7	APD >45L	Yes	NR
European Best Practice Guidelines (2005) [19]	≥1.7	APD>45L for patients with frequent short exchanges and slow transport status	NR	1.0L
UK Renal Association(2007) [20]	≥1.7	≥50L	NR	≥750ml
Indian Guideline (2007) [21]	≥1.7	≥45L	Yes (anuric patients)	NR

The optimal duration of performing the solute clearance and peritoneal equilibrium test (PET) has been summarized in the following table. (**Table 2).**

Table 2: Optimal Duration of Solute Clearance and Peritoneal Equilibrium Test

Assessment	Frequency
Kt/V_{urea} Total (RRF +PD) clearance	After the first month on PD [17] Repeat when PD prescription or clinical status changes (but no less than every 6 months)
PET	4 - 8 weeks after initiation of PD [18] Thereafter whenever clinically indicated
Residual Renal Function (RRF) [If urine output > 100ml/24hr]	Every 2 months [17]

What are the Methods to Increase the Clearance in APD?

The methods include;

1. increasing the fill volume,
2. increasing the number of exchanges and
3. addition of a day time fill.

Increasing the Fill Volume and Exchanges

Increasing the fill volume is better for increasing clearance in APD than increasing the number of exchanges. Increasing the fill volume did not result in significant discomfort to the patient and also tolerance of the fill volume was not related to the body size [22]. It was also seen that recumbancy in APD favours larger volumes of solution for higher dialysis dose at lower intra peritoneal pressures. Both recumbancy and higher volumes permit better contact between dialysate and the peritoneal membrane which may increase solute removal.

Addition of a Day Time Fill

The last fill on the cycler provides an opportunity to individualize the daytime component of the therapy in APD. This is of particular importance for adequate clearance and Ultra filtration. The last dwell can be the same dextrose solutions that are being used in the night exchanges or it can be a different concentration of dextrose solution, it could also be an icodextrin solution. The choice of the day time fill will depend on the clearance and ultra filtration that is needed to be achieved.

The disadvantage of having a day time dwell is that the solution is in the peritoneum for a longer period of time when compared to CAPD; hence there is a high risk of absorption of the fluid.

Initiation of RRT with APD

APD has been used initiate patient on to dialysis in America and Europe. It has been driven more by the patient convenience than any medical indications. A retrospective study comparing the results of acute unplanned start of dialysis using APD *vs.* a planned start, found that outcomes were the same, though mechanical complications were significantly higher with an unplanned start [23].

References

1. Rabindranath, K. S., J. Adams, T. Z. Ali, C. Daly, L. Vale, and A. M. Macleod, 2007: Automated *vs.* continuous ambulatory peritoneal dialysis: A systematic review of randomized controlled trials. *Nephrol. Dial. Transplant.,* 22, 2991–2998.

2. R. F. Velasco, J. L. Muñoz, V. S. Saavedra, J. E. Mena Brito Trejo, A. R. Qureshi, E. J. García-López, and C. D. Filho, 2008: Automated peritoneal dialysis as the modality of choice: a single-center, 3-year experience with 458 children in Mexico. *Pediatr. Nephrol.,* 23, 465-471.

3. de Wit, G.A., M. P. Merkus, R. T. Krediet, and F. T. de Charro, 2001: A comparison of quality of life of patients on automated and continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* 21, 306–312.

4. Bernardini, J., M. Nagy, and B. Piraino, 2000: Pattern of noncompliance with dialysis exchanges in peritoneal dialysis patients. *Am. J. Kid. Dis.,* 35, 1104-1110.

5. Rao, C. S. S., P. Charan, G. D. Naidu, G. Swarnalatha, R. Ram, and K. V. Dakshinamurty, 2013: A 2-year follow-up study of patients on automated peritoneal dialysis. *Ind. J. Nephrol.,* 23, 327–331.

6. C. W. de Fijter, L. P. Oe, J. J. Nauta, M. J. van der, H. A. Verbrugh, J. Verhoef, and J. M. Danker, 1994: Clinical efficacy and morbidity associated with continuous cyclic compared with continuous ambulatory peritoneal dialysis. *Ann. Intern. Med.,* 120, 264-271.

7. Badve, S.V., C. M. Hawley, S. P. McDonald, D. W. Mudge, J. B. Rosman, F. G. Brown, and D. W. Johnson, 2008: Automated and continuous ambulatory peritoneal dialysis have similar outcomes. *Kid. Int.,* 73, 480–488.

8. Sanchez, A.R., C. Madonia, and R. A. Rascon-Pacheco, 2008: Improved patient/technique survival and peritonitis rates in patients treated with automated peritoneal dialysis when compared to continuous ambulatory peritoneal dialysis in a Mexican PD center. *Kid. Int.,* 73, 76–80.

9. Mujais, S., and K. Story, 2006: Peritoneal dialysis in the U.S.: evaluation of outcomes in contemporary cohorts. *Kid. Int.,* 70, 21–26.

10. Sun, C. Y., C. C. Lee, Y. Y. Lin, and M. S. Wu, 2011: In younger dialysis patients, automated peritoneal dialysis is associated with better long-term patient and technique survival than is continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* 31, 301–307.

11. Hiroshige, K., K. Yuu, T. M. Soejima, M. Takasugi, and A. Kuroiwa, 1996: Rapid decline of residual renal function in patients on automated peritoneal dialysis. *Perit. Dial. Int.,* 16, 307-315.

12. Hufnagel, G., C. Michel, G. Queffeulou, H. Skhiri, H. Damieri, and F. Mignon, 1999: The influence of automated peritoneal dialysis on the decrease in residual renal function. *Nephrol. Dial. Transplant.,* 14, 1224-1228.

13. Moist, L. M. P., 2000: Predictors of loss of residual renal function among new dialysis patients. *J. Am. Soc. Nephrol.,* 11, 556–564.

14. Holley, J. L., J. Bernardini, and B. Piraino, 1990: Continuous cycling peritoneal dialysis is associated with lower rates of catheter infections than continuous ambulatory peritoneal dialysis. *Am. J. Kid. Dis.,* 16, 133–136.

15. Rippe, B., and L. Levin, 2000: Computer simulations of ultra filtration profiles for an Icodextrin-based peritoneal fluid in CAPD. *Kid. Int.,* 57, 2546–2556.

16. Westra, W. M., J. D. Kopple, R. T. Krediet, M. Appell, and R Mehrotra, 2007: Dietary protein requirements and dialysate protein losses in chronic peritoneal dialysis patients. *Perit. Dial. Int.,* 27, 192–195.

17. NKF-K/DOQI, 2006: Clinical practice guidelines for peritoneal dialysis adequacy. Guideline 2. Peritoneal dialysis solute clearance targets and measurements. *Am. J. Kid. Dis.,* 49, 103–116.

18. Lo, W. K., M. J. Bargman, J. Burkart, R. T. Krediet, C. Pollock, H. Kawanishi, and P. G. Blake, 2006: Guideline on targets for solute and fluid removal in adult patients on chronic peritoneal dialysis. ISPD Guidelines/Recommendations. *PDI,* 26, 520-522.

19. European Best Practice Guidelines working group on Peritoneal Dialysis, 2005: Adequacy of dialysis. *Neprol. Dial. Transpl.,* 2005; 20, 24–27.

20. Davies, S., 2007: Clinical Practice Guidelines: 3b - Peritoneal Dialysis UK Renal Association Clinical Practice Guidelines; 5th Edition.

21. Adequacy of PD Prescription and Membrane Transport Characteristics. India Peritoneal Dialysis Practice Guidelines 2007. Chapter 3. Peritoneal Dialysis Society of India

22. Sarkar, S., J. Bernardini, L. Fried, J. R. Johnston, and B. Piraino, 1999: Tolerance of large exchange volumes by peritoneal dialysis patients. *AJKD,* 33, 1136-1141.

23. J. V. Povlsen, and P. Ivarsen, 2006: How to start the late referred ESRD patient urgently on chronic APD. *Nephrol. Dial. Transplant.,* 21, 56–59.

Chapter 17

Tidal Peritoneal Dialysis

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Tidal Peritoneal Dialysis

The concept of tidal peritoneal dialysis

An automated peritoneal dialysis (APD) session usually extends for 8–10 hours and involves 3–15 cycles per therapy, depending on the modality. Each cycle is comprised of a dialysate inflow, a dwell (30–120 min), and the dialysate outflow time. The dialysate outflow occurs in two phases. Up to 80% of dialysate is usually drained within the first (fast) phase in a few minutes. The remaining part of the outflow volume is drained in the second (slow) phase. The slow segment contributes little to the dialysis efficacy as only a little amount of dialysate is in contact with the peritoneal membrane, but more time is needed in draining this last part of the outflow volume. The point in time between the first (fast) and second (slow) outflow phase is called 'transition point' or 'breakpoint' [1].

When trying to increase the dialysate flow (treatment volume/per time) during therapy on a cycler, the duration of each dwell declines. In such a scenario, the time spent for inflow and outflow of dialysate becomes a significant issue in the total treatment.

Durand *et al*. [2] showed that with high dialysate flows, a maximal treatment volume (maximal effective dialysate flow) is attained, where clearances do not change *i.e*. increase or even decrease, because dwell times become too short for significant diffusion to occur. The maximal dialysate flow varies according to the molecular weight of uremic toxins and is therefore reached earlier for larger than for smaller molecules.

The idea of draining only a part of the initial fill volume and replacing it with fresh or regenerated dialysate fluid after short dwell times was first described by Stephen in the late 1970s as 'reciprocating peritoneal dialysis' [3]. It was named 'semi continuous peritoneal dialysis' by Di Paolo [4]. At the same time, the better efficiency of this technique when compared to other modalities of peritoneal dialysis (PD) was also demonstrated in an animal study (using 20% exchange volume) [5]. In the subsequent years, attention was diverted from this kind of treatment to other modalities of PD, especially to continuous ambulatory peritoneal dialysis (CAPD), which was much more convenient to handle. In an attempt to increase efficiency of PD, in the late 1980s and early 1990s, there was renewed interest in the cycler technique, mentioned earlier, which was modified and named tidal peritoneal dialysis (TPD) by Twardowski [6, 7].

Tidal peritoneal dialysis (TPD) was described as a technique in which an initial infusion of dialysate fluid into the peritoneal cavity is followed, after a short dwell time (of varying duration), by drainage of only a part of the dialysate fluid (the tidal drain volume). Part of the dialysate fluid (the reserve volume) remains in constant contact with the peritoneal membrane. The tidal drain out volume is replaced with

fresh dialysate fluid (the tidal fill volume) to restore the initial intra-peritoneal volume with each cycle (the tidal cycle). At the termination of the dialysis session, the entire volume of dialysate is drained as completely as possible [8].

Rationale for TPD

The reasoning behind the idea of tidal peritoneal dialysis was to improve the efficacy of the dialysis technique by decreasing time lost during inflow and outflow of the dialysate fluid and to improve solute clearances because of the continuous contact between dialysate fluid and the peritoneal membrane [7]. It has been shown that, in intermittent peritoneal dialysis (IPD), the time required for performing the exchanges can account for 35% – 55% of the total time on dialysis. The end result is a loss of efficiency of the dialysis technique. The exchanges take up about 15% of the total time on dialysis, on TPD [9]. Moreover, in TPD, the continuous contact between dialysate fluid and peritoneal membrane avoids the dry periods that occur in IPD during exchanges. Sustained diffusion of solutes across the peritoneal membrane is thus sustained in TPD. It was felt that these two factors would potentially lead to improved clearances in TPD. It would diminish the length of time needed to achieve a similar dialysis adequacy, thus improving the dialysis efficiency [9].

Comparison of clearances between TPD and non- tidal APD

Small solute clearance

In the early 1990s, after the conceptualization of TPD, initial studies comparing the adequacy of various APD techniques reported favourable results for TPD regarding improvement of dialysis efficiency.

Flanigan *et al*. showed similar creatinine and urea nitrogen clearances with 8 hour intermittent TPD, compared to continuous cyclic peritoneal dialysis (CCPD) with 10 hour treatment time at night. The treatment volume was 9.5 l/session in CCPD and 16 l/session in TPD. Thus, the enhancement in dialysate flow during TPD played a substantial part in improving solute clearances [10].

In another study, Flanigan demonstrated that TPD proffered better creatinine clearances and Kt/V values than CCPD when the dialysate flow was increased from 30 to 50 ml/kg/h, again a volume much higher than in CCPD [11].

Ho ltta *et al*. showed significantly higher creatinine clearances, similiar Kt/V values, and phosphate loss into the dialysate fluid in children with high (H)/ high average (HA) peritoneal transport characteristics, during TPD (50% tidal volume, 50% TPD) when compared to CCPD [12].

Ferna´ndez Rodrı´guez *et al.* found in their study that 50% TPD with wet daytime led to higher creatinine and urea nitrogen clearances than CCPD [13].

In a study by Edefonti *et al*., 7 pediatric patients were treated with nightly intermittent peritoneal dialysis (NIPD) for 15 months and then with TPD for 13.7 months. They reported a significant enhancement of creatinine and urea clearances during TPD as compared to NIPD [14]. In all these four studies, dialysate flow during TPD was significantly higher than during non-tidal APD. [11, 12, 13, 14].

Studies comparing CAPD with TPD also showed similar or superior clearances with TPD [7, 13, 15, 16]. The difference in dialysate fluid treatment volumes between CAPD and TPD patients was even larger than in the previously quoted studies, making interpretation of these results difficult.

Thus, all the initial studies showed that TPD with a rather high dialysate flow is more or at least as efficient as other modalities of PD, but they could not provide an answer to the important query- does the tidal mode, independent of other variables (e.g. dialysate flow), increases efficiency of PD. This query could be only answered when TPD and non-tidal APD are compared under identical conditions.

Balaskas *et al*. in a cross- over study, treated 12 patients with TPD and intermittent peritoneal dialysis (IPD) for 3 months each [17]. Treatment volume and treatment time were identical for both the treatments (dialysate flow about 4 l/h). No differences were seen in the biochemical parameters (serum sodium, potassium, calcium, phosphate, urea, creatinine total protein, and albumin) or haematological indices (hemoglobin, hematocrit) between the two treatment groups. Clearances were, however, not measured.

Steinhauer *et al*. compared IPD and 50% TPD with identical mean dialysate volumes (23 l), treatment time (7.5 h), dialysate fluid glucose concentration and total fill volume per cycle (1.5 or 2 l), in 6 patients. They found a significantly increased phosphate clearance during TPD, but clearances of creatinine, urea and potassium were similar between the two treatment modalities [18].

Piraino *et al*. also compared 50% TPD and IPD in six patients and no significant differences were found in clearances of urea nitrogen, creatinine, phosphate, and potassium, when identical dialysate flow rate (3.7 l/h for IPD, 3.8 l/h for TPD), initial fill volume (2 l), and dialysate fluid glucose concentration (1.9 g/dl on average) was used [19].

Quellhorst *et al*. treated 12 patients with TPD and IPD (10 months of each) using a treatment volume of 60 l/cycler therapy and a similar composition of dialysate in both the sessions [20]. Along with a 25% reduction in treatment time, TPD provided significantly better urea and creatinine clearances than IPD and decreased serum phosphate levels as well. Serum parathyroid hormone levels tended to normalize during TPD but remained high in IPD patients.

Though, the later studies compared TPD and non-tidal APD under nearly identical conditions, nearly all of them used dialysate flow rates of 3.5–5 l/h; flow rates which are not usually prescribed in patients undergoing APD at home. There are

only a handful of studies investigating efficiency of TPD with lower dialysate flow rates [21].

In a multicenter study conducted in Spain, patients underwent treatment with either CAPD, CCPD or TPD for 2 months each [16]. The treatment volume (14–15 l/night, 1.8–2.0 l/daytime) was similar between CCPD and TPD. Urea nitrogen and creatinine clearances were found to be significantly lower with CAPD compared to all the APD techniques. Within the APD modalities, urea clearances were seen to be highest on CCPD. Creatinine clearances were similar between CCPD and 50% TPD.

Aasarød *et al*. in a study on six patients (all H/ HA transporters), found that with a treatment volume of 10 l (fill volume 2 l and treatment time 9 h), clearances of urea, creatinine and uric acid were seen to be higher with IPD than with 50% TPD [22]. After increasing the treatment volume to 14 or 24 l, no definite difference was seen between the two modalities of treatment.

Vychytil *et al*. demonstrated similar creatinine and phosphate clearances and higher urea nitrogen clearances with non-tidal APD (IPD), when compared to 50% TPD, using a dialysate flow of 1.7 l/h (15 l/9 h). The initial fill volume (2500 ml) and also the dialysate glucose concentration (1.36%) were similar with both the treatments. Even after enhancing the dialysate flow rate to 3 l/h (30 l/10 h), no significant difference could be delineated in small solute clearances between the two treatment modalities [23].

Juergensen *et al*. using dialysate volumes of 15 or 24 l, showed comparable Kt/V and creatinine clearances values between 50% TPD and non-tidal APD (fill volume 25–35 ml/kg and treatment time 9.5 h for both the modalities) [24].

In a more recent study on 10 patients, Juergensen *et al*. demonstrated that during non-tidal APD, creatinine clearances increased by 27% and phosphate clearances by 19% when the night time dialysate volume was enhanced from 14 to 24 l. With TPD, an enhancement of treatment volume to 24 l also showed higher creatinine and phosphate clearances. However, the values achieved on TPD were less than those achieved with the 24 l non-tidal APD regimen [25].

Therefore, it may be inferred from the majority of studies, that in patients having APD at home, there is no evidence that TPD has an advantage over other modalities of PD in improving small solute clearances, provided that glucose concentration, fill volume and dialysate flow are kept constant.

Middle molecule clearance

Vychytil *et al*. studied clearances of larger molecules in TPD and conventional APD (IPD). There was no difference in b2-microglobulin clearances between low (1.7 l/h) or high dialysate flow (3 l/h) in both APD modalities when duration of

treatment, glucose concentration, dialysate volume and fill volume were kept constant [23].

Comparison of protein loss between TPD and non- tidal APD

Steinhauer *et al*. showed that protein loss was markedly higher in TPD as compared to IPD [18]. In contrast, Ho ltta *et al*. in his study on paediatric patients found that total albumin losses in the dialysate on CCPD and TPD were identical [12]. Perez *et al*. found that there was no difference in protein loss when comparing non-tidal APD (5 x 2, 7 x 2 and 9 x 2 l) and 50% TPD (treatment volume 14 l) [26].

Comparison of Sodium Removal and Ultrafiltration between TPD and Non- tidal APD

Most studies focus on solute clearance but factors such as sodium removal and ultrafiltration have a significant effect on patient's morbidity and mortality [21]. Steinhauer *et al*, in a study on 6 patients, showed that TPD resulted in significantly better ultrafiltration than IPD, provided treatment time, dialysate volume and dialysate glucose concentration were identical (mean dialysate flow was 3.1 l/h) [18].

Contrary to this, in the study by Aasarød *et al*., on 6 patients with H/ HA peritoneal transport rates, when a treatment volume of 10 or 14 l was used, peritoneal ultrafiltration was higher with IPD than with TPD (treatment time 9 h). However, when dialysate volume was increased to 24 l, there was no remarkable difference between the two modalities [22].

In the Spanish multicentre study, peritoneal ultrafiltration was found to be similar between CAPD, CCPD, 25% TPD, and 50% TPD [16].

Sodium removal is less in APD when compared to patients with CAPD because of the phenomenon of sodium sieving, which occurs early in the dwell phase. During this initial phase of the dwell time, transcellular water transport is high, through aquaporin channels, which results in peritoneal removal of relatively greater water than sodium. In the later phase, diffusive and convective sodium transport into the peritoneum increases continuously. Therefore, sodium sieving is seen more during short dwell times. It has to be taken into consideration that, treatment regimes with high dialysate flow and short dwell times may be associated with less sodium elimination, even if they have greater small solute clearances [21]. Only a sparse number of studies have focussed on sodium removal in patients on TPD.

Quellhorst *et al*., compared IPD and TPD in which he used a very high dialysate flow (60 l/session and observation period 10 months/ treatment modality) [20]. Sodium elimination was seen to be higher with TPD, but results of peritoneal ultrafiltration were not mentioned.

Vychytil *et al*, compared sodium removal and ultrafiltration in low flow (1.7l/h) and high flow (3l/h) regimes between IPD and TPD [23]. In low (L)/ low average (LA)

transporters, peritoneal ultrafiltration tended to be lesser during TPD compared to IPD (not statistically significant). There was no significant difference in sodium removal between the two treatment regimens either with the low dialysate or with the high dialysate flow. The evidence, therefore, suggests a possible benefit of TPD when compared to non-tidal APD when the dialysate flow rate is enhanced (as in L/ LA transporters).

Comparison of Host Defence between TPD and Non- tidal APD

It may be conjectured that, the function of granulocytes and peritoneal macrophages may be better in TPD, when compared to non-tidal APD. The reason is that only a little part of fresh, bio-incompatible solution is being mixed with the reserve volume, with a higher pH. Moreover, because of the presence of a reserve volume during the cycles, washout of cells, opsonins and antibodies may be expected to be less in this modality when compared to non-tidal APD [21].

de Fijter *et al.* did a randomised crossover trial in which he studied the function of peritoneal macrophages procured during a 3 hour CCPD and a 3 hour 50% TPD session in 8 patients [27]. The pH of the dialysate fluid was marginally higher during TPD (pH 6–7) than during IPD (pH 5–7), but osmolality was found to be similar between the two modalities. Dialysate cytotoxicity for peritoneal mesothelial cells was less marked during TPD than during CCPD. The uptake of *Escherichia coli* was definitely better in TPD-derived macrophages when compared to CCPD, but there was no remarkable difference in uptake of *Staphylococcus epidermidis*, killing capacity and chemiluminescence response of *S. epidermidis* or *E. coli*. The total IgG and white blood cells lost in the dialysate effluent was also same in TPD and CCPD.

Balaskas *et al*., noted the incidence of peritonitis rates in the two treatment modalities. Two episodes of peritonitis were noted in 12 patients during 12 weeks of TPD, compared to no infection during IPD treatment [17]. Of course, definitive conclusions should not be drawn in view of the small patient numbers and the short period of observation.

It may be inferred that there is a small advantage of TPD when compared to non-tidal APD with regards to the preservation of peritoneal host defences but whether this would translate to less rates of peritonitis is still uncertain.

Comparison of Various Tidal Volumes and Efficacy

Juergensen *et al*., assessed small solute clearances in 10%, 25% and 50% TPD, and compared it with non-tidal APD [24]. For the treatment regimes, a fill volume of 2 l, a total dialysate volume of 15 l was utilised over 9.5 hours. Peritoneal Kt/V and creatinine clearances were lesser during 10% TPD and 25% TPD than with 50% TPD or non-tidal APD.

Subsequently, he used 24 l/sessions and found that peritoneal Kt/V and creatinine clearances tended to be lower with 25% TPD when compared with both 50% TPD and non-tidal APD (10% TPD was not done in this subgroup). The differences noted were not statistically significant, which could be attributed to the small patient numbers.

It may be concluded that when kinetic studies are done, in a totally supervised setting, the duration of dialysis is fixed and total dialysate volume is controlled, TPD does not significantly improve the efficacy of the dialysis regime when compared with APD, at least in dialysate volumes up to 24 L. Leaving aside theoretical considerations, the ideal tidal volume is > 50%.

Patient Comfort Factor with TPD

Dialysate outflow pain

Juergensen *et al*. noted that abdominal pain was reported by 13% of the 136 patients on chronic PD during the phase of initial fill or at the time of outflow from the peritoneal cavity. All the patients were free of pain after switching to TPD [28].

Ho ltta *et al*. in his study on children reported that 3 of 17 (23%) patients complained of pain induced by dialysis during non-tidal APD, but again the pain was found to be alleviated in all the patients after switch to TPD [12].

A case report also elucidates the use of TPD in a pregnant patient on PD, who had symptoms of pain during drainage of the PD fluid [29]. TPD with increased total dialysate volumes improved solute clearance and also relieved abdominal symptoms. Furthermore, Farmer *et al*. reported a case of TPD used in a patient who had diffuse peritoneal calcification as a consequence of severe secondary hyperparathyroidism [30]. Abdominal pain and a haemorrhagic dialysate effluent were reported in the patient. TPD was commenced and after 4–5 days, the dialysate effluent became clear and remained free of blood. Pain improved remarkably. The benefit may be explained by the fact, that the presence of reserve fluid continuously in the peritoneal cavity probably prevented opposition of calcified loops of bowel, resultant trauma and haemoperitoneum.

Mechanical outflow problems

TPD seems to be the preferred modality in patients with mechanical outflow problems (*i.e.*, secondary to incorrect position of catheter in the peritoneal cavity or intra-abdominal adhesions) [31, 32]. The transition point is reached earlier in these patients and the second part of the dialysate outflow phase is seen to be prolonged when compared to other patients.

Frequency of Alarms

In TPD, outflow can be halted before the transition point is reached, resulting in a decrease in total drain time and number of alarms [33]. In few of these patients only the combination of a higher intra-peritoneal fill volume (*i.e.*, initial fill volume 3 l) along with a low tidal volume (800–1000 ml) facilitates continuous cycler sessions without frequent alarms at night.

Ascites

TPD is the modality of choice in patients with ascites [34]. In these cases, a controlled dialysate outflow is often preferred, which can be done with TPD, as compared to non-tidal APD where the whole fill volume fluid is drained out at the end of each cycle.

Role of TPD In current practice of peritoneal dialysis

In patients undergoing PD at home, TPD usually provides no added advantage of better small solute or middle molecule clearances or improvement in fluid removal as compared to non-tidal APD.

Switching from non-tidal APD to TPD may be considered in patients with dialysate outflow pain, mechanical outflow problems, ascites or peritoneal calcifications, to reduce abdominal discomfort and multiple alarms at night, during cycler therapy. The tidal volume should be maintained as high as possible in these patients (> 50%), especially in patients with LA peritoneal transport rates.

TPD could result in better clearances than non-tidal APD if a very high dialysate flow is utilised (> 5 l/h). Such dialysate flow rates are rarely prescribed in patients undergoing APD at home, but may be studied in-centre IPD patients.

To enhance solute clearances above those values achieved by conventional APD, novel treatment modalities like continuous flow PD (CFPD) may be a promising option in the future [35].

References

1. Brandes, J. C., W. J. Packard, S. K. Watters, and C. Fritsche, 1995: Optimization of dialysate flow and mass transfer during automated peritoneal dialysis. *Am. J. Kidney Dis.* **25,** 603–610.
2. Durand, P. Y., P. Freida, B. Issad, and J. Chanliau, 1996: How to reach optimal creatinine clearances in automated peritoneal dialysis. *Perit. Dial. Int.* **16,** 167–170.
3. Stephen, R. L., 1978: Reciprocating peritoneal dialysis with a subcutaneuous peritoneal catheter. *Dial. Transplant.,* **7,** 834–838.
4. Di Paolo, N., 1978: Semicontinuous peritoneal dialysis. *Dial. Transplant.* **7,** 839–842.
5. Finkelstein, F. O., and A. S. Kliger, 1979: Enhanced efficiency of peritoneal dialysis using rapid small volume exchanges. *ASAIO J.,* **2,** 103–106.
1. Twardowski, Z. J., 1989: Peritoneal dialysis. Current technology and techniques. *Postgrad. Med.,* **85,** 161–164, 167, 170 passim.
2. Twardowski, Z. J., B. F. Prowant, K. D. Nolph, D. Kari, R. Khanna, L. M. Schmidt, and R. J. Sataiowich, 1990: Chronic nightly tidal peritoneal dialysis. *ASAIO Trans*. **36,** 584–588.
3. Twardowski, Z. J., 1990: Peritoneal dialysis glossary III. *Perit. Dial. Int.* **10,** 173–175.
4. Flanigan, M. J., 1999: Rationale for tidal peritoneal dialysis. *Contrib. Nephrol.*, **129,** 62–68.
5. Flanigan, M. J., C. Doyle, V. S. Lim, and G. Ullrich, 1992: Tidal peritoneal dialysis: preliminary experience. *Perit. Dial. Int.,* **12,** 304–308.
6. Flanigan, M. J., T. A. Pflederer, and V. S. Lim, 1994: Is 8 hours of nightly peritoneal dialysis enough? *ASAIO J.,* **40,** 24–26.
7. Ho ltta, T., K. Rönnholm, and C. Holmberg, 2000: Adequacy of dialysis with tidal and continuous cycling peritoneal dialysis in children. *Nephrol. Dial. Transplant.* **15,** 1438–1442.
8. Ferna´ndez Rodrı´guez, A. M., N. Vega Diaz, L. Palop Cubillo, E. B. Laborda, A. M. Umpierrez, P. P. Borges, M. N. Zurita and C. P. Toledano, 1997: Adequacy of dialysis in automated peritoneal dialysis: a clinical experience. *Perit Dial Int*; **17,** 442–448.
9. Edefonti, A., G. Consalvo, M. Picca, M. Giani, B. Damiani, L. Ghio, and R. Galato, 1995: Dialysis delivery in children on nightly intermittent and tidal peritoneal dialysis. *Pediatr. Nephrol*., **9,** 329–332.

15. Flanigan, M. J., V. S. Lim, and T. A. Pflederer, 1993: Tidal peritoneal dialysis: kinetics and protein balance. *Am. J. Kidney Dis.,* **22,** 700–707.

16. Rodrı´guez, A. M. F., N. V. Dı´az, L. P. Cubillo, J. T. Plana, M. A. Riscos, R. M. Delgado, C. M. Herrera, E. A. Ribes, F. T. Molina, M. M. Heras, A. T. González, C. G. Cantón, A. R. Fernández, E. B. Laborda, M. N. Zurita, F. F. Girón, and P. S. Santana, 1998: Automated peritoneal dialysis: a Spanish multicentre study. *Nephrol. Dial. Transplant.* **13,** 2335–2340.

17. Balaskas, E. V., S. Izatt, M. D. Chu, and D. G. Oreopoulos, 1993: Tidal volume peritoneal dialysis versus intermittent peritoneal dialysis. *Adv. Perit. Dial.* **9,** 105–109.

18. Steinhauer H. B., I. Keck, I. Lubrich-Birkner, and P. Schollmeyer, 1991: Increased dialysis efficiency in tidal peritoneal dialysis compared to intermittent peritoneal dialysis. *Nephron.* **58,** 500–501.

19. Piraino B, F. Bender, and J. Bernardini, 1994: A comparison of clearances on tidal peritoneal dialysis and intermittent peritoneal dialysis. *Perit. Dial. Int.,* **14,** 145–148.

20. Quellhorst, E., A. Solf, and U. Hildebrand, 1991: Tidal peritoneal dialysis (TPD) is superior to intermittent peritoneal dialysis (IPD) in long term treatment of patients with chronic renal insufficiency (CRI). *Perit. Dial. Int.,* **11,** 217.

21. Vychytil, A. and W. H. Hörl, 2006: The role of tidal peritoneal dialysis in modern practice: A European perspective. *Kid. Int.,* **70,** 96–103.

22. Aasarød, K., T. E. Widerøe, and S. C. Flakne, 1997: A comparison of solute clearance and ultrafiltration volume in peritoneal dialysis with total or fractional (50%) intraperitoneal volume exchange with the same dialysate flow rate. *Nephrol. Dial. Transplant.* **12,** 2128–2132.

23. Vychytil, A., T. Lilaj, B. Schneider, H. H. Walter, and M. Haag-Weber, 1999: Tidal peritoneal dialysis for home-treated patients: should it be preferred? *Am. J. Kid. Dis.*, **33,** 334–343.

24. Juergensen, P.H., A. L. Murphy, K. A. Pherson, A. S. Kliger, and F. O. Finkelstein, 2000: Tidal peritoneal dialysis: comparison of different tidal regimens and automated peritoneal dialysis. *Kid. Int.*, **57,** 2603–2607.

25. Juergensen, P., J. Eras, B. McClure, A. S. Kliger, and F. O. Finkelstein, 2005: The impact of various cycling regimens on phosphorus removal in chronic peritoneal dialysis patients. *Int. J. Artif. Organs,* **28,** 1219–1223.

26. Perez, R.A., P. G. Blake, S. McMurray, L. Mupas, and D. G. Oreopoulus, 2000: What is the optimal frequency of cycling in automated peritoneal dialysis? *Perit. Dial. Int.,* **20:** 548–556.

27. de Fijter, C. W. H, H. A. Verbrugh, P. L. Oe, E. C. J. M. Heezius, J. Verhoef, and A. J. M. Donker, 1994: Antibacterial peritoneal defence in automated peritoneal dialysis: advantages of tidal over continuous cyclic peritoneal dialysis? *Nephrol. Dial. Transplant.,* **9,** 156–162.

28. Juergensen, P. H., A. L. Murphy, K.A. Pherson, W. S. Chorney, A. S. Kliger, and F. O. Finkelstein, 1999: Tidal peritoneal dialysis to achieve comfort in chronic peritoneal dialysis patients. *Adv. Perit. Dial.,* **15,** 125–126.

29. Chang H., M. A. Miller, and F. J. Bruns, 2002: Tidal peritoneal dialysis during pregnancy improves clearance and abdominal symptoms. *Perit. Dial. Int.,* **22,** 272–274.

30. Farmer, C. K., D. J. Goldsmit, P. Sharpstone, and J. C. Kingswood, 1998: Maintenance of adequate dialysis in a patient with peritoneal calcification using tidal peritoneal dialysis. *Clin. Nephrol.*, **49,** 55–58.

31. Twardowski, Z. J., 1998: Influence of different automated peritoneal dialysis schedules on solute and water removal. *Nephrol. Dial. Transplant.,* **13,** 103–111.

32. Agrawal, A., and K.D. Nolph, 2000: Advantages of tidal peritoneal dialysis. *Perit. Dial. Int.,* **20,** 98–100.

33. Neri, L., G. Viglino, A. Cappelletti, C. Gandolfo, 2001: Evaluation of drainage times and alarms with various automated peritoneal dialysis modalities. *Adv. Perit. Dial.*, **17,** 72–74.

34. Vychytil, A., 2005: Automated peritoneal dialysis – actual clinical aspects. *Wien. Klin.*

Wochenschr., **117,** 98–108.

35. Diaz-Buxo, J. A., 2004: Continuous-flow peritoneal dialysis: update. *Adv. Perit. Dial.,* **20,** 18–22.

Chapter 18

Tests for the Measurement of Solute and Fluid Transport

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Tests for the Measurement of Solute and Fluid Transport

Introduction

Peritoneal dialysis (PD) uses the peritoneal membrane as a semi-permeable membrane for solute transfer and ultra filtration. There is a considerable variability in both solute transport and ultra filtration capacity among patients and even within the same patient with time [1]. These differences necessitate that a therapy should be tailored to the specific needs of the patient in terms of the ideal length of dwell, the number of exchanges and the type of dialysis solution used. An inappropriate prescription can lead to substantial underachievement in terms of solute clearance and ultra filtration or unnecessary exposure to hypertonic solutions. The peritoneal membrane characteristics can be assessed in practice by performing various types of equilibration tests. These tests should be performed at the initial assessment of peritoneal dialysis, and periodically (at least once a year, ideally once in six months)

towards understanding the changes in membrane transport with time and following peritonitis episodes, in a patient with ultra filtration failure or inadequate dialysis.

Peritoneal equilibration test (PET) developed by Twardowski [2] characterises the transport nature of the patient's peritoneal membrane. He studied the solute transport across the peritoneal membrane with time towards deciding if the patients transport the solutes fast (high / high average) or slow (low / low Average). Patients who are low (L) transporters' need longer dwells and have an excellent long term prognosis compared to patients who are high (H) transporters who need shorter dwells and have poor long-term prognosis on PD. [3, 4]

Changes in the membrane character have been widely reported in the literature [5-8]. With time and after peritonitis episodes, the membrane transport character changes to the H transporter status in patients who were L transporters initially.

How to perform the PET test? The standardized four-hour PET procedure consists of the following sequential steps:

1. An overnight 8 to 12 hour pre-exchange is performed.

2. While the patient is in an upright position, the overnight exchange is drained (drain time not to exceed 25 minutes).

3. Two liters of 2.5 % dialysis solution is infused over 10 minutes with the patient in the supine position.

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4. The patient is rolled from side to side after every 400 ml infusion.

5. After the completion of infusion (D0) and at 2 hours dwell time (D2), 200 ml of dialysate is drained. A 10 ml sample is taken and the remaining 190 ml is infused back into the peritoneal cavity and the glucose and creatinine is estimated in these samples (D0 and D2 glucose and D2 Cr). A serum sample is obtained for creatinine at 2 hours (P 2 Cr).

6. At the end of the dwell (4 hours), the dialysate is drained in the upright position (drain time not to exceed 20 minutes). The drain volume is measured and a 10 ml sample is taken from the drain and glucose and creatinine are estimated (D4 Cr and D4 glucose). A serum sample is obtained at 4 hours. (D4 Cr)

7. The D2/D0 & D4/D0 glucose, and the D/P ratios for creatinine at 2nd second and fourth hour are calculated and the values are plotted in the standard graph towards defining the transport character of the patient.

Using the D/P ratio of creatinine and D/D0 glucose, patients can be classified into one of four transport categories: high (H), high average (HA), low average (LA), and low (L) (**Figure 1**).

Fast transporters generally have a D/P creatinine greater than 0.80 [9, 11]. These patients achieve rapid and complete equilibration of small solutes due to a larger functional membrane surface area and higher membrane permeability [9, 12]. However, fast transporters quickly lose their osmotic gradient and achieve poor ultrafiltration because dialysate glucose is rapidly absorbed into the blood. Thus, fast transporters have the greatest D/P ratios for creatinine and urea, but the lowest D/D0 glucose.

Unlike fast transporters, slow transporters have the lowest D/P ratios for creatinine and urea, where the D/P creatinine is typically less than 0.55 [9, 11]. These patients achieve a slower and less complete equilibration for small solutes. On the other hand, slow transporters have the greatest D/D0 glucose due to slower glucose transport across the peritoneal membrane. As a result, they can sustain their osmotic gradient for longer periods and therefore achieve better ultrafiltration [10].

Patients who are high-average or low-average transporters have moderately high or moderately low diffusion and ultrafiltration characteristics [10]. Typically, the D/P creatinine for high-average transporters will range from 0.65 to 0.80, while low-average transporters will have a D/P creatinine ranging from 0.55 to 0.64 [11].

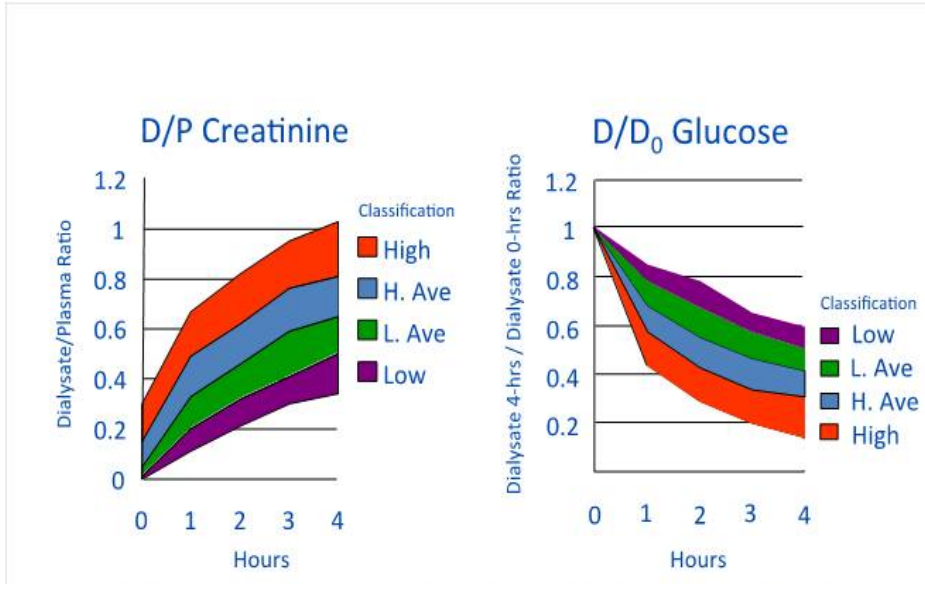

Figure 1: (Left) Dialysate Creatinine *versus* Plasma Creatinine at 4 hours (D/P Creatinine);

(Right) Ratio of Dialysate Glucose at 4 hours *versus* Dialysate Glucose at Time Zero (D/D_0)

However, it is important to remember that such cut-offs may vary based on the geographical area, time on PD, and other factors related to the testing process or population studied. Twardowski suggested each center should define transport character of their patients and a PET graph created for that center, as differences in the membrane character is reported universally [13-19]. Unfortunately, not many such analyses are available.

In our center, we analysed the peritoneal transport characteristics of 240 patients (441 PET data) and have defined a PET graph. The standard PET graph defines the transport status over a period of 4 hours that is not practically needed. Since, we measure the glucose and creatinine ratios at second and at fourth hours, we modified the graph in our center - MODIFIED PET GRAPH. (**Figure 2**) This is easy to use and is tailored to our patients. [20].

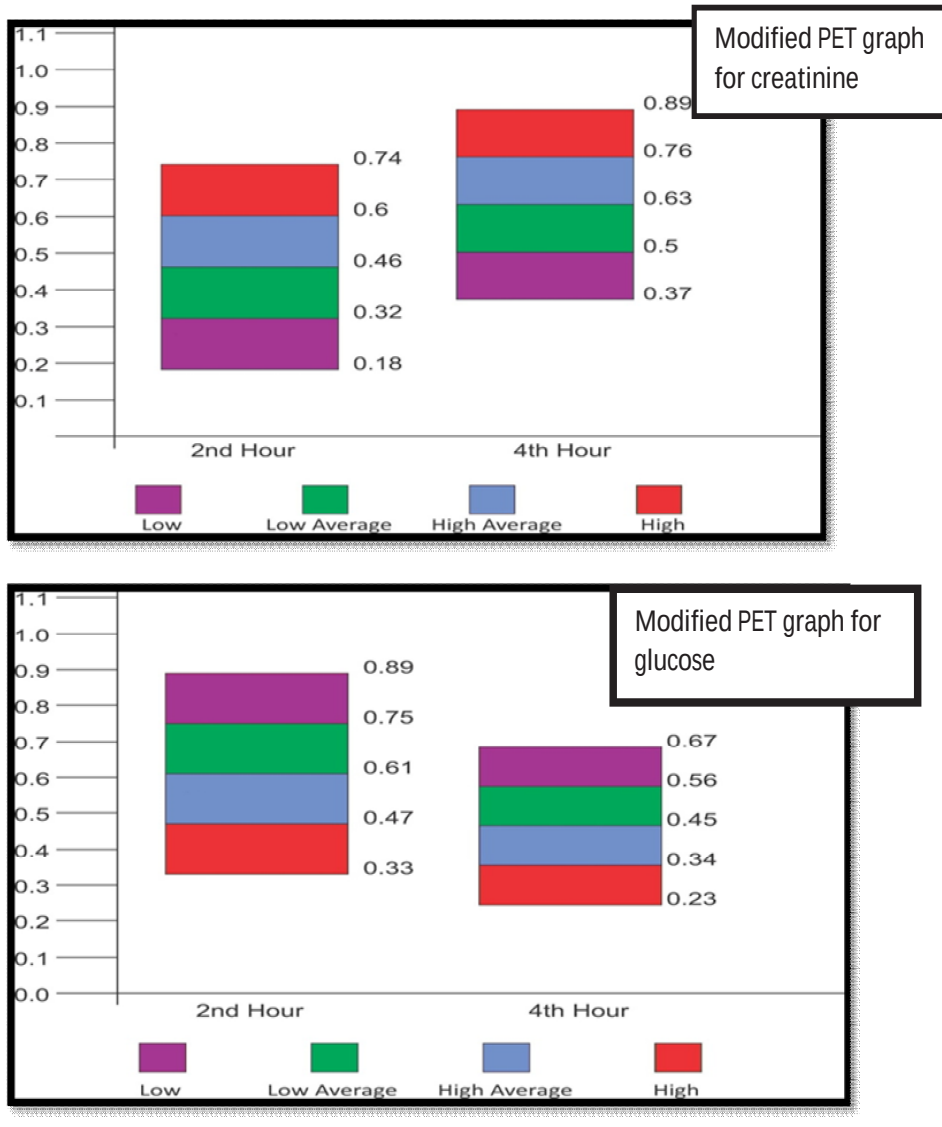

Figure 2: Modified PET graph.

This graph is easy to use in practice as the values defining the transport characteristics are given along side the graph.

Timing of the First PET test

The standard recommendation by NKF-KDOQI guidelines for the first PET measurement is 4-8 weeks after the PD commencement. These are based on the

PET test performed by Rocco *et al*, [21], Johnson *et al*, [22]. Both the authors agreed that the initial equilibration tests (at 1 week and <2 weeks) are preliminary and the test performed at 4 weeks correlated well with the later tests performed (at 6^{th} month and at 1^{st} year). No study is available where PET is performed between 2 week and 4 week after PD commencement that is compared to the subsequent PET.

We performed the first PET test at 2 weeks of catheter insertion and compared it with the subsequent PET test done at 6 months. We excluded patients with peritonitis in the first 6 months. Of the 126 patients PET characteristics were compared and we found out that 115 patients (91.2%) had similar PET at sixth month. We proposed EARLY PET is an alternative to the standard PET at 6 weeks of PD initiation. The advantage is that we could give an appropriate prescription as early as 2 weeks. This is the first study done in the literature where the PET test at 2 weeks is compared with the subsequent PET at 6 months [23].

Fast PET

The fast PET requires the analysis of dialysate and plasma samples only at 4 hours. The fast PET protocol therefore becomes less laborious, requires less sampling and nursing time, and limited use of medical processes without changing the total procedure time. It eliminates the supervised inflow procedure, the baseline and two hour measurements, and substitute dialysate glucose at 4 hours for the ratio of the 4 hour value to baseline glucose dialysate value (D4/D0). 4th hour D/P for creatinine is estimated .The results of this single dialysate sample are interpreted using a standard table that classifies the data by transport categories [24].

Short PET

The original PET was standardized for a long overnight exchange. Recent studies confirmed the minimal impact of the prior long exchange on small solute equilibration. Twardowski et al. introduced the "short PET" accepting any dwell time between 3 and 12 hours for the prior exchange and simplifying the test to include either a 2 or 4 hour dwell [25].

The Fast PET and the Short PET have significant concordance with the standard PET tests and could be used as alternative methods in defining the transport nature of the peritoneal membrane.

The dialysis adequacy and transport test (DATT) defines both the transport character and the solute clearance of the patient in a single test. This test was introduced by Rocco *et al,* in an attempt to develop an easier test for classifying peritoneal transport type [26]. Only a serum sample and a 10 ml aliquot from a pooled, well-mixed 24-hour dialysate are required for the calculation of the 24-hour D/P. Available studies show that the value for the 24-hour dialysate to-plasma ratio of creatinine (D/P Cr) derived from the DATT correlates significantly with the 4-hour D/P Cr value derived from the PET. That is, the DATT can be used instead of the PET to determine peritoneal transport [27, 28]. Moreover, the DATT has the

additional advantage of proving the daily solute clearance and ultrafiltration volume from dialysis.

The accelerated peritoneal examination (APEX) test was designed by Verger *et al*, It summarizes in a single number the peritoneal permeability for both glucose and urea [29]. It represents the time at which the glucose and urea equilibration curves cross. Serial measurements of Dt /D0 glucose and D/P creatinine at various time points are calculated. The intersection point of these graphs is called as APEX POINT. The shorter APEX time indicates higher (faster) peritoneal permeability and, conversely, the longer time is indicative of lower (slower) peritoneal permeability (**Figure 3**). If ultrafiltration is the major goal, short dwell times should be used. If solute clearance is the major goal, longer dwell times should be used.

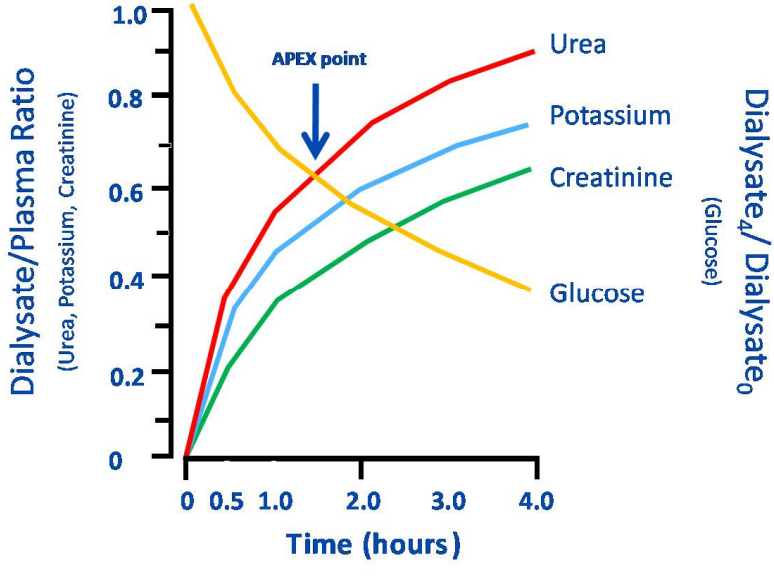

Figure 3: Illustration of APEX time, the crossing point of dialytic urea appearance (red), and glucose appearance curve (yellow). APEX time indicates the optimal time for ultrafiltration.

The **standard peritoneal permeability analysis (SPA)** is a more sophisticated way to assess peritoneal function. It uses intra peritoneally administered dextran 70 (1 gram per liter) to study fluid kinetics during a 4-hour dwell using an infusion volume consistent with the patient's usual prescription. The study is performed at the center over a period of 4 hours and requires two blood samples and many timed

peritoneal effluent samples. The SPA is useful in assessing MTAC (mass transfer-area coefficient) of small solutes, clearance of proteins, and changes in ultrafiltration volume [30].

Tests for fluid kinetics in CAPD

Ultrafiltration failure (UFF) is one of the most important causes of long-term PD failure in patients. Osmotic forces acting across small and ultra-small pores generate a UF with solutes through the small pore and free water transport (FWT) through the ultra-small pore (aquaporins). The ability of glucose to exert an osmotic pressure sufficient to cause UF is the so-called 'osmotic conductance to glucose' (OCG) of the peritoneal membrane. Patient with fluid overload after eliminating dietary noncompliance and mechanical problems need to undergo evaluation towards identifying the cause of his/ her ultrafiltration failure (UFF). Modified PET, Mini PET and Double Mini PET would help us to understand the different types of UFF.

Modified PET test

It is used as a first line evaluation in detecting UFF on PD, that is defined when the ultrafiltration volume is less than 400 ml after 4 hours dwell with 4.25 % dextrose solution. But this test will not define the exact reason for UFF in a given patient – like aquaporin deficiency, decreased peritoneal membrane capacity or increased lymphatic re-absorption that needs separate evaluation [31].

MINI PET and Double MINI PET

The peritoneal membrane has 3 types of pores as defined by Rippe. These are large pores, small pores and the ultrasmall pores (AQUAPORINS). The ultrasmall pores transport only water. In the initial phase of the dialysis the sodium content in the dialysate and the serum are near normal. The movement of water across the aquaporins in the first hour causes the sodium levels to drop, if the D/P sodium is done at the end of one hour. In the first part of the dwell, the osmotic gradient over the aquaporins is strongest and gradually decreases as glucose is absorbed. In the second part of the dwell, diffusive transport of sodium from the plasma to the dialysate will increase as a consequence of the increase in concentration difference. Therefore, using the 1-h value of D/P_{sodium} to estimate the free water transport is advocated, a procedure named the mini PET using a 4.25% solution. The ratio of D/P ratio of sodium at one hour >0.93 indicates poor aquaporin function. The ultrafiltration volume can also be assessed by draining the fluid at one hour. This test can be performed periodically towards monitoring for peritoneal membrane sclerosis.

The double mini-PET consists of two consecutive 1-hour PETs: the first is performed with a 1.5% glucose solution, and the second, with a 4.25 % glucose solution. Using formulae validated by La Milia and colleagues [32], UF through the small pores (UFSP), FWT, and OCG are calculated using the results of the double

mini-PET. The reduction in osmotic conductance of glucose indicates poor ultrafiltration through small pores (osmotically driven) and ultrasmall pores (free water transport) that predicts membrane failure.

Other tests

Combined PET test: (Mini PET & PET using 4.25 % glucose)

Here, using a 4.25 % glucose solution the Mini PET is performed first that gives information on the ultrafiltration capacity that can be measured by sodium sieving and calculating the ultrafiltration volume, re-infusing the fluid and doing a standard PET calculation at the end of 4 hours to assess the transport characteristics [33]. With a single 4.25 % exchange we can find both the ultrafiltration capacity and transport characteristics of the peritoneal membrane.

Uni PET

Here the PET test using 4.25 % solution is combined with Mini PET using 1.5 % solution (Combined PET test is combined with Mini PET using 1.5% solution). This test provides the advantages of Double Mini PET and PET test using 4.25 % solution. We can calculate the difference in osmotic conductance of glucose using 1.5 % and 4.25 % solutions and also performing the PET test using 4.25 % dextrose [21]. This test takes 5 hours to perform – one hour for the Mini PET with 1.5 % glucose and 4 hours for the PET test using 4.25 % glucose.

References

1. Coester, A. M., W. Smit, D. G. Struijk, and R. T. Krediet, 2009: Peritoneal function in clinical practice: the importance of follow-up and its measurement in patients. Recommendations for patient information and measurement of peritoneal function. *NDT Plus,* **2,** 104-110.

2. Twardowski, Z. J., K. O. Nolph, R. Khanna, B. F. Prowant, L. P. Ryan, H. L. Moore, and M. P. Nielsen, 1987: Peritoneal equilibration test. *Perit. Dial. Bull.,* **7,** 138-147.

3. Daugirdas, J. T., P. G. Blake, and T. S. Ing, 2007: Handbook of Dialysis: Chapter 13. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 330-337.

4. La Milia, V., 2010: Peritoneal transport testing. *J. Nephrol.*, **23,** 633-647.

5. Blake, P. G., G. Abraham, K. Sombolos, S. Izatt, J. Weissgarten, A. Ayiomamitis, and D. G. Oreopoulos, 1989: Changes in peritoneal membrane transport rates in patients on long term CAPD. *Adv. Perit. Dial.,* **5,** 3–7.
6. Passlick-Deetjen, J., H. Chlebowski, M. Koch, and B. Grabensee, 1990: Changes of peritoneal membrane function during long-term CAPD. *Adv. Perit. Dial.,* **6,** 35–43.
7. Procaccini, D. A., M. Querques, A. Tappi, and P. Strippoli, 1998: Peritoneal clearances. Long-term study. *ASAIO Trans.,* **34,** 437–440.
8. Struijk, D. G., R. T. Krediet, G. C. Koomen, E. W. Boeschoten, F. J. Hoek, and L. A. Arisz, 1994: A prospective study of peritoneal transport in CAPD patients. *Kid. Int.,* **45,** 1739–1744.

9. Twardowski, Z. J., K. O. Nolph, R. Khanna, B. F. Prowant, L. P. Ryan, H. L. Moore, and M. P. Nielsen, 1987: Peritoneal equilibration test. *Perit. Dial. Bull.,* **7,** 138-147.

10. Daugirdas, J. T., P. G. Blake, and T. S. Ing, Handbook of Dialysis: Chapter 13. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2007. 330-337p.

11. La Milia, V., 2010: Peritoneal transport testing. *J. Nephrol.,* **6,** 633-647.

12. Twardowski, Z. J., B. F. Prowant, H. L. Moore, L. C. Lou, E. White, and K. Farris, 2003: Short peritoneal equilibration test: impact of preceding dwell time. Adv. Perit. Dial., **19,** 53-58.

13. Raj, D. S., V. Langos, N. Gangam, and J. Roscoe, 1997: Ethnic variability in peritoneal equilibration test and urea kinetics. *Am. J. Kid. Dis.,* **30,** 374–381.
14. Cueto-Manzano, A. M., A. Díaz-Alvarenga, and R. Correa-Rotter, 1999: Analysis of the peritoneal equilibration test in Mexico and factors influencing the peritoneal transport rate. *Perit. Dial. Int.,* **19,** 45–50.

15. Chakravarthy, R., S. Surjith, K. C. Prakash, V. Subba Rao, V. K. Gupta, and M. K. Mani, 2002: Pattern of peritoneal permeability in Indian CAPD population. *J. Indian Soc. Perit. Dial.,* **4,** 19–23.
16. Abraham, G., V. Kumar, K. S. Nayak, R. Ravichandran, G. Srinivasan, M. Krishnamurthy, A. K. Prasath, S. Kumar, T. Thiagarajan, M. Mathew, and N. Lesley, 2010: Predictors of long-term survival on peritoneal dialysis in South India: A multicenter study. *Perit. Dial. Int.*, **30,** 29–34.
17. Agarwal, D. K., A. P. Sharma, A. Gupta, R. K. Sharma, C. M. Pandey, R. Kumar, S. P. Mahis, 2000: Peritoneal equilibration test in Indian patients on continuous ambulatory peritoneal dialysis: Does it affect patient outcome? *Adv. Perit. Dial.,* **16,** 148–151.
18. Ram, R., G. Swarnalatha, C. S. Rao, G. D. Naidu, C. L. Margaret, and K. V. Dakshinamurthy, 2013: Peritoneal Equilibration Test. A single center study from India. *Indian J. Nephrol.,* **23,** 156-157.
19. Balasubramaniyam, R., V. R. Nirmala, V. Yogesh, J. Vijayalakshmi, and Rekha, 2011: Peritoneal Equilibration Test profile in our CAPD patients. A retrospective single center analysis. *Indian J. Perit. Dial.,* **21,** 27-29.

20. Balasubramaniyam, R., S. B. Devi, V. R. Nirmala, S. Gokila, and J. Vijayalakshmi, 2014: Analysis of peritoneal membrane transport characteristics in Indian patients using Peritoneal Equilibration test. (PET): Modification of PET graph. *Indian J. Perit. Dial.,* **27,** 55-60.

21. Rocco, M. V., J. R. Jordan, and J. M. Burkart, 1994: Determination of peritoneal transport characteristics with 24-hour dialysate collections: dialysis adequacy and transport test. *J. Am. Soc. Nephrol.,* **5,** 1333-1338.

22. Johnson, D. W., D.W. Mudge, S. Blizzard, M. Arndt, A. O'Shea, R. Watt, J. Hamilton, S. Cottingham, N. M. Isbel, and C. M. Hawley, 2004: A comparison of peritoneal equilibration tests performed 1 and 4 weeks after PD commencement. *Perit. Dial. Int.,* **24,** 460-465.

23. Balasubramaniyam, R., V. R. Nirmala, V. Yogesh, R. Sethuraman, S. B. Devi, N. M. Balakrishnan, and G. Bakthavathsalam, 2013: Comparison of peritoneal transport characteristics at the second week and at six months of peritoneal dialysis commencement. *Indian J. Nephrol.,* **23,** 346–350.

24. Twardowski, Z. J., 1990: The fast peritoneal equilibration test. *Semin. Dial.,* **3,** 141-142.

25. Twardowski, Z. J., B. F. Prowant, H. L. Moore, L. C. Lou, E. White, and K. Farris 2003: Short peritoneal equilibration test: impact of preceding dwell time. *Adv. Perit. Dial.,* **19,** 53-58.

26. Rocco, M. V., J. R. Jordan, and J. M. Burkart, 1994: Determination of peritoneal transport characteristics with 24-hour dialysate collections: dialysis adequacy and transport test. *J. Am. Soc. Nephrol.,* **5,** 1333–1338.

27. Szeto, C. C., T. Y. Wong, K. K. Chow, C. B. Leung, and P. K. Li, 2002: Dialysis adequacy and transport test for characterization of peritoneal transport type in Chinese peritoneal dialysis patients receiving three daily exchanges. *Am. J. Kid. Dis.,* **39,** 1287–1291.

28. Paniagua, R., D. Amato, R. Correa–Rotter, A. Ramos, E. F. Vonesh, and S. K. Mujais, 2000: Correlation between peritoneal equilibration test and dialysis adequacy and transport test, for peritoneal transport type characterization. *Perit. Dial. Int.,* **20,** 53–59.

29. Verger, C., L. Larpent, G. Veniez, N. Brunetot, and B. Corvaisier, 1991: L'APEX description et utilisation [French]. *Bull. Dial. Perit.,* **1,** 36-40.

30. Pannekeet, M. M., A. L. Imholz, D. G. Struijk, G. C. Koomen, M. J. Langedijk, N. Schouten, R. de Waart, J. Hiralall, and R. T. Krediet, 1995: The standard peritoneal permeability analysis: A tool for the assessment of peritoneal permeability characteristics in CAPD patients. *Kid. Int.,* **48,** 866—875.

31. Teitelbaum, I., 2015: Ultrafiltration Failure in Peritoneal Dialysis: A Pathophysiologic Approach. *Blood Puri.,* 39, 1-3.

32. La Milia, V., M. Limardo, G. Virga, M. Crepaldi, and F. Locatelli, 2007: Simultaneous measurement of peritoneal glucose and free water osmotic conductances. *Kid. Int.,* **72,** 643–650.

33. Cnossen, T. T., W. Smit, C. J. Konings, J. P. Kooman, K. M. Leunissen, and R. T. Krediet, 2009: Quantification of free water transport during the peritoneal equilibration test. *Perit. Dial. Int.,* **29,** 523-527.

Chapter 19

Adequacy of Peritoneal Dialysis

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Adequacy of Peritoneal Dialysis

Introduction

Adequacy of peritoneal dialysis (PD) is a prescription of PD which ensures overall well being of the patient. It is usually determined by a unitless number Kt/V which is based on urea clearance. Kt/V of PD patients is actually the sum of kt/v of the kidneys, which depends on the residual renal function and kt/v of the PD. The current guideline is to prescribe PD to ensure weekly kt/v > 1.7 based on data from the 3 major randomised control trials (CANUSA, ADEMEX and the Hong Kong trial). In this chapter, we will describe how and when to measure kt/v and how to interpret it.

Well being of the patient is not solely determined by small solute clearance but also depends on the maintenance of volume status, blood pressure control, homeostasis of mineral metabolism, clearance of middle molecules and maintenance of nutritional status. That is why urea clearance of the residual kidneys is not the same as the urea clearance of PD. In spite of this major caveat, Kt/V based on urea clearance is the globally accepted measure of PD adequacy, well supported by strong evidence of randomised control outcome trials.

What is Kt/V?

As mentioned earlier Kt/V is a measure of urea clearance and given as a number with no unit. In PD patients,

Total Kt/Vd= Kt/Vd (renal) + Kt/Vd (dialysate) over 7 days

Where, K = Volume cleared of urea/time (Liters/day)

t in days

Vd urea is volume of distribution of urea ~ TBW (in Liters)

K urea (renal) is measured as Urine urea/ Plasma urea x volume of urine / day

$$\text{So, Kt/V (renal)} = \frac{\text{K urea (renal)} \times 7}{\text{Vd urea}}$$

$$= \frac{\{\text{Urine urea/Plasma urea} \times \text{volume of urine}\} \times 7}{\text{Body weight} \times 0.6} \quad \text{eq. 1}$$

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In the same manner, Kt/V of PD is calculated as

K urea (PD) = Dialysate urea/ Plasma urea x dailysate volume

So Kt/V (PD) = $\frac{\text{K urea (PD) x 7}}{\text{Vd (urea)}}$

$$= \frac{\{(\text{Dialysate urea/ Plasma urea}) \text{ x volume of dialysate}\} \text{ x 7}}{\text{Bodyweight x 0.6}} \quad \text{eq. 2}$$

The sum of equation 1 and 2 gives the weekly Kt/V in PD patients, if urine output is more than 100 ml per day. If output is less than 100 ml/day, dialysate urea clearance alone is used to calculate Kt/V. (1)

There are online calculators to do the calculation and one such link is http://touchcalc.com/calculators/ktv_pd.

How is Kt/ V measured?

To calculate weekly Kt/V we need the following measurements1. Patient collects a 24 hour urine sample, if the output is more than 100 ml and urea is estimated which is U u.

2. Volume of urine is measured in litres and gives V urine

3. Plasma urea is measured as close to the end of the collection period as possible which is P u

4. PD effluent is collected for the entire 24 hours or 1% of each drain bag is collected and pooled together and a sample is taken for urea measurement which is the D u

5. Volume of 24 hours PD effluent is measured in litres and it gives V di

6. Volume of distribution of urea in the body is taken as the total body water which is Bodyweight x 0.6 (Vd urea)

7. The calculation is as follows.

a. $\frac{[(\text{U u/Pu}) \text{ x V u}] \text{ x 7}}{\text{V d urea}}$

b. $\frac{[(\text{ Du/P u}) \text{ x Vd}] \text{ x 7}}{\text{V d urea}}$

8. The final value is a+ b.

Goals for Kt/V:

The current recommendation is to deliver a dose of small solute clearance as measured by a total of renal and peritoneal Kt/V of at least 1.7 in both patients with and without residual renal function. It is a grade B recommendation meaning there is a moderately strong evidence. The evidence comes from the data of the three major trials [2].

Initially, Kt/V > 2.0 was recommended as adequate solute clearance based on CANUSA trial. But, the reanalysis of the CANUSA trial showed that improved survival was related to residual renal function and not the peritoneal clearance. For each 5 L/wk / 1.73 m2 increase in GFR, there was a 12% decrease in the relative risk (RR) of death (RR, 0.88; 95% confidence interval [CI], 0.83 to 0.94) but no association with peritoneal creatinine clearance (RR, 1.00; 95% CI, 0.90 to 1.10) [3].

ADEMEX was a prospective, randomized, controlled, clinical trial. Overall, 965 patients were randomised (1:1) to either the control group where they continued to receive standard 4 x 2 l exchanges or to intervention group where PD prescription was modified to achieve peritoneal creatinine clearance of 60 L/ week/1.73 m^2. The patients were followed for 2 years and the primary outcome studied was death. Mean peritoneal Kt/v was 1.80 in the control group and 2.27 in the treatment group. There was no difference in the 2 year survival rates between the groups, 68.3% in control group vs. 69.3% in the intervention group [4].

In the Hong Kong trial by Lo *et al,* published in 2003, 320 new PD patients with renal Kt/V less than 1 were randomised to 3 groups based on Kt/ V target, Group A 1.5 to 1.7, Group B 1.7 to 2.0 and Group C greater than 2.0. All the patients were on standard 3x 2L exchanges and once randomised PD prescription was altered to achieve Kt/v targets. These patients were followed for 2 years and they achieved separation of Kt/v by the end of 1 month which was maintained throughout the study period and the difference was mainly due to difference in peritoneal Kt/v and not renal Kt/V. The primary outcome was patient survival. The 2-year survival in group A was 87.3%, group B was 86.1%; and group C, 81.5% and there was no statistically significant difference in the survival rates [5].

Though, there was no difference in patient survival in the 3 groups in the Hong Kong trial, there were more patients withdrawn and higher requirement of EPO therapy in group A [5]. Again in the ADEMEX trial, though deaths were equal in both the groups, the causes of death were different. More patients in the lower target died of congestive heart failure and uraemia and hyperkalaemia, whereas in the higher target more patients died of coronary artery disease and peritonitis [4].

These randomised trials have shown no benefit of increasing PD prescription beyond 1.7 in the short term at least, but there is no prospective trial to answer the acceptable lowest target. The NECOSAD study, a prospective multicentre cohort study of new adult dialysis patients, examined the relationship between small-solute

clearances and survival in auric PD patients (n = 130). At the point of anuria, patients had been on PD therapy (primarily CAPD) for an average of 13 months and peritoneal weekly Kt/Vurea was 1.8. When Kt/Vurea was analysed as a time dependent continuous variable corrected for age, Davies score, Subjective Global Assessment score, time on dialysis therapy, serum albumin level, and haemoglobin concentration, there was no relationship with survival. When Kt/Vurea was analyzed as a dichotomous value, <1.7 *versus* >1.7, there was no relationship with survival. Only when Kt/Vurea was analyzed as a dichotomous value, <1.5 *versus* >1.5, relationship with survival was seen (RR, 3.28; 95% CI, 1.25 to 8.60; P< 0.02) [6].

In the Hong Kong trial, the patients were only on 3 x 2 L exchanges per day similar to most of the Indian patients. These patients also had low Body Mass Index (BMI) (22kg/m2) as compared to the ADEMEX trial patients (25.3 and 25.8 kg/m2 in the 2 groups), that might be a reason why patients with lower Kt/v did not have an increased mortality. Also, their overall 2 year survival was better at 84.7% as compared to 68.3% and 69.3% in the control and interventional group, respectively in the ADEMEX trial. There could be different targets for patients with different BMI. The Australian guidelines state that the adequate targets might be different in patients with BMI < 20 or > 26 kg/m^2 [7].

When to measure Kt/V?

The recommendation by NKF/ DOQI is to measure Kt/V, 1 month after starting of PD and at least once every 4 months, thereafter. If the patient is dependent on residual renal function for solute clearance then urine collection should be done every 2 months. This is a Grade B recommendation [2]. In a patient with residual renal function, there is a progressive loss of renal function over the years and the rate of loss is different in different patients. In the CANUSA study, renal creatinine clearance decreased from 38.8 L/ week to 14.3 L/ week over 2 years follow up which is at the rate of 0.1 ml/min/month [3]. In the Hong Kong study by Lo et al, the renal Kt/V was 0.44, 0.46 and 0.49 in the 3 groups of patients respectively. During the follow up period of 37 months residual renal function declined in all the 3 groups and the average Kt/V was less than 0.1 [5]. Hence, if the patient is dependent of residual renal function to achieve weekly Kt/V of 1.7 then urine output is to be measured every 2 months.

Both these studies measured peritoneal clearances once in 6 months, but the guideline formulated based on these major trials is to measure Kt/V every 4 months. The guidelines of other major societies also differ in this aspect. International Society of Peritoneal Dialysis recommends monitoring of residual renal function at an appropriate frequency (every 1-2 months if practicable or no less than every 4-6 months). It also suggests measuring residual renal function sooner if there is a decrease in urine volume or change in blood chemistries [8]. The Canadian society

of nephrology recommends renal Kt/V measurement once in 3 to 6 months and total Kt/V only when clinically indicated [9]. The Renal association (UK) guidelines recommend measurement 6 to 8 weeks after start of dialysis and then 6 monthly. It recommends that clearances be measured more often if residual renal function is declining rapidly [10].

Caveats to Kt/V

It is important to remember that renal Kt/V and peritoneal Kt/V are not the same as clearly demonstrated by the 3 major trials, though they are added for calculation of peritoneal adequacy. In the CANUSA trial, the renal Kt/V was associated with survival benefits and in the ADEMEX and the Hong Kong trials, increasing peritoneal Kt/V did not offer survival advantage.

Though creatinine clearance and Kt/V urea are markers of small solute clearance, they are not the same. In patients on APD, depending on dwell time creatinine clearance can be greatly different. The association between small solute clearance in PD and other kidney functions like fluid removal, middle molecule clearance, electrolyte, acid base and mineral homeostasis, blood pressure control are only weak. For example, in low transporters the creatinine clearance is lower than urea clearance but fluid removal is better. So use of Kt/V urea alone for adequacy measurement is very simplistic.

Hence, the first recommendation in ISPD guidelines reads "Adequacy of dialysis should be interpreted clinically rather than by targeting only solute and fluid removal. Clinical assessment should include clinical and laboratory results, peritoneal and renal clearances, hydration status, appetite and nutritional status, energy level, haemoglobin concentration, responsiveness to erythropoietin therapy, electrolytes and acid–base balance, calcium phosphate homeostasis, and blood pressure control" [8].

The second recommendation in the ISPD guidelines is "In order to emphasize that there is more to adequate dialysis than a focus on small solute kinetics and ultrafiltration targets, the committee decided to name this guideline, Guideline on Targets for Solute and Fluid Removal in Adult Patients on Chronic Peritoneal Dialysis instead of Guideline on Adequacy of Peritoneal Dialysis" [8].

Other adequacy targets: As mentioned earlier, there are many limitations to the use of Kt/V urea target alone for PD adequacy and renal societies around the world have incorporated other targets. In the ISPD guidelines [8] and the European best practice guidelines [11], there is a recommendation of additional target of weekly creatinine clearance of 45L/week/1.73 m^2 in APD patients, because their creatinine clearance can be very low if dwell times are short.

The other component of PD adequacy recommended in guidelines is the ultrafiltration volume. In the European APD Outcome Study (EAPOS) of anuric APD patients, ultrafiltration volume less than 750 ml/day at baseline was predictor

of poor survival though in time averaged analysis UF volume lost the statistical significance in predicting survival [12]. In the NECOSAD study of predictors of survival in anuric PD patients, ultrafiltration as a continuous variable was a strong predictor of survival [6]. The European best practice guidelines includes minimal UF target of 1.0 L in anuric patients [11].

In the Canadian society of Nephrology PD adequacy guidelines, solute clearance target is only one of the six major sections, others being maintenance of residual renal function, optimisation of volume status, CV disease management, nutrition and hyperglycemia management [9].

How to measure creatinine clearance?

Creatinine clearance is calculated similar to Kt/V but using creatinine values and is normalised to body surface area.

To calculate weekly Creatinine clearance we need the following measurements

1. Patient collects a 24 hour urine sample if the output is more than 100 ml and creatinine is estimated which is U Cr.

2. Volume of urine is measured in litres and gives V urine

3. Plasma creatinine is measured as close to the end of the collection period as possible which is P Cr.

4. PD effluent is collected for the entire 24 hours or 1% of each drain bag is collected and pooled together and a sample is taken for urea measurement which is the D Cr.

5. Volume of 24 hours PD effluent is measured in litres and it gives V di

6. The calculation is as follows.

i. $\frac{U\,Cr}{P\,Cr} \times Vu \times 7$ which is then normalised to 1.73 m2

ii. $\frac{D\,Cr}{P\,Cr} \times V\,di \times 7$ which is then normalised to 1.73 m2

7. The final value is a+ b.

Conclusion

Based on 2 recent major prospective trials, prescription of dialysis that delivers weekly Kt/V urea of atleast 1.7 is recommended as adequate PD. But, the data is far from adequate. We do not have enough studies on patients with APD and CCPD. We do not have enough long term follow up trials. Issues with middle molecule

clearance, mineral metabolism homeostasis and malnutrition are likely to manifest during later years. Still, within the limitations as discussed above Kt/V urea provides a standard, reproducible tool to assess dialysis adequacy in peritoneal dialysis patients.

References

1. Watnick, S., 2011: Peritoneal dialysis adequacy. [https://ispd.org/NAC/wp-content/uploads/2010/11/Peritoneal-Dialysis-Adequacy-Watnick-April-2011-Notes.pdf].
2. KDOQI Advisory Board Members, 2006: Clinical Practice Guidelines For Peritoneal Dialysis Adequacy, Update 2006. National Kidney Foundation 2006. [http://kidneyfoundation.cachefly.net/professionals/KDOQI/guideline_upHD_PD_VA/index.htm].
3. Bargman, J. M., K. E. Thorpe, and D. N. Churchill, 2001: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J. Am. Soc. Nephrol*., **12,** 2158-2162.
4. Paniagua, R., D. Amato, E. Vonesh, R. Correa-Rotter, A. Ramos, J. Moran, and S. Mujais, 2002: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J. Am. Soc. Nephrol*., **13,** 1307-1320.
5. Lo, W. K., Y. W. Ho, C. S. Li, K. S. Wong, T. M. Chan, A. W. Yu, F. S. Ng, and I. K. Cheng, 2003: Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study.*Kid. Int.* **64,** 649-656.
6. Jansen, M. A., F. Termorshuizen, J. C. Korevaar, F. W. Dekker, E. Boeschoten, and R. T. Krediet, 2005: Predictors of survival in anuric peritoneal dialysis patients.*Kid. Int.* **68,** 1199-1205.
7. Johnson, D., F. Brown, H. Lammi, and R. Walker, 2005: Caring for Australians with Renal Impairment (CARI) -The CARI guidelines. Dialysis adequacy (PD) guidelines. *Nephrol.,* **10,** 81-107.
8. Lo, W. K., J. M. Bargman, J. Burkart, R. T. Krediet, C. Pollock, H. Kawanishi, P. G. Blake, 2006: ISPD Adequacy of Peritoneal Dialysis Working Group -Guideline on targets for solute and fluid removal in adult patients on chronic peritoneal dialysis. *Perit. Dial. Int*., **26,** 520-522.

9. Blake, P. G., J. M. Bargman, K. S. Brimble, S. N. Davison, D. Hirsch, B. B. McCormick, R. S. Suri, P. Taylor, N. Zalunardo, and M. Tonelli, 2011: Canadian Society of Nephrology Work Group on Adequacy of Peritoneal Dialysis - Clinical Practice Guidelines and Recommendations on Peritoneal Dialysis Adequacy.*Perit. Dial. Int*., **2,** 218-39.

10. Woodrow, G., and S. Davies, 2012: Clinical Practice Guidelines Peritoneal Dialysis. [http://www.renal.org/docs/default-source/guidelines-resources/old-guidelines/peritoneal-dialysis.
11. Dombros, N., M. Dratwa, M. Feriani, R. Gokal, O. Heimbürger, R. Krediet, J. Plum, A. Rodrigues, R. Selgas, D. Struijk, C. Verger, 2005: EBPG Expert Group on Peritoneal Dialysis. European best practice guidelines for peritoneal dialysis. 7 Adequacy of peritoneal dialysis. *Nephrol. Dial. Transplant.,* **9,** ix24-ix27.

12. Brown, E. A., S. J. Davies, P. Rutherford, F. Meeus, M. Borras, W. Riegel, J. C. Divino Filho, E. Vonesh, and M. van Bree, 2003: Survival of functionally anuric patients on automatedperitoneal dialysis: the European APD Outcome Study. *J. Am. Soc. Nephrol.,* **14,** 2948-2957.

Chapter 20

Residual Renal Function in Peritoneal Dialysis

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Residual Renal Function in Peritoneal Dialysis

Introduction

Residual renal function (RRF) is in general defined as the residual glomerular filtration rate (GFR) in the patients with ESRD. Rottembourg *et al*, [1] were the first to observe that RRF is better preserved in patients with peritoneal dialysis (PD) than in those treated with conventional thrice-weekly hemodialysis (HD) and later confirmed by several other reports [2-7]. Observational studies to date have reported an association between even small amounts of RRF and improved patient survival. Dialysis therapies predominantly provide clearance for small water-soluble solutes, volume and acid-base control, but cannot reproduce the metabolic functions of the kidney. As such, protein-bound solutes, advanced glycosylation end-products, middle molecules and other azotaemic toxins accumulate over time in the patients with chronic kidney disease (CKD) without RRF. Thus, preservation of RRF is of paramount importance in a patient on PD.

Impact of RRF on Survival on PD Patients

Persistence of RRF is associated with a better patient survival in patients with PD. The first evidence highlighting the above fact was presented by Maiorca *et al*, [8]. They identified the persistence of RRF, as a separate variable in the analysis of outcome, as conferring survival benefit. The landmark Canada-United States (CANUSA) study concluded that a higher dose of dialysis, inclusive of RRF, was associated with a better patient survival [9]. This led to the belief that the total dose of small solute clearance, achieved by both peritoneal and renal contributions, are equally important.

This led to changes in the PD guidelines, which then placed more emphasis on peritoneal small solute clearance, with definitions of PD adequacy being directly related to both Kt/V urea and creatinine clearance. However, quality evidence has now accumulated indicating that RRF and the delivered dose of dialysis have a well-differentiated influence on the global results of PD therapy.

Rocco *et al*, reported that for each 10 L/week/ 1.73 m^2 increase in renal CrCl, there was a 40% reduced risk for death [10] and no effect of peritoneal solute clearances on survival was observed. Many other studies found similar results of decreased mortality with preserved RRF [11-15].

This led to reanalysis of the CANUSA study which concluded that mortality was solely associated with RRF, and not with peritoneal small-solute clearance [16]. The reanalysis identified a 12% decrease in relative risk of death associated with each 5 L/wk/1.73 m^2 increase in GFR. The ADEMEX s % risk reduction in patient mortality for each 10 L/wk/1.73 m^2 inc ith no change in survival with increased peritoneal small-solute clearance [17]. The

Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) found a 12% reduction in the mortality rate for each 1mL/min/1.73 m2 increase in residual GFR, again with no significant effect of peritoneal creatinine clearance on survival [18]. Various other studies have shown better survival in patients with persistence of RRF (**Table 1**).

All the above evidence clearly show an association of RRF and outcome of patients on PD. One potential confounder to all these studies is one of lead-time bias, in that patients with a greater residual renal function may have initiated dialysis at a relatively earlier time than those with a lower residual renal function.

Table 1: Studies Linking Residual Renal Function (RRF) with Increased Survival in Peritoneal Dialysis [19]

Author Study	Duration	Submodality	Outcome
Maiorca *et al*, 1995	Prospective single center, 3 y	CAPD *n* = 68	Mean GFR significantly improved survival, with an associated risk reduction of 48%
Diaz-Buxo *et al*, 1999	Prospective multicenter, 1 y	CAPD/CCPD *n* = 2,686	Every ml/min increase in rCrCl associated with 12% risk reduction of death
Rocco *et al*, 2000	Prospective multicenter, 7 month	CAPD/CCPD *n* = 1,446	Every increase in rCrCl of 10 L/wk/1.73 m2 associated with 40% risk reduction of death
Szeto *et al*, 2000	Prospective single center, 22 month	CAPD *n* = 370	Every mL/min/1.73 m2 increase in renal GFR associated with 35% risk reduction of death
Shemin *et al*, 2000	Prospective multicenter, 2 y	PD *n* = 990	rCrCl greater than 12.3 L/wk/1.73 m^2 associated with 39% risk reduction of death
Bargman *et al*, 2001	Prospective multicenter, 2 y	CAPD *n* = 680	Every increase in rCrCl of 5 L/wk/1.73 m^2 associated with 12% risk reduction of death
Paniagua *et al*, 2002	RCT 2y	CAPD *n* = 965	Every increase in rCrCl of 10 L/wk/1.73 m^2 associated with 11% risk reduction of death

Termorshuizen *et al*, 2004	Prospective multicenter, 3 y	CAPD/CCPD *n* = 413	Every mL/min/1.73 m^2 increase in GFR associated with 12% risk reduction of death
Liao *et al*, 2009	Retrospective single center, 45 mo mean	CAPD/APD *n* = 270	Every mL/min/1.73 m^2 increase in GFR associated with 39% risk reduction of death, and increased rate in decline of GFR associated with greater risk of death
van der Wal *et al*, 2011	Marginal structural model	PD *n* = 609	Full loss of GFR results in HR of death of 2.15

Mechanism by Which RRF Improves Survival

There are various factors by which RRF leads to better outcomes.

Improved Clearance

It is believed that in addition to its effect on small-solute clearance, RRF helps in removal of middle molecules and protein-bound substances which may have a positive influence on the survival. It has been demonstrated that the renal contribution to middle-molecule and protein-bound substances is greater than its contribution to total small-solute clearance in PD [20-22].

Decreased cardiovascular morbidity and mortality

Cardiovascular disease is the primary cause of death in end-stage renal disease (ESRD) patients [23]. The loss of RRF contributes to hypertension, LVH, volume overload, inflammation, anemia, malnutrition, which increases the cardiovascular risk leading to increased mortality and morbidity [24]. RRF may influence survival by attenuating risk factors known to increase both cardiovascular morbidity and mortality.

Decreased Vascular Disease

The development of vascular calcification and atherosclerosis is associated with increased cardiovascular mortality in ESRD patients [25-27]. Loss of RRF is associated with high serum phosphate levels and inflammation both of which promote vascular calcification [28, 29]. Declining RRF is also associated with endothelial dysfunction contributing to development of atherosclerosis and arteriosclerosis [30, 31]. Therefore, maintaining RRF leads to reduced vascular disease that may translate into improved survival.

Improved Nutritional Status

Maintenance of RRF is associated with a better nutritional status and may contribute to the observed increased survival benefit.[32] RRF is more important than dialysis dose for preservation of appetite [33], likely related to its ability to clear molecules that inhibit satiety that are not adequately cleared by current dialysis methods [34]. This benefits observed may be due to enhanced removal of the inflammatory cytokines known to induce anorexia. Moreover as RRF declines, resting energy expenditure increases which may result in protein-energy malnutrition.

Decreased Systemic Inflammation

Systemic inflammation is linked with increased mortality in patients with chronic kidney disease, particularly due to cardiovascular disease [35-37]. Maintained RRF has been directly associated with reduced markers of inflammation, including CRP, IL-6, and TNF-α which leads to better survival.

Reduced Peritonitis Rates

Preserved RRF has been associated with both reduced peritonitis rates and peritonitis-associated mortality. Initiating PD without significant RRF is often a consequence of delayed referral, secondary selection of PD (e.g., after HD technique failure), or stormy renal disease. Thus, the absence of RRF at the start of PD could simply be a marker of the poor overall condition of the patient. Moreover, preserved RRF may result in a more competent immune system. In 2005, Perez-Fontan *et al*, [38] in a cohort of 565 PD patients identified RRF at the start of therapy as an independent predictor of the risk of peritonitis (risk reduction 4% per ml per min per 1.73m^2 of GFR) and peritonitis-related mortality (risk reduction 25% per ml per min per 1.73m^2).

Improved Quality of Life (QoL)

Lower QoL scoring has been associated with higher rate of death and hospitalization in patients with ESRD [39]. The NECOSAD study found that preserved RRF, rather than PD clearance, had benefits on certain generic and disease-specific aspects of QoL especially physical functioning, vitality, kidney disease-specific symptoms, daily life and sleep disorders [18].

Strategies to Maintain RRF in PD Patients

Dietary intervention

An increased protein intake leading to both hyperfiltration and increased renal tubular work load to maintain acid-base homeostasis have been proposed as mechanisms for continued renal injury. Thus, protein restriction may potentially reduce the rate of loss of RRF. However, there are limited data in PD patients in this regard. A small single centre trial reported that RRF was better maintained in

incident PD patients (with a urine output ≥800 mL/day or an eGFR ≥2 mL/min/1.73 m^2) over 12 months period when prescribed a low-protein diet with supplemental ketoacids (protein intake 0.6–0.8 g/kg/day with keto acids 0.12 g/kg/day) *versus* a low- 0.6–0.8 g/kg/day and a high-protein diet group 1.0–1.2 g/kg/day [40].

Avoidance of Hemodialysis

It has been well described that HD is associated with increased rate of loss of RRF compared with that seen with PD.A study concluded that a group of PD patients who had received a period of HD prior to the start of PD had a greater rate of loss of RRF compared with those who had no previous HD [41]. Thus, temporary HD should be avoided whenever possible by planning PD initiation at an appropriate time.

Selection of PD modality (CAPD or APD)

It is still controversial whether the decline in RRF might be different in CAPD or APD regimes. Some studies found better preservation of RRF in CAPD compared to APD while others found no differences. Various studies comparing CAPD and APD with regards to RRF are shown in **Table 2.**

Table 2: Summary of Studies Reported Effect of Dialysis Modality on RRF **[42]**

Reference (year)	Study design	Subject Characteristics	Favour CAPD	Details
Hiroshige *et al.* (1996)	6-month prospective	Prevalent 8 NIPD, 5 CCPD, 5 CAPD	Yes	Rate of change of RRF in -0.29 (NIPD) versus -0.34 (CCPD) versus +0.01(CAPD) ml/min/month
Rodriguez *et al.* (1998)	3-year prospective	Prevalent 25 CAPD, 20 APD	No	
Hufnagel *et al.* (1999)	18-month prospective	Incident 6 NIPD, 12 CCPD, 18 CAPD	Yes	Rate of change of RRF in -0.26 (APD) versus -0.13 (CAPD) ml/min/month
Bro *et al.* (1999)	6-month RCT	Prevalent 13 CAPD, 12 APD	No	
Moist *et al.* (2000)	3-year retrospective	Incident 722 CAPD, 310 APD	No	
De Fijter *et al.* (2000)	2-year RCT	Incident 13 CCPD, 11 CAPD	No	
Gallar *et al.* (2000)	1-year prospective	Incident 11 CAPD, 9 APD	No	
Singhal *et al.* (2000)	4-year prospective	Incident 211 CAPD, 31 APD	No	
Holley *et al.* (2001)	9-year retrospective	Incident 11 CAPD, 9 APD	No	
Jansen *et al.* (2002)	1-year prospective	Incident 243 PD subjects	No	

Hidaka *et al.* (2003)	6-year prospective	Incident 27 CAPD, 7 APD	Yes	Approximate time to decrease 50%of RRF in CAPD is 15 months versus APD 4 months, P<0.001
Johnson *et al.* (2003)	6-year prospective	Incident 134 CAPD, 12 APD	No	
Rodriguez-Carmona (2004)	1-year prospective	Incident 53 CAPD, 51 APD	Yes	Hazard ratio of APD versus CAPD= -1.2(-2.25 to -0.15, P=0.02)
Rabindranath (2007)/Liao (2009)	Systemic review of 3 RCT 10-year retrospective	49 PD subjects Incident 188 CAPD, 82 APD	No	
Su *et al.* (2010)	9-year retrospective	Prevalent 140 CAPD, 32 APD	No	
Cnossen *et al.* (2010)	7-year retrospective	Incident 179 CAPD, 441 APD	No	
Balasub ramanion *et al.* (2011)	5-year retrospective	Incident 178 CAPD, 13 APD	No	
Micheis *et al.* (2011)	3-year retrospective	Incident 505 CAPD, 7 APD	Yes	Higher risk of loss of RRF in APD compared to CAPD in first year of treatment (a adjusted hazard ration 2.66, CI 1.66-4.44)

Avoiding peritonitis

Peritonitis can be associated with hypotension, systemic inflammation, and also the use of nephrotoxic antibiotics have all been implicated as a mechanism of decline in RRF. Thus, an emphasis should be given on adequate sterile technique to the patients to prevent peritonitis.

Avoidance of nephrotoxic insults

Nephrotoxic agents such as NSAIDS, aminoglycoside antibiotics and radio-contrast iodine are recognized to increase the risk of acute kidney injury in patients with CKD [43]. Use of these agents with caution may lead to a better preservation of RRF.

Use of Biocompatible Solutions

It has been proposed that biocompatible PD solutions are protective towards RRF as they do not induce the adverse metabolic sequelae linked to systemic absorption of glucose and glucose degradation products [44]. There are a number of studies exploring the effect of these solutions on RRF, but unfortunately no clear pattern of association has emerged.

Use of icodextrin decreases extracellular water (ECW) that may lead to dehydration and loss of RRF. One small single-centre study reported that icodextrin usage helped preserve RRF [45], whereas five other studies showed no effect [46-50]. However, as icodextrin can lead to a reduction in ECW, patients could potentially be at increased risk of dehydration and acute kidney injury, as dehydration is linked to loss of RRF [51].

To date, consistent evidence is not available regarding superiority of any PD solution on RRF preservation.

Renin-Angiotensin-Aldosterone Blockade

The role of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in delaying progression of CKD has been well described 52-54. It is interesting to assume that this renoprotection may continue while an individual is on dialysis. The results of the observational studies have been mixed, with a large retrospective study from USRDS on incident and prevalent PD reporting ACEIs had a protective effect on RRF [3], whereas a study of 160 incident PD patients from Australia, and 451 from the Netherlands showed no benefit [51-55], although more diabetics were treated with ACEIs in the latter study. Two randomized controlled trials, one with ramipril and the other with valsartan, both indicated that use in their selected population was associated with preservation of RRF; however, both studies excluded patients in whom withdrawal of an ACE inhibitor or ARB was not appropriate, therefore making the study population unrepresentative of what is managed in daily practice [56, 57].

More recently, a systematic review from the Cochrane library reported that ACEIs or ARBs may provide some protection in preserving RRF in PD patients, but did not reduce proteinuria. However, as the number of studies and quality of studies was markedly limited, no recommendation that ACEIs/ARBS should be the antihypertensive agents of choice for PD patients could be made [58].

Other Factors

The use of furosemide is associated with increased urinary volume, as it has been shown to increase sodium and water excretion leading to improvement of fluid overload; however, this has not been associated with preservation of RRF [59, 60].

Cardiac events and cardiac morbidity are associated with an increased loss in RRF, so efforts to treat cardiovascular disease, such as BP and glycemic control, may benefit RRF [3, 61, 62]. Uncontrolled BP, a known risk factor for cardiac disease, is also associated with increased rate of decline in RRF and so adequate control is necessary.

Residual Renal Function in Peritoneal Dialysis after Renal Transplant Failure

The management of PD patients after renal transplantation is difficult. Stoppage of immunosuppressive agents may lead to a decline in RRF whereas continuation of

immunosuppressive may lead to an increased risk of infection. Various studies have shown that patients starting PD following renal allograft failure leads to an accelerated loss of RRF [63-65].

Factors leading to a faster loss of RRF in the failed renal transplant population

The most obvious one is the cessation of immunosuppression, which is expected to result in a decline in GFR in subjects with a failing renal transplant.

Jassal *et al*, [64] concluded that maintaining long-term immunosuppression may prolong life expectancy of patients commencing PD after chronic graft failure. Messa *et al*, [66] recently proposed that immunosuppression should be discontinued relatively rapidly upon return to dialysis. The variety of the proposed protocols reflects the absence of good evidence with respect to management of these patients and the need for randomized controlled studies.

Additionally, inflammation may play a role in the rapid loss of RRF in these patients. It has been suggested that increase in circulating cytokines after cessation of immunosuppression may play a role in the decrease in RRF in dialysis patients [67].

RRF in Children

PD is the treatment of choice as the modality of renal replacement therapy (RRT) in children with ESRD. Advantages of PD over HD in pediatric patients are related to a twofold higher peritoneal membrane surface per kilogram of body mass compared to adults, difficulties related to creation and maintenance of adequate vascular access for HD in the youngest patients, elimination of pain related to punctures of the arteriovenous fistula, and no need for anticoagulant use. A greater degree of patient freedom with this approach allows home dialysis therapy, regular schooling, and engaging in normal everyday life activities [68].

In children with PD, RRF was shown to

- Help preserve adequacy of renal replacement therapy.
- To accelerate growth rate.
- Improve nutrition.
- Improve blood pressure control.
- Reduce the risk of adverse myocardial changes.
- Facilitate treatment of anemia and calcium-phosphorus balance abnormalities.
- Result in reduced serum and dialysate fluid levels of advanced glycation end-products.

Factors contributing to RRF loss in children treated with PD include:

- The underlying renal disease such as hemolytic-uremic syndrome and hereditary nephropathy.

- Small urine volume.
- Severe proteinuria at the initiation of renal replacement therapy.
- Hypertension.

Several approaches can be suggested to decrease the rate of RRF loss in pediatric patients treated with chronic PD:

- Avoid potentially nephrotoxic drugs (e.g., aminoglycosides).
- Avoid episodes of hypotension.
- Uncontrolled hypertension should be avoided.
- Urinary tract infections should be treated promptly.
- Loop diuretics may be used with caution to increase salt and water excretion.

References

1. Rottembourg, J., B. Issad, J. L. Gallego, P. Degoulet, F. Aime, B. Gueffaf, and M. Legrain, 1983: Evolution of residual renal function in patients undergoing maintenance haemodialysis or continuous ambulatory peritoneal dialysis. *Proc. EDTA*, **19,** 397–403.

2. Lysaght, M. J., E. F. Vonesh, F. Gotch, L. Ibels, M. Keen, B. Lindholm, K. D. Nolph, C. A. Pollock, B. Prowant, and P. C. Farrell PC, 1991: The influence of dialysis treatment modality on the decline of remaining renal function. *ASAIO Trans.*, **37,** 598–604.

3. Moist, L. M., F. K. Port, S. M. Orzol, E. W. Young, T. Ostbye, R. A. Wolfe, T. Hulbert Shearon, C. A. Jones, and W. E. Bloembergen, 2000: Predictors of loss of residual renal function among new dialysis patients. *J. Am. Soc. Nephrol.,* **11,** 556–564.

4. Misra, M., E. Vonesh, J. C. Van Stone, H. L. Moore, B. Prowant, and K. D. Nolph, 2001: Effect of cause and time of dropout on the residual GFR: a comparative analysis of the decline of GFR on dialysis. *Kid. Int.,* **59,** 754–763.

5. Lang, S. M., A. Bergner, M. Topfer, and H. Schiffl, 2001: Preservation of residual renal function in dialysis patients: effects of dialysis-technique-related factors. *Perit. Dial. Int.,* **21,** 52–57.

6. Jansen, M. A., A. A. Hart, J. C. Korevaar, F. W. Dekker, E. W. Boeschoten, and R. T. Krediet, 2002: Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kid. Int.,* **62,** 1046–1053.

7. Cancarini, G. C., G. Brunori, C. Camerini, S. Brasa, L. Manili, and R. Maiorca, 1986: Renal function recovery and maintenance of residual diuresis in CAPD and hemodialysis. *Perit. Dial. Bull.,* **6,** 77–79.

8. Maiorca, R., G. Brunori, R. Zubani, G. C. Cancarini, L. Manili, C. Camerini, E. Movilli, A. Pola, G. d'Avolio, and U. Gelatti, 1995: Predictive value of dialysis adequacy and nutritional indices for mortality and morbidity in CAPD and HD patients. A longitudinal study. *Nephrol. Dial. Transplant.,* **10,** 2295-2305.

9. Canusa, 1996: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. Canada-USA (CANUSA) Peritoneal Dialysis Study Group. *J. Am. Soc. Nephrol.,* **7,** 198-207.

10. Rocco, M., J. M. Soucie, S. Pastan, and W. M. McClellan, 2000: Peritoneal dialysis adequacy and risk of death. *Kid. Int.,* **58,** 446–457.

11. Shemin, D., A. G. Bostom, C. Lambert, C. Hill, J. Kitsen, and A. S. Klister, 2000: Residual renal function in a large cohort of peritoneal dialysis patients: change over time, impact on mortality and nutrition. *Perit. Dial. Int.,* **20,** 439–444.

12. Rocco, M. V., D. L. Frankenfield, B. Prowant, P. Frederick, and M. J. Flenigan, 2002: Risk factors for early mortality in U.S. peritoneal dialysis patients: impact of residual renal function. *Perit. Dial. Int.,* **22,** 371–379.

13. Szeto CC, Wong TY, Chow KM, C. B. Leung, M. C. Law, and P. K. Li, 2004: Independent effects of renal and peritoneal clearances on the mortality of peritoneal dialysis patients. *Perit. Dial. Int.,* **24,** 58–64.

14. Szeto CC,Wong TY, Leung CB, A. Y. Wang, M. C. Law, S. F. Law, and P. K. Li, 2000: Importance of dialysis adequacy in mortality and morbidity of Chinese CAPD patients. *Kid. Int.,* **58,** 400–407.

15. Ateş, K., G. Nergizoğlu, K. Keven, A. Sen, S. Kutlay, S. Ertürk, N. Duman, O. Karatan, and A. E. Ertuğ, 2001: Effect of fluid and sodium removal on mortality in peritoneal dialysis patients. *Kid. Int.,* **60,** 767–776.

16. Bargman, J. M., K. E. Thorpe, D. N. Churchill, 2001: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J. Am. Soc. Nephrol.,* **12,** 2158–2162.

17. Paniagua, R., D. Amato, E. Vonesh, R. Correa-Rotter, A. Ramos, J. Moran, and S. Mujais, 2002: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J. Am. Soc. Nephrol.,* **13,** 1307-1320.

18. Termorshuizen, F., J. C. Korevaar, F. W. Dekker, J. G. van Manen, E. W. Boeschoten, and R. T. Krediet, 2003: The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Am. J. Kid. Dis.,* **41,** 1293- 1302.

19. Curran, S. P., and J. M. Bargman, 2011: The Importance of Residual Renal Function in Peritoneal Dialysis. *Dial. Transplant.,* **40,** 349-355.

20. Amici, G., G. Virga, G. D. Rin, S. Grandesso, A. Vianello, P. Gatti, and C. Bocci, 1993: Serum beta- 2-microglobulin level and residual renal function in peritoneal dialysis. *Nephron.,* **65,** 469- 471.

21. Bammens, B., P. Evenepoel, K. Verbeke, and Y. Vanrenterghem, 2003: Removal of middle molecules and protein-bound solutes by peritoneal dialysis and relation with uremic symptoms. *Kid. Int.,* **64,** 2238-2243.

22. Pham, N. M., N. S. Recht, T. H. Hostetter, and T. W. Meyer, 2008: Removal of the protein-bound solutes indican and p-cresol sulfate by peritoneal dialysis. *Clin. J. Am. Soc. Nephrol.,* **3,** 85-90.

23. Foley, R. N., P. S. Parfrey, and M. J. Sarnak, 1998: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am. J. Kid. Dis.,* **32,** 112-119.

24. Wang, A. Y., M. Wang, J. Woo, C. W. Lam, S. F. Lui, P. K. Li, and J. E. Sanderson, 2004: Inflammation, residual kidney function, and cardiac hypertrophy are interrelated and combine adversely to enhance mortality and cardiovascular death risk of peritoneal dialysis patients. *J. Am. Soc. Nephrol.,* **15,** 2186–2194.

25. Blacher, J., A. P. Guerin, B. Pannier, S. J. Marchais, and G. M. London, 2001: Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension,* **38,** 938-942.

26. Sidhu, M. S., and K. C. Dellsperger, 2010: Cardiovascular problems in dialysis patients: impact on survival. *Adv. Perit. Dial.,* **26,** 47-52.

27. Block, G. A., T. E. Hulbert-Shearon, N. W. Levin, and F. K. Port, 1998: Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am. J. Kid. Dis.,* **31,** 607-617.

28. Wang, A. Y., and K. N. Lai, 2006: The importance of residual renal function in dialysis patients. *Kid. Int.,* **69,** 1726-1732.

29. Wang, A. Y., J. Woo, M. M. Sea, M. C. Law, S. F. Lui, and P. K. Li, 2004: Hyperphosphatemia in Chinese peritoneal dialysis patients with and without residual kidney function: what are the implications? *Am. J. Kid. Dis.,* **43,** 712-720.

30. Han, S. H., S. C. Lee, E. W. Kang, J. K. Park, H. S. Yoon, T. H. Yoo, K. H. Choi, D. S. Han, and S. W. Kang, 2010: Reduced residual renal function is associated with endothelial dysfunction in patients receiving peritoneal dialysis [published online ahead of print September 23, 2010]. *Perit. Dial. Int.*

31. Davignon, J., and P. Ganz, 2004: Role of endothelial dysfunction in atherosclerosis. *Circul.,* **109,** 27-32.

32. Perez-Flores, I., F. Coronel, S. Cigarran, J. A. Herrero, and N. Calvo, 2007: Relationship between residual renal function, inflammation, and anemia in peritoneal dialysis. *Adv. Perit. Dial.,* **23,** 140-143.

33. Aguilera, A., R. Codoceo, R. Selgas, P. Garcia, M. Picornell, C. Diaz, C. Sanchez, M. A. Bajo, 1998: Anorexigen (TNF-a, cholecystokinin) and orexigen (Neuropeptide Y) plasma levels in peritoneal dialysis (PD) patients: their relationship with nutritional parameters. *Nephrol. Dial. Transplant.,* **13,** 1476–1483.

34. Plata-Salama´n, C., 1995: Cytokines and feeding suppression: an integrative view from neurologic to molecular levels. *Nutrition,* **11,** 674–677.

35. Tripepi, G., F. Mallamaci, and C. Zoccali, 2005: Inflammation markers, adhesion molecules, and all-cause and cardiovascular mortality in patients with

ESRD: searching for the best risk marker by multivariate modeling. *J. Am. Soc. Nephrol.,* **16,** 83-88.

36. Stenvinkel, P., and A. Alvestrand, 2002: Inflammation in endstage renal disease: sources, consequences, and therapy. *Semin. Dial.,* **15,** 329-337.

37. Wanner, C., and T. Metzger, 2002: C-reactive protein: a marker for all-cause and cardiovascular mortality in haemodialysis patients. *Nephrol. Dial. Transplant.,* **17,** 29-32.

38. Pe´rez-Fonta´n, M., A. Rodrı´guez-Carmona, R. Garcı´a Naveiro, M. Rosales, P. Villaverde, and F. Valdés, 2005: Peritonitis-related mortality in patients undergoing chronic peritoneal dialysis. *Perit. Dial. Int.,* **25,** 274–284.

39. Mapes, D. L., A. A. Lopes, S. Satayathum, K. P. McCullough, D. A. Goodkin, F. Locatelli, S. Fukuhara, E. W. Young, K. Kurokawa, A. Saito, J. Bommer, R. A. Wolfe, P. J. Held, and F. K. Port, 2003: Healthrelated quality of life as a predictor of mortality and hospitalization: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kid. Int.,* **64,** 339-349.

40. Jiang, N., J. Qian, W. Sun, A. Lin, L. Cao, Q. Wang, Z. Ni, Y. Wan, B. Linholm, J. Axelsson, and Q. Yao, 2009: Better preservation of residual renal function in peritoneal dialysis patients treated with a low-protein diet supplemented with keto acids: a prospective, randomized trial. *Nephrol. Dial. Transplant.,* **24,** 2551–2558.

41. Kim, D. J., J. A. Park, W. Huh, Y. G. Kim, and H. Y. Oh, 2000: The effect of hemodialysis during break-in period on residual renal function in CAPD patients. *Perit. Dial. Int.,* **20,** 784-785.

42. Nongnuch, A., M. Assanatham, K. Panorchan, and A. Davenport, 2015: Strategies for preserving residual renal function in peritoneal dialysis patients. *Clin. Kid. J.,* **8,** 202–211.

43. Siew, E., and A. Davenport, 2014: The growth of acute kidney injury. A rising tide of just attention to injury? *Kid. Int.,* doi: 10.1038/ki.2014.293.

44. Perl, J., S. J. Nessim, and J. M. Bargman, 2011: The biocompatibility of neutral pH, low-GDP peritoneal dialysis solutions: benefit at bench, bedside, or both? *Kid. Int.,* **79,** 814-824.

45. Adachi, Y., Y. Nakagawa, and A. Nishio, 2006: Icodextrin preserves residual renal function in patients treated with automated peritoneal dialysis. *Perit. Dial. Int.,* **26,** 405–407.

46. Posthuma, N., P. M. ter Wee, H. A. Verbrugh, P. L. Oe, E. Peers, J. Sayers, A. J. Donker, 1997: Icodextrin instead of glucose during the daytime dwell in CCPD

increases ultrafiltration and 24-h dialysate creatinine clearance. *Nephrol. Dial. Transplant.,* **12,** 550–553.

47. Plum, J., S. Gentile, C. Verger, R. Brunkhorst, U. Bahner, B. Faller, J. Peeters, P. Freida, D. G. Struijk, R. T. Krediet, B. Grabensee, A. Tranaeus, and J. C. Filho, 2002: Efficacy and safety of a 7.5% icodextrin peritoneal dialysis solution in patients treated with automated peritoneal dialysis. *Am. J. Kid. Dis.,* **39,** 862–871.

48. Wolfson, M., B. Piraino, R. J. Hamburger, A. R. Mortan, 2002: A randomized controlled trial to evaluate the efficacy and safety of icodextrin in peritoneal dialysis. *Am. J. Kid. Dis.,* **40,** 1055–1065.

49. Takatori, Y., S. Akagi, H. Sugiyama, J. Inoue, S. Kojo, H. Morinaga, K. Nakao, J. Wada, and H. Makino, 2011: Icodextrin increases technique survival rate in peritoneal dialysis patients with diabetic nephropathy by improving body fluid management: a randomized controlled trial. *Clin. J. Am. Soc. Nephrol.,* **6,** 1337–1344.

50. Posthuma, N., P. M. ter Wee, A. J. Donker, P. L. Oe, E. M. Peers, and H. A. Verbrugh, 2000: Assessment of the effectiveness, safety, and biocompatibility of icodextrin in automated peritoneal dialysis. *Perit. Dial. Int.,* **20,** 106–113.

51. Johnson, D. W., D. W. Mudge, J. M. Sturtevant, C. M. Hawley, S. B. Campbell, N. M. Isbel, and P. Hollett, 2003: Predictors of decline of residual renal function in new peritoneal dialysis patients. Perit. Dial. Int., **23,** 276–283.

52. Codreanu, I., N. Perico, and G. Remuzzi, 2005: Dual blockade of the renin-angiotensin system: the ultimate treatment for renal protection? *J. Am. Soc. Nephrol.,* **16,** 34-38.

53. Ruggenenti, P., A. Remuzzi, G. Remuzzi, E. Perticucci, R. Trevisan, A. Dodesini, V. Gambara, B. Ene-Iordache, S. Carminati, N. Rubis, G. Gherardi, A. Perna, and P. Cravedi, 2011: The Remission Clinic approach to halt the progression of kidney disease. *J. Nephrol.,* **24,** 274- 281.

54. Ruggenenti, P., A. Perna, G. Gherardi, G. Garini, C. Zoccali, M. Salvadori, F. Scolari, F. P. Schena, and G. Remuzzi, 1999: Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet,* **354,** 359-364.

55. Kolesnyk, I., M. Noordzij, F. W. Dekker, E. W. Boeschoten, and R. T. Krediet RT, 2011: Treatment with angiotensin II inhibitors and residual renal function in peritoneal dialysis patients. *Perit. Dial. Int.,* **31,** 53–59.

56. Suzuki, H., Y. Kanno, S. Sugahara, H. Okada, and H. Nakamoto, 2004: Effects of an angiotensin II receptor blocker, valsartan, on residual renal function in patients on CAPD. *Am. J. Kid. Dis.,* **43,** 1056-1064.

57. Li, P. K., K. M. Chow, T. Y. Wong, C. B. Leung, and C. C. Szeto, 2003: Effects of an angiotensin-converting enzyme inhibitor on residual renal function in patients receiving peritoneal dialysis. A randomized, controlled study. *Ann. Intern. Med.,* **139,** 105- 112.

58. Zhang, L., X. Zeng, P. Fu, and H. M. Wu, 2014: Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for preserving residual kidney function in peritoneal dialysis patients. Cochrane Database Syst. Rev., **6,** CD009120.

59. Medcalf, J. F., K. P. Harris, and J. Walls, 2001: Role of diuretics in the preservation of residual renal function in patients on continuous ambulatory peritoneal dialysis. *Kid. Int.,* **59,** 1128-1133.

60. van Olden, R. W., H. J. Guchelaar, D. G. Struijk, R. T. Krediet, and L. Arisz, 2003: Acute effects of high-dose furosemide on residual renal function in CAPD patients. *Perit. Dial. Int.,* **23,** 339-347.

61. Liao, C. T., C. C. Shiao, J. W. Huang, K. Y. Hung, H. F. Chuang, Y. M. Chen, K. D. Wu, and T. J. Tsai, 2008: Predictors of faster decline of residual renal function in Taiwanese peritoneal dialysis patients. *Perit. Dial. Int.,* **28,** 191-195.

62. Coronel, F., I. Perez-Flores, N. Calvo, M. Martinez-Villaescusa, and S. Cigarran, 2007: Impact of cardiovascular events on residual renal function during the first year of peritoneal dialysis. *Perit. Dial. Int.,* **27,** 454-456.

63. Davies, S. J., Peritoneal dialysis in the patient with a failing renal allograft. *Perit. Dial. Int.,* **21,** 280–284.

64. Jassal, S. V., C. E. Lok, A. Walele, and J. M. Bargman, 2002: Continued transplant immunosuppression may prolong survival after return to peritoneal dialysis: results of a decision analysis. *Am. J. Kid. Dis.,* **40,** 178–183.

65. Madar, H., A. Korzets, Y. Ori, M. Herman, R. S. Levy-Drummer, and U. Gafter, 2010: Residual renal function in peritoneal dialysis after renal transplant failure. *Perit. Dial. Int.,* **30,** 470-474.

66. Messa, P., C. Ponticelli, and L. Berardinelli, 2008: Coming back to dialysis after kidney transplant failure. *Nephrol. Dial. Transplant.,* **23,** 2738–2742.

67. Chung, S. H., O. Heimbürger, P. Stenvinkel, J. Bergström, and B. Lindholm, 2001: Association between inflammation and changes in residual renal function and peritoneal transport rate during the first year of dialysis. *Nephrol. Dial. Transplant.,* **16,** 2240–2245.

68. Warady, B. A., S. R. Alexander, and F. Schaefer, 2009: Peritoneal dialysis in children. *Textbook of Peritoneal Dialysis*. R. Khanna, and R. T. Krediet, Eds., Springer, New York, 803–860.

Chapter 21

Prescription of Peritoneal Dialysis

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Prescription of Peritoneal Dialysis

The peritoneal membrane is a dialysis membrane for the peritoneal dialysis (PD) patient. Ideally, the permeability of the peritoneum and the surface area, membrane recruitment capacity should be determined as a part of the prescription process. Knowledge about the contact surface area recruitment capacity, the so called "wetted" membrane, and vascular surface area changes, is important because of the desire to prevent hyper perfusion of the peritoneal membrane, as it may contribute to the development of membrane failure.

Nevertheless, in practice, greater significance is given to the following clinical parameters:

1. Choice of peritoneal dialysis fluid (PDF), with particular reference to dextrose concentration (and the associated ability to meet ultrafiltration needs) and its biocompatibility for peritoneal membrane preservation.

2. Tolerance of the prescribed fill volume, determined by patient report, at times with the assistance of intraperitoneal pressure (IPP) measurement.

3. Dwell time of dialysis exchanges adapted to the individual patient's needs.

All these factors play key roles in achieving adequate PD.

Finally, it must be emphasized that the PD prescription should be individualized and adapted to achieve at least two main goals:

1. Adequate ultrafiltration to avoid hypervolemia because of its contribution to cardiovascular morbidity and mortality, and

2. Blood purification of solute, not limiting only to urea.

When total solute clearance is used to assess adequacy, one measure employed is weekly Kt/V urea, a unit less measure of clearance distributed over total body water per unit of time.

Peritoneal Kt/V urea and residual kidney Kt/V urea are summed to determine the total weekly Kt/V urea. Both urine and the peritoneal fluid volumes are collected at regular intervals and can be determined more frequently when there are changes in clinical status or the PD prescription.

Clearances for urea and creatinine are easy to measure and have been shown to correlate with patient survival in many studies. Their clearance is generally normalized to some measure of body mass. In the case of urea, a popular index is the dimensionless Kt/V, where K denotes urea clearance in mL/min, t is time in min

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and V is the volume of distribution of urea or total body water. Creatinine clearance (C_{Cr}) is usually normalized for body surface area and expressed as L/wk/1.73 m^2.

The National Kidney Foundation Dialysis Outcomes Initiative (KDOQI) workgroup was the first to set formal guidelines for PD adequacy. Their methodology is based on a scientifically rigorous process, using evidence-based rationale whenever possible, a critical review of the literature, and a clear distinction between evidence-based and opinion-based recommendations. Despite limitations, these guidelines have generated much discussion and heightened the interest in quantitation of dialysis dose. Analyses derived from the Canada-United States (CANUSA) Study generated recommendations that peritoneal dialysis therapies should target a total weekly Kt/V_{urea} of 2.0 and creatinine clearance (C_{Cr}) of 60 L/wk/1.73 m^2 for CAPD patients.

Current guidelines aim for a Kt/V urea target of at least 1.7. Previously this target has been set higher, at 2.0 or even greater for non-continuous forms of PD, but the guidelines were lowered based on further trial evidence, and in particular, the randomized ADEMEX study, which found no difference in outcomes between patients assigned to receive a higher versus a lower dose of PD. In the ADEMEX trial, the average weekly Kt/V was 2.1 in the patients assigned to more dialysis, compared to 1.6 in the lower dose group.

Creatinine clearance (C_{Cr}) was usually normalized for body surface area and expressed as L/wk/1.73 m^2 and was in the range of 60/1.73 m^2L /wk. Most current guidelines no longer recommend a minimum level of weekly CrCl as such targets have not been shown to be of any additional value over Kt/V targets. However, they do reflect clearance of slightly larger molecules than urea and so European, but not US guidelines suggest an additional CrCl target of 45/1.73 m^2L/wk.

Evaluation of patients with low delivered Kt/V —Patients with a low delivered Kt/Vurea despite a seemingly adequate dialysis prescription should be evaluated. The possible causes for a low delivered Kt/V include:

1. Lack of adherence to the dialysis prescription.

2. Actual dwell times that is different from those that are prescribed.

3. A change in peritoneal transport type.

4. Loss of residual renal function.

5. Incomplete drain.

6. Ahypercatabolic state.

Frequency of monitoring— Total solute clearance (i. e., Kt/Vurea) and residual renal function should be measured four weeks after initiating peritoneal dialysis. Thereafter, peritoneal solute clearance should be measured every four months. If

residual renal function (RRF) is contributing to total solute clearance, it should be measured at a least every two months.

Control of uremic symptoms, mineral metabolism, and electrolytes

The Kt/V defines the minimum, but not necessarily the optimal, amount of dialysis that must be performed. The optimal dialysis prescription is individualized and is based upon careful assessment of uremic symptoms, electrolyte balance, mineral metabolism, volume status, and nutritional status.

The following are the indications to increase the amount of dialysis despite achieving the minimum target Kt/V of 1.7:1 (**Figure 1**).

1.Persistent uremic symptoms such as anorexia or nausea.

2. Persistent acidosis.

3. Hyperphosphatemia despite dietary restriction and medical therapy.

4. Evidence of malnutrition.

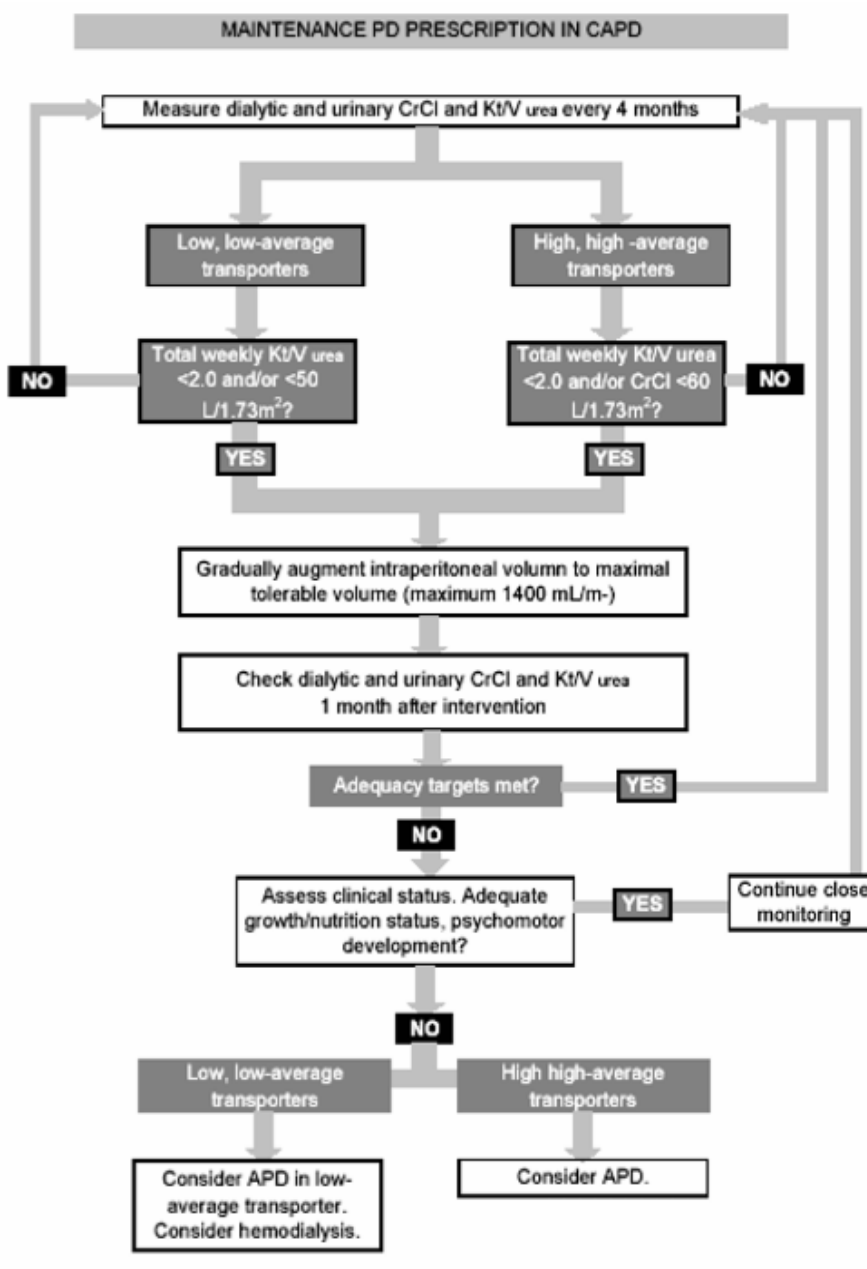

Figure 1: Maintenance PD Prescription in CAPD.

How should the PD prescription be changed when adequacy targets are not met?

1. Increase inflow volume per exchange (most effective, especially in low, low average, and high average transporters).

2. Increase the number of day exchanges (typically less effective than increasing the inflow volume).

3. Increase the ultrafiltration volume (ultrafiltration causes solvent drag, which leads to additional solute clearance) by either using hypertonic fluid or using icodextrin for the long overnight dwell (icodextrin should not be used for dwell times less than 8-9 hours).

4. Consider changing to APD (particularly in high/rapid transporters).

Typical initial CAPD prescription

The most common initial CAPD prescription in Indian CAPD patients is probably the 3x2L prescription, meaning 3 exchanges per day, with 2L inflow volume for each exchange (**Table 1**). The most common variations on this standard prescription take into consideration patient size and residual kidney function (RKF).

Table 1: Considerations when Writing the Initial CAPD Prescription

BMI	Inflow volume	Exchanges/day	Comments
< 25	1,500 - 2000 mL	3-4	If needed, larger fill volumes should be used at night (supine)
25 - 30	2000 mL	4	
>30	2500 - 3000 mL	4-5	Larger fill volumes should be used at night (supine)

Considerations when writing the initial CAPD prescription:

1. Smaller patients can usually meet solute clearance targets with smaller inflow volumes of 1,500 - 2000 mL, whereas large patients typically require inflow volumes of 2,500 mL or more.

2. Inflow volumes which are too large for a particular patient can be associated with discomfort (abdominal distension, back pain, decreased appetite from bloated sensation); however, some patients may grow accustomed to the inflow volume with time.

3. Larger inflow volumes increase intraperitoneal pressure, and therefore increase the risk of developing a new hernia or peritoneal leak. To decrease the intraperitoneal pressure, larger inflow volumes should be preferentially used at night, while supine; if the patient has large inflow volumes during the day the patient should avoid any activity or position which could further increase intraperitoneal pressure (e.g. Valsalva maneuver, squatting, chronic coughing, heavy lifting, etc.).

4. If significant residual kidney function is present, fewer exchanges per day may be sufficient (as long as the total peritoneal + renal Kt/V meets targets); in these cases NIPD (nocturnal dialysis only) can also be considered. In these patients, residual kidney function must be measured frequently (***i.e.*** every 2 months) to detect any decrement in RKF that would necessitate a change in the PD prescription in order to meet solute clearance targets.

5. The term "incremental PD" refers to the process of initiating peritoneal dialysis using fewer exchanges (and often at least one "dry" period during the day without a PD fluid dwell) when a patient has significant residual kidney function, and subsequently increasing the PD "dose" over time, as needed to meet solute clearance and ultrafiltration targets.

How to Reach the Goals

In order to reach PD therapeutic goals, a good understanding of the factors that determine peritoneal mass transfer and enhance clearance is required. As residual renal function or RRF is lost, it is necessary to adjust the dialysis dose to maintain adequacy, defined by the NFK/KDOQI guidelines as a minimal weekly total $Kt/V_{urea} \geq 1.71$). In patients who fall short of this goal, prescription parameters can be adjusted by the physician accordingly. These adjustments may include:

1. Increasing dialysate flow rate (DFR)-

The term dialysate flow rate refers to the total volume of dialysate exchanged over time. Increasing DFR is one of the most effective means of increasing solute removal. This can be achieved by either increasing the number of exchanges or by increasing the intraperitoneal volume. It is known that there are limitations to the use of high DFR in terms of clearance. Several studies have shown that when the

DFR is greater than 2.7 L to 3.0 L/hr, clearance plateaus or diminishes when intermittent techniquesare used. The most likely explanation for this phenomenon is that during frequent fast exchanges, the dialysis solution spends significantly more time (non-dialytic time) in transit, i.e., in and out of the peritoneal cavity, rather than in contact with the membrane. Keshaviah and colleagues reported that the optimal intraperitoneal volume is approximately 1500 mL/m^2 of body surface area (BSA) in sitting adults Durand et al. further suggest that the optimal prescribed volume depends on the maximum tolerated volume and the intraperitoneal pressure (IPP, not exceeding 18 cmH_2O). It is therefore important that the intraperitoneal volume prescribed is individualized for each patient, taking into consideration the patient's BSA, tolerance of fill volumes (measurement of IPP), expected ultrafiltration (each 500 mL of dialysate increases IPP by 1 cmH_20 and increases fluid absorption by 35 mL/hr), and drain profile.

2. Increasing the exchange volume

An increase in Vip significantly increases the effective peritoneal surface area and the mass transfer area coefficient (MTAC). An increase in volume also means that a higher amount of solute can be cleared until equilibrium is reached.

3. Performing PD in the supine position

Both position and Vip affect MTAC. The improvements in mass transfer observed by assuming the supine position provides an increase in effective peritoneal transfer area and could result in greater clearance during that time. Dialyzing in supine position may also allow an increased fill volume while staying within the limits of IPP.

4. Optimizing dwell time

Attention must also be given to optimal timing of the exchanges. Continuous therapy throughout the day and night is needed by most patients, with the exception of those with a very high solute transport. This is particularly important in order to maintain a high clearance of larger solutes such as the middle molecules. Larger solutes are more dependent on time and peritoneal surface area than dialysate flow rate (DFR). It is important to avoid very long dwell times, since UF diminishes due to glucose absorption and attenuation of the osmotic gradient. Dwell times in excess of 6 hours require higher glucose concentrations such as 2.5 or 4.25%or polyglucose solutions in order to prevent negative UF. If needed, patients on automated PD (APD) could incorporate an additional manual or automated exchange in the afternoon or evening in order to optimize both clearances and UF.

Optimizing dwell time for different solutes might also be accomplished by using methods developed by Fischbach and colleagues. They hypothesized that the sequential use of shorter dwells with smaller intra-peritoneal volumes (IPV) and longer dwells with larger IPVs are superior to uniform cycles. They suggested that short-dwell exchanges with small volumes could lead to greater UF capacity, and

long-dwell exchanges with large volumes would favor "saturation" of the dialysate with creatinine and phosphate. Thus, sequential use of both could provide more effective clearances and UF at lower glucose absorption *i.e.*, at lower metabolic costs. Such a regimen would be especially valid in average to high (fast) transporters.

5. Optimizing catheter function

Adequate catheter flows cannot be over emphasized since they are intimately related to DFR. It is therefore important to monitor the patient for factors that may impede flow *e.g.*, obstructions or kinks in the tubing.

Evaluating clearances

With regards to the total solute clearances, the KDOQI Guidelines recommend that renal and peritoneal Kt/V should be measured within the first month after initiating dialysis therapy and at least once every 4 months thereafter. This has been deemed appropriate since the peritoneal Kt/V_{urea} does not change much over time unless the prescription changes or a change in residual renal function (RRF) is observed. For patients with greater than 100 mL per day of residual kidney volume, 24-hour urine collection for solute clearance and urine volume should be obtained at a minimum of every 2 months or when a decrease in RRF is suspected (such as, decreasing urine output or recent exposure to a nephrotoxin). There is a substantial variability in the rate of RRF loss in PD patients. Therefore, to prevent patients from falling below the minimum total Kt/V_{urea} target of 1.7, obtaining a 24-hour urine measurement at this frequency seems appropriate. In addition, it is important to measure clearance when there is a problem, such as can occur with peritonitis episodes. Creatinine clearance can be obtained using 24-hour collection or peritoneal function test. However, determination of peritoneal creatinine clearance is of little added value for predicting risk for death, but may be used to monitor estimates of muscle mass over time. During the monthly evaluation of the patient on PD, nutritional status should also be estimated.

Serum albumin levels should be monitored and when obtaining 24-hour total solute clearances, an estimation of dietary protein intake should be undertaken.

Chapter 22

Ultrafiltration Failure

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Ultrafiltration Failure

Introduction

Peritoneal dialysis (PD) is an established treatment modality for end stage renal disease (ESRD) since last 4-5 decades. In 2008, worldwide, 1.9lakhs out of 1.77 million patients, who started on dialysis, received PD. After hemodialysis (HD) (69%) and renal transplant (25%); it is the third form of treatment opted by ESRD population [1]. Peritoneal membrane, which has a surface area equal to that of the body surface area (BSA), is being used as a permeability barrier. Survival of patients on PD depends on both solute clearance and ultrafiltration. Failure to maintain any of these leads to technique failure. UFF is one of a major cause of decreased ultrafiltration/ drain volume but both are not necessarily synonymous [2]. UFF is a peritoneal membrane defined clinical situation. It is a major complication after long duration of PD and a major factor deciding patient survival. The risk ranges from 2.6% after 1 year of PD to 30.9% after 6 years of dialysis [3]. It is characterized by sustained reduction in ultrafiltration for more than one month which is associated with features of fluid overload that persists despite of fluid restriction and use of three or more exchanges per day [4]. However, all the episodes of decreased ultrafiltration and/or oedema and/or fluid overload are not due to UFF. Hence, prior to diagnosing UFF, other causes must be ruled out (**Table 1**) [5]. Features of fluid overload may be associated either with preserved (apparent loss of ultrafiltration) or decreased (true loss of ultrafiltration) drain volume. Poor compliance to salt and water, poor adherence to PD prescription and loss of residual renal function (RRF) are associated with preserved ultrafiltration volume. Decreased ultrafiltration can be reversible or irreversible. Reversible causes include catheter malfunction, dialysate leak, hyperglycemia or recent peritonitis.

Table 1: Causes of Volume Overload other than UFF

Hyperglycemia (especially diabetic patients)
Poor compliance to salt and water
Poor adherence to PD prescriptions
Inappropriate bag selection
Inappropriate prescription as per PET test
Inappropriate prescription as per loss of RRF
Unable to use Icodextrin based PD solution
Catheter malfunction – migration, inflow and outflow issues
Dialysate leak – pericatheter leak, parietal leak, leak into pleura and genital wall

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UFF is an irreversible cause of decreased drain volume which can be Type 1-4 UFF as described below [4].

Histopathological Changes of Peritonium

Prolonged exposure to PDF leads to anatomical, histological and functional changes in peritoneum called peritoneal remodeling. This ultimately leads to peritoneal fibrosis, UFF and technique failure. Grossly, there is thickening of peritoneal membrane. On light microscopy, there is an infiltration of the inflammatory cells, mesothelial denudation, increase in submesothelial thickness, and vascular changes. On immunofluorescence microscopy, there is an extensive deposition of extracellular matrices such as type IV collagen and laminin. Electron microscopy revealed increase in collagenous fibers and degeneration of smooth muscle cells in the media. These changes in peritoneum appears even prior to start of dialysis but are aggravated by PD [6]. The structural changes are not followed by functional changes during the first 4 years on PD [7]. Study by William *et al*, (2002) shows that, thickness of the submesothelial CZ was 50 μm for normal subjects; 140-150 μm for uremic patients and those on HD; and 270 μm for patients undergoing PD. Vascular changes seen in patients with UFF includes progressive subendothelial hyalinization of postcapillary venule with luminal narrowing or obliteration and neovascularization. These vascular changes were absent in normal subjects but were present in 28% of uremic patients and 56% of patients undergoing PD. Thickness of CZ and vascular changes have been demonstrated to increase with the duration of PD and a strong correlation existed between thickness of CZ and solute transporter status [8, 9]

Aetiopathogenesis

Continuous exposures to bio-incompatible PDFs can leads to UFF. High glucose load and GDPs of conventional PDF cause peritoneal membrane inflammation leading to fibrosis, neovascularisation and UFF [10]. Study conducted by Kim *et al*, on rat model concluded that low GDP PDFs attenuates inflammatory responses and fibrosis seen with conventional PDF [11]. Study on animal models have shown that PD catheter acts as a foreign body and increases inflammatory response [12]. Similarly, peritoneal inflammation caused by peritonitis also plays a role in UFF [10]. Though PDF, PD catheter and peritonitis are factors responsible for UFF; PD itself is a major risk factor [13]. Study conducted by Honda et al found that peritoneal membrane thickness and hyalinizing vasculopathy correlates with duration on PD; and those with UFF have a thicker peritoneal membrane than those without UFF [13]. Other risk factors include diabetes and uremia [13]. The process of peritoneal fibrosis starts even prior to the initiation of PD explaining; uremia is an independent risk factor [14].

Epithelial mesenchymal transition (EMT) of MCs is central to the above processes and starts within six months of initiation of PD [15]. It leads to a decreased expression of E-cadherin; and an increased expression of collagen I and IV,

fibronectin, TGF-β, VEGF and endothelial nitric oxide synthase (eNOS) [16-18]. Release of TGF-β by MCs has a key role in EMT [15, 19]. VEGF regulates neoangiogenesis and is responsible for the high transporter status [20]. Excess of GDPs generated from dextrose based PD fluid and carbonyl compounds from uremia together lead to an accumulation of AGEs. Interaction of AGEs with its receptor (RAGEs) is responsible for damage of peritoneal membrane by activation of TGF-β which induces peritoneal fibrosis [14, 21]. High glucose resulted in a decreased expression of the antifibrotic cytokines, hepatocyte growth factor (HGF) and bone morphogenic protein 7 (BMP-7) [17]. 3,4-dideoxyglucosone-3-ene (3,4-DGE), the most bioactive GDP has been found to induce apoptosis of peritoneal MCs by caspase pathway [22]. Leptin also plays a significant role in peritoneal inflammation and fibrosis [23-25]. Uremia is associated with excess of leptin. It induces TGF-β synthesis in MCs through leptin receptor which is up regulated by glucose in PDF [24]. Uremia itself leads to an increased expression of VEGF, RAGEs, smooth muscle actin (SMA) and NFκBp65 on peritoneal membrane [21].

Peritoneal lymphangiogenesis is responsible for Type-3 UFF. Rat models suggest that, TGF-β mediated upregulation of VEGF-C on peritoneal mesothelial cell and macrophage is responsible for peritoneal lymphangiogenesis. Also, treatment with a TGFβR-I inhibitor suppresses VEGF-C expression, the lymphangiogenesis and fibrosis [26]. Hence, TGF-β1 also promotes lymphangiogenesis during process of peritoneal fibrosis. Aquaporin1 (AQP1) plays a major role in the solute-free water transport and mediates approximately 50% of ultrafiltration [27]. It is also important for angiogenesis [28]. Nonfunctioning of AQP1 leads to type-4 UFF, loss of sodium sieving and delayed wound healing. Role of mast cell in peritoneal remodeling has been evident from animal study. Its expression is up regulated in omentum associated with increased milky spot and vascular density [29]. Though the exact mechanism of peritoneal remodeling is unclear but supposed to act by producing profibrotic and angiogenic factors like VEGF, fibroblastic growth factor 2 (FGE-2), tumor necrosis factor α (TNF-α) and IL-8.(30) It also plays a major role in the omental tissue remodeling and synechiae formation [29].

Types of Ultrafiltration Failure

There are four types of ultrafiltration failure from Type1 to Type 4 [18]. Each is characterized by a different etiology and pathophysiologic mechanism. Type 1 UFF (UFF with High transporter) is the most common type of UFF and is due to a transition to the fast transporter status. It is characterized by a rapid loss of osmotic gradient due to absorption of glucose. The hallmark is new onset D/P Creatinine > 0. 81. It usually develops after a long duration of PD, typically 3 years or more. Probable mechanism is an increase in the effective surface area secondary to an increased vascularity [10, 31, 32]. They have high mass transfer area of coefficients and normal lymphatic flow rates. They have a high rate of net fluid absorption between 240-360 mins at the start of PD. Uremia; high glucose load, GDPs, AGEs, lactate and low pH of PDFs; and recurrent peritonitis are presumed aetiology [11, 13]. Acute episode of peritonitis can lead to transient UFF. Many patients who are

high transporters at the baseline develop features of fluid overload as RRF decreases. These patients are wrongly diagnosed as Type 1 UFF if baseline PET is not available.

Fast transporter can be either late acquired or early inherent. The late acquired phenotype (Type3) is already described above. In early inherent phenotype, pathology can be either due to vasculopathy (Type-1) or increased surface area (Type-2). Type-1 is due to a systemic inflammation and has poor prognosis. Increased C-reactive protein and IL-6 in serum and PD effluent are the surrogate markers of Type 1 phenotype. Type 2 and 3 have better prognosis. Increased CA125 in PD effluent is a surrogate marker of Type 2 phenotype [33]. Early inherent type usually doesn't respond to peritoneal membrane resting.

Type 2 UFF (UFF with Low transporter) is characterized by a decreased solute clearance and ultrafiltration secondary to decrease in effective surface area. Pathology is related to the adhesion and scarring after severe peritonitis and other intra-abdominal complications. It is caused by TGF-β causing epithelial mesenchymal transition, submesothelial fibrosis and obliterative vasculopathy [18]. These patients have low rates of glucose absorption from dialysate with no decrease in dialysate sodium concentrate. They have low ultrafiltration despite adequate transperitoneal osmotic gradient. More severe form may end with encapsulating peritoneal sclerosis (EPS), a syndrome characterized by the symptoms of bowel obstruction with extensive adhesion by hypertrophied and calcified peritoneum. Its frequency increases as the duration on PD increases and is seen mostly after 8 years.

UFF with Normal transporter (high average and low average) can be either due to increased lymphatic drainage of peritoneal fluid (Type 3) or due to aquaporin deficiency (Type 4). Type 3 UFF is due to peritoneal lymphangiogenesis [26]. It diagnosed by rate of reabsorption of dextran 70 or radiolebeled albumin from peritoneal cavity [18]. Failure to achieve desired ultrafiltration with icodextrin is the usual clinical scenario in this type of UFF, as icodextrin is reabsorbed through lymphatics [18]. These patients have poor prognosis and are usually managed by permanent shifting to hemodialysis or renal transplant. Type 4 UFF is diagnosed by comparing changes in dialysate sodium after a dwell of 30-60 mins with 4.25% and 1.5% dextrose respectively. Aquaporin deficiency leads to an impaired initial fall in dialysate sodium with 4.25% dextrose and difference in dialysate sodium <5mmol/l between 4.25% and 1.5% dextrose at 30-60mins [18, 34]. Aquaporine-1 found in peritoneal membrane mediates 50% of ultrafiltration [10, 27]. Aquaporin transport water but not sodium (sodium sieving), responsible for initial fall in dialysate sodium by 5-10mmol/l with 4.25% dextrose dwell, that doesn't occurs in aquaporin deficiency [35]. Free water clearance is less than 26% of total ultrafiltration is consistent with AQP-1 dysfunction. Free water clearance is calculated by mini-PET [36]. Again AQP deficiency is not quantitative; rather it is a functional defect. Common cause of UFF of patients on PD for more than 4 years is dysfunction of peritoneal water channels in combination with increased peritoneal surface area.

Increase lymphatic reabsorption is common cause of UFF in patients who are on PD for less than 2 years [32].

Genetics

There is a positive correlation between polymorphism of VEGF, IL-6 and eNOS with transporter property of patients. Other genes whose mutation may affect transporter properties are plasminogen activator inhibitor (PAI), aquaporin-1 and TGF-β [37].

Diagnosis of UFF **(Figure 1)**

Three essential features of ultrafiltration failure (UFF) are

1. Always implies peritoneal membrane dysfunction.
2. Presence of features of volume overload, *i.e.,* oedema, breathlessness, etc.
3. Sustained reduction in ultrafiltration volume to < 400ml by modified peritoneal equilibrium test (PET) which is conducted twice at one month gap [38, 39].

Prior to diagnosis of UFF, other causes of fluid overload as described in **Table 1** should be ruled out. Presence of features of fluid overload like oedema and ultrafiltration; and ultrafiltration volume less than 400ml are *sine qua non* to diagnose UFF. Modified PET test should be carried out to quantify ultrafiltration volume and determine solute transport characteristics. To determine solute transport characteristics, PET or modified PET makes no difference but latter is usually preferred, as it can be used for both quantifying ultrafiltration volume and determining solute transport characteristics in same sitting. Standard PET test uses 2.5% 2L dextrose while modified peritoneal equilibrium test uses 4.25% 2L dextrose.

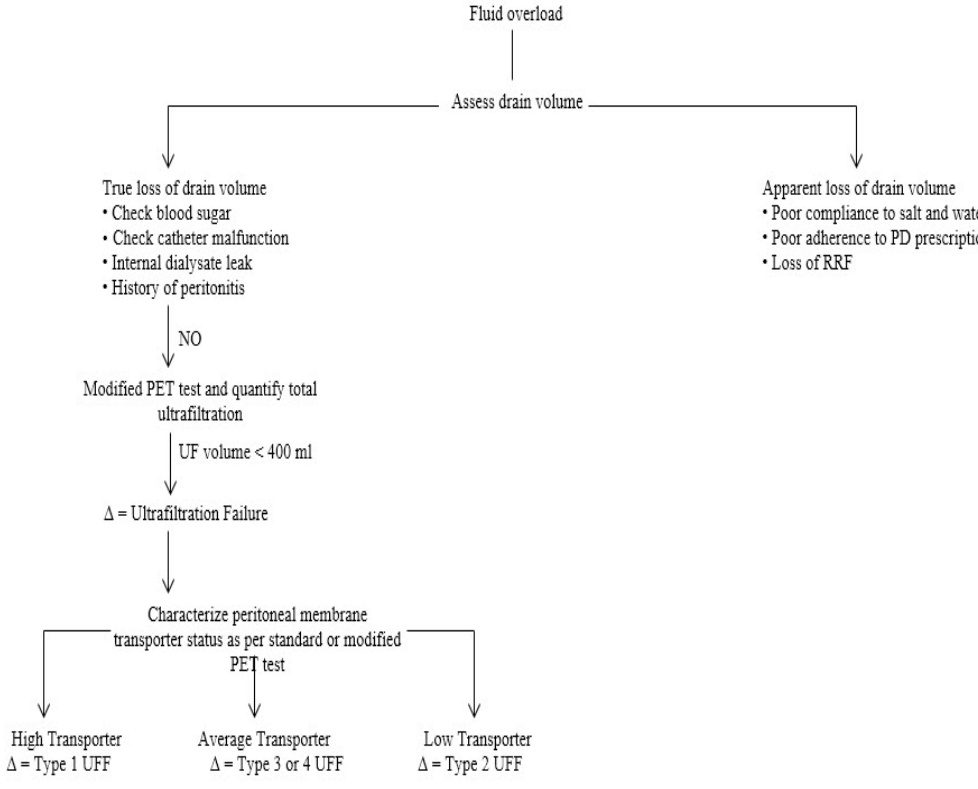

Figure 1: Approach to a patient with ultrafiltration failure

Preventive Measures

Asepsis to prevent peritonitis, early treatment of peritonitis and timely catheter removal in refractory peritonitis may help. Drugs targeting RAAS like ACEIs, ARBs and aldosterone antagonist retard peritoneal membrane remodeling significantly by slowing fibrosis and angiogenesis [40]. Their action is probably mediated by TGF-β [41]. Captopril has additional action on VEGF which is not seen with enalapril and losartan [30]. Avoidance of exposure to high dextrose containing PDF and use of biocompatible PDF like icodextrin or amino-acid based PDF and Glucose containing pH-neutral low GDP PDF retard progression to UFF due to their biocompatible nature, less GDP generation that prevent inflammation, angiogenesis and fibrosis [42, 43].

Management

General measures

Prior to diagnosis of UFF, other causes of fluid overload (**Table 1**) need to be ruled out. Diabetic patients are at a high risk of developing uncontrolled blood sugar, due to an absorption of glucose from PD fluid. Even some patients with normal or impaired blood sugar become overtly diabetic after starting PD. Deranged blood sugar leads to a loss of osmotic gradient and UFF. Using higher strength or decreasing dwell time will not solve the issue, rather this may aggravate it. Hence, diabetic patients should be subjected to an intense sugar monitoring. Non-diabetic patients should also be subjected to routine screening. Excess salt intake can lead to a volume overload secondary to increased thirst. Hence, salt (<3 gm/day) and water restriction is essential, especially those with no RRF. Non-adherence to PD prescription is an important cause of volume overload and should be suspected in all the patients. They usually do less number of exchanges or use low concentration bags. It can be confirmed by interrogating the patients or their relatives. They usually have good Kt/V, but the serum urea and creatinine remains high. While writing the PD prescription, PET results should always be considered. Managing high transporter with long dwell (CAPD) or low transporter with short dwell can lead to decreased ultrafiltration. Using higher strength bag or Icodextrin can solve issue of low ultrafiltration especially in high transporter and those on APD. Catheter malfunction like migration, nicking and omental wrap should also be excluded prior to the diagnosis of UFF. All the patients with decreased ultrafiltration should be subjected to X-ray KUB and chest. X-ray KUB can diagnose catheter migration and nicking. It can be managed by with better bowel preparation. If any mechanical cause, other than constipation, is suspected, it should be managed surgically. X-ray chest is useful for diagnosis of pleura-peritoneal shunt leading to hydrothorax and decreased ultrafiltration. Leak into parietal and genital organ is suspected clinically and USG may help in diagnosis. Suspected case of any leak can be confirmed by CT peritoneograhy or peritoneal scintigraphy using Technetium-labeled albumin colloid (5 mCi). These are usually managed conservatively with rest to peritoneum or low volume supine dwell or closure of surgical tract. After all patient education regarding blood sugar monitoring, low salt diet, compliance to PD prescription and regarding change of strength of bag is an essential step in managing decreased ultrafiltration.

Treatment strategy for any type of UFF includes achieving maximum urine output with or without high dose of diuretics, restricting fluid intake and dietary counseling regarding salt restriction. Type 1 UFF can be managed with short dwell (APD). Single daily exchange of icodextrin is an attractive option for these patients which is associated with less deterioration in membrane function [44-46]. It is neither absorbed across peritoneal membrane nor metabolized. It is slowly taken up by the lymphatics. Hence, osmotic gradient maintained up to 10-12 hour. Temporary cessation of PD for a period of 4 week may improve outcome by resting peritoneum except for inherent fast transporters [18, 47, 48]. It results in significant decrease in

mass transfer coefficient for creatinine and urea along with doubling of ultrafiltration [2].

Type 2 UFF is usually managed by transfer to HD unless the patient has a significant RRF. Patients with severe form of UFF, *i.e.*, EPS; immunosuppressive agents such as corticosteroid, azathioprine, mycophenolate, CNI inhibitors and mTOR inhibitors may be tried with variable success [49]. Tamoxifen has been found to be beneficial in EPS with increase in patient survival and can be tried as mono- or add-on therapy [50]. Severe form of EPS needs surgical enteroclysis but carries high mortality risk.

UFF with normal transporters (Type-3 and 4) are managed by general measures such as decreased salt and water, diuretics and short dwell time. Bethanechol, a cholinergic agent that improves ultrafiltration by contraction of diaphragmatic lymphatic stomata without change in transporter status in type-3 UFF [18, 51]. Icodextrin is particularly useful in aquaporin deficiency as it induces ultrafiltration by non-aquaporin channel not in type-3 UFF [52]. Though, high dose of corticosteroid upregulates peritoneal expression of AQP but it is rarely advised for type-4 UFF [53].

Novel Therapeutic Approach

These agents can act through multiple mechanisms to prevent or retard peritoneal membrane remodeling. First, they can act on several mediators like cytokines and growth factors to halt inflammations. Secondly, they can act on signaling pathway. It can be either directed against inflammation (Disodium chromoglycate, COX-2 inhibitor), AGES (PPAR-γ agonist, Benfothiamine, pyridoxamine and aminoguanidine), RAAS (ACEIs, ARBs and aldosterone blockers) and fibrinolytic system (statin) (**Table-2**).

Mast cell number is upregulated in the omentum of patients on PD. Disodium chromoglycate, a mast cell stabilizer, has been found to decreases inflammation, fibrosis and angiogenesis. It acts by decrease production of angiogenesis factors like VEGF, FGF-2 and IL-8; and preventing omental tissue remodeling [29]. COX-2 mediates angiogenesis by increasing survival of endothelial cell and VEGF production. Cox-2 inhibitors like Coxibs prevent UFF by inhibiting angiogenesis, lymphangiogenesis and fibrosis of peritoneal membrane [54]. They also have anti-inflammatory property. It decreases collagen-I production and TGF-β expression, but no effect on EMT. Study on animal models reveals that it can cause partial recovery of UFF [55]. But, it is associated with an increased risk of cardiac failure.

Table 2: Various Agenst and their Mechanism of Action

Class	Agents	Mechanism of action
Targeting Inflammation	Disodium chromoglycate	Mast cell stabilizer Decreases fibrosis, angiogenesis and inflammation No effect on AGES
	COX-2 inhibitors	Decreases fibrosis, angiogenesis and inflammation No effect on AGES and EMT
Targeting AGES	PPAR-γ agonist	Decreases AGES and EMT Decreases fibrosis, angiogenesis and inflammation
	Benfothiamine	Activation of transketolase. Decreases AGES, angiogenesis and inflammation. No effect on EMT.
	Aminoguanidine	Inhibition of nitric oxide synthase. Decreases AGES, angiogenesis and fibrosis.
	Alagebrium	Remove preformed AGEs
	Zopolrestat	Inhibitor of Aldose reductase Decreases AGES, angiogenesis and fibrosis.
	Pyridoxamine	Decreases AGES, angiogenesis and fibrosis
Targeting RAAS	ACEI/ARB Aldosterone antagonist	Inhibit TGF-β Slowing fibrosis and angiogenesis
Others	Vitamin D	Inhibits fibrosis, angiogenesis and inflammation. Anti-proliferative property RAAS inhibition TGF-β inhibition
	BMP-7	AntagonizeTGF-β Prevents EMT
	Octreotide	Inhibits VEGF
	Sunitinib	Inhibits VEGF and platelet derived growth factor receptors.
	Statins	fibrinolytic activity by increasing t-PA and PAI-1 synthesis Inhibit EMT was mediated via the mevalonate pathway

Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist has anti-inflammatory and antifibrotic property. Study on mice model suggests that it reduces AGEs, preserves peritoneal thickness and decreases MCs apoptosis; improves peritoneal function. It prevents fibrosis and angiogenesis. Its protective role on peritoneum is regulatory T cells mediated. It increases the recruitment of CD3+ lymphocytes and anti-inflammatory cytokine like interleukin (IL)-10. It does not prevent or reverse the EMT [56]. But its use in advanced renal failure patients is

limited by increased incidence of myocardiac infarction, hypoglycemia, abnormal lipid profile and bone fractures. Benfothiamine inhibits AGEs production through by activation of transketolase. By reducing VEGF and IL-6, it prevents inflammation and neoangiogenesis. It also has antioxidant property [57]. Aminoguanidine inactivates NO synthase, prevents the formation of AGEs and scavenges GDPs. It has also inhibitory effects on peritoneal mesothelial denudation and submesothelial monocyte infiltration. Thus, it prevents peritoneal angiogenesis and fibrosis preserving the functional capacity of peritoneal macrophages, peritoneal permeability and ultrafiltration [58]. In contrast to aminoguanidine which can't remove preformed AGEs, intraperitoneal alagebrium, an AGEs crosslink breaker can do so by cleavage of tissue AGEs [59].
Drug targeting RAAS have been addressed under heading "prevention". In addition to lipid lowering property, statins have fibrinolytic activity by increasing tissue plasminogen activator (t-PA) and decreasing plasminogen activator inhibitor type-1(PAI-1) synthesis. This action of statins on peritoneal membrane causes removal of fibrin deposition; and thereby reversing peritoneal thickening and preventing synechiae formation [60]. It also inhibit EMT was mediated via the mevalonate pathway [61].

Vitamin D has an anti-inflammatory, anti-angiogenic and anti-proliferative property. It also inhibits RAAS and reduced expression of TGF-β. PD patients treated with paricalcitol shows diminished peritoneal protein loss and increased ultrafiltration [62]. Ex vivo study suggests BMP-7 has the potential to reverse peritoneal EMT and thus can halt peritoneal fibrosis [63]. Treatment with HGF blocks high glucose–induced EMT in an animal model of peritoneal dialysis [17]. Smad signaling is a key pathway of TGF-β mediated renal fibrosis. Overexpression of Smad7 results in a marked inhibition of TGF-β mediated Smad2 activation and thus inhibits EMT [64]. Treatments targeting the inactivation of Smad2 or overexpression of Smad7 may provide a new therapeutic strategy. Sunitinib and octreotide have anti-VEGF property. In addition, sunitinib blocks at receptor level [30].

Recent Advances in Monitoring of Peritoneal Membrane Function

Though PET test is used routinely to monitor transporter status of peritoneal membrane, but it has poor predictive value. It can be used clinically to establish diagnosis but not for intervention to retard peritoneal fibrosis. Hence, scientists are in search of biomarker to monitor membrane status. βig-h3 may be a marker for biologically active TGF-β. The animal study demonstrated that dialysate effluent βig-h3 positively correlated with peritoneal solute transport; and increased in the dialysis group with alterations in peritoneal structure and function during PD [65]. CA125, which is a biomarker of healthy mesothelial cell, can be measured in PD effluent [66]. There is a positive correlation between dialysate to plasma creatinine and dialysate CA125 [67]. This positive correlation disappears as the duration of PD

passes on. Peritoneal resting has been found to increase the effluent CA125. No increase in CA125 after resting is predictive of peritoneal sclerosis [67]. Dialysate CA125 is a useful marker of biocompatibility assessment of PDF, as its concentration increases with more biocompatible PDFs like icodextrin, amino acid solution and glucose containing pH-neutral low GDP PDF in comparison to standard PDF [67]. There are no recommendations regarding frequency of monitoring of peritoneal membrane function. CA125 monitoring is advisable once every 3–4 months. PET to be done at 1 month after the start of PD and then once every year [67].

Conclusion

PD is self limited by structural and functional alternation of peritoneal membrane called peritoneal remodeling. UFF is an irreversible outcome of peritoneal dysfunction and leading cause that affects technique and patient survivals. It occurs as a result of various exogenous and endogenous stimuli such as PDF, PD catheter, uremia, cytokines and growth factors that ultimately leading to EMT and neovascularization. In most of the time treatment is conservative and unsatisfactory. Though ongoing research on animal model suggests some intervention options to retard the progression, but at present only few are in clinical use. Hence, efforts should be made to prevent UFF.

References

1. Lameire, N., and W. Van Biesen, 2010: Epidemiology of peritoneal dialysis: a story of believers and nonbelievers. *Nat. Rev. Nephrol.,* **6,** 75–82.
2. de Alvaro, F., M. J. Castro, and F. Dapena, 1993: Peritoneal resting is beneficial in peritoneal hyperpermeability and ultrafiltration failure. *Adv. Perit. Dial. Conf. Perit. Dial.,* **9,** 56–61.
3. Heimbürger, O., J. Waniewski, and A. Werynski, 1990: Peritoneal transport in CAPD patients with permanent loss of ultrafiltration capacity. *Kid. Int.*, **38,** 495–506.
4. Mactier, R. A., 1991: Investigation and management of ultrafiltration failure in CAPD. *Adv. Perit. Dial.,* **7,** 57–62.
5. Daugirdas, J. T., G. Peter, P. Blake, and S. Todd, 2014: Handbook of Dialysis. Ing. Philadelphia, PA: Lippincott Williams & Wilkins.
6. Honda, K., K. Nitta, and S. Horita, 1996: Morphological Changes in the Peritoneal Vasculature of Patients on CAPD with Ultrafiltration Failure. *Nephron.,* **72,** 171–176.
7. Savidaki, I., D. Karavias, and F. Sotsiou, 2003: Histologic change of peritoneal membrane in relation to adequacy of dialysis in continuous ambulatory peritoneal dialysis patients. *Perit. Dial. Int. J. Int. Soc. Perit. Dial.,* **23,** 26–30.
8. Williams, J. D., K. J. Craig, and N. Topley, 2002: Morphologic changes in the peritoneal membrane of patients with renal disease. *J. Am. Soc. Nephrol.,* **13,** 470–479.
9. Williams, J. D., K. J. Craig, and N. Topley, 2003: Peritoneal dialysis: changes to the structure of the peritoneal membrane and potential for biocompatible solutions. *Kid. Int. Suppl.,* **84,** 158–161.
10. Kim, Y. L., 2009: Update on mechanisms of ultrafiltration failure. *Perit. Dial. Int. J. Int. Soc. Perit. Dial.,* **29,** 123–127.
11. Kim, C. D., H. M. Kwon, and S. H. Park, 2007: Effects of low glucose degradation products peritoneal dialysis fluid on the peritoneal fibrosis and vascularization in a chronic rat model. *J. Int. Soc. Apher. Jpn. Dial. Ther.,* **11,** 56–64.
12. Flessner, M. F., K. Credit, and K. Henderson, 2001: Peritoneal changes after exposure to sterile solutions by catheter. *J. Am. Soc. Nephro.,* **18**, 2294–2302.
13. Honda, K., C. Hamada, and M. Nakayama, 2008: Impact of Uremia, Diabetes, and Peritoneal Dialysis Itself on the Pathogenesis of Peritoneal Sclerosis: A Quantitative Study of Peritoneal Membrane Morphology. *Clin. J. Am. Soc. Nephrol.,* **3,** 720–728.
14. De Vriese, A. S., R. G. Tilton, and S. Mortier, 2006: Myofibroblast transdifferentiation of mesothelial cells is mediated by RAGE and contributes to peritoneal fibrosis in uraemia. *Nephrol. Dial. Transplant.,* **21**, 2549–2555.
15. Yáñez-Mó, M., E. Lara-Pezzi, and R. Selgas, 2003: Peritoneal Dialysis and Epithelial-to-Mesenchymal Transition of Mesothelial Cells. *N. Engl. J. Med.,* **348**, 403–413.

16. Aroeira, L. S., A. Aguilera, and R. Selgas, 2005: Mesenchymal conversion of mesothelial cells as a mechanism responsible for high solute transport rate in peritoneal dialysis: role of vascular endothelial growth factor. *Am. J. Kid. Dis.,* **46**, 938–948.
17. Yu, M. A., K. S. Shin, and J. H. Kim, 2009: HGF and BMP-7 Ameliorate High Glucose–Induced Epithelial-to-Mesenchymal Transition of Peritoneal Mesothelium. *J. Am. Soc. Nephrol.,* **20**, 567–581.
18. Teitelbaum, I., 2015: Ultrafiltration failure in peritoneal dialysis: a pathophysiologic approach. *Blood Purif.,* **39**, 70–73.
19. Margetts, P. J., P. Bonniaud, and L. Liu, 2005: Transient overexpression of TGF-{beta} 1 induces epithelial mesenchymal transition in the rodent peritoneum. *J. Am. Soc. Nephrol.,* **16**, 425–436.
20. Boulanger, E., N. Grossin, and M. P. Wautier, 2007: Mesothelial RAGE activation by AGEs enhances VEGF release and potentiates capillary tube formation. *Kid. Int.,* **71**, 126–133.
21. Kihm, L. P., D. Wibisono, and S. Müller-Krebs, 2008: RAGE expression in the human peritoneal membrane. *Nephrol. Dial. Transplant.,* **23,** 3302–3306.
22. Lee, D. H., S. Y. Choi, and H. M. Ryu, 2009: 3,4-dideoxyglucosone-3-ene induces apoptosis in human peritoneal mesothelial cells. *Int. J. Perit. Dial.,* **29,** 44–51.
23. Leung, J. C. K., L. Y. Y. Chan, and M. F. Lam, 2012: The role of leptin and its short-form receptor in inflammation in db/db mice infused with peritoneal dialysis fluid. *Nephrol. Dial. Transplant.,* **27**, 3119–3129.
24. Leung, J. C. K., L. Y. Y. Chan, and S. C. W. Tang, 2006: Leptin induces TGF-beta synthesis through functional leptin receptor expressed by human peritoneal mesothelial cell. *Kid. Int.,* **69,** 2078–2086.
25. Yang, A. H., S. W. Huang, and J. Y. Chen, 2007: Leptin augments myofibroblastic conversion and fibrogenic activity of human peritoneal mesothelial cells: a functional implication for peritoneal fibrosis. *Nephrol. Dial. Transplant.,* **22,** 756–762.
26. Kinashi, H., Y. Ito, and M. Mizuno, 2013: TGF-β1 promotes lymphangiogenesis during peritoneal fibrosis. *J. Am. Soc. Nephrol.,* **24,** 1627–1642.
27. Ni, J., J. M. Verbavatz, and A. Rippe, 2006: Aquaporin-1 plays an essential role in water permeability and ultrafiltration during peritoneal dialysis. *Kid. Int.,* **69,** 1518–1525.
28. Saadoun, S., M. C. Papadopoulos, and M. Hara-Chikuma, 2005: Impairment of angiogenesis and cell migration by targeted aquaporin-1 gene disruption. *Nature,* **434,** 786–792.
29. Zareie, M., P. Fabbrini, and L. H. P. Hekking, 2006: Novel Role for Mast Cells in Omental Tissue Remodeling and Cell Recruitment in Experimental Peritoneal Dialysis. *J. Am. Soc. Nephrol.,* **17,** 3447–3457.
30. Farhat, K., A. W. D. Stavenuiter, and R. H. J. Beelen, 2014: Pharmacologic targets and peritoneal membrane remodeling. *Int. J. Perit. Dial.,* **34,** 114–123.

31. Smit, W., N. Schouten, and N. van den Berg, 2004: Analysis of the prevalence and causes of ultrafiltration failure during long-term peritoneal dialysis: a cross-sectional study. *J. Int. Perit. Dial.,* **24**, 562–570.
32. Smit, W., A. Parikova, D. G. Struijk, and D. T. Krediet, 2005: The difference in causes of early and late ultrafiltration failure in peritoneal dialysis. *Perit. Dial. Int.,* **25,** 41–45.
33. Chung, S. H., O. Heimbürger, and B. Lindholm, 2008: Poor outcomes for fast transporters on PD: the rise and fall of a clinical concern. *Semin. Dial.,* **21,** 7–10.
34. Ho-dac-Pannekeet, M. M., and R. T. Krediet, 1996: Water channels in the peritoneum. *Perit. Dial. Int.,* **16,** 255–259.
35. Smit, W., D. G. Struijk, M. M. Ho-Dac-Pannekeet, and R. T. Krediet, 2004: Quantification of free water transport in peritoneal dialysis. *Kid. Int.,* **66,** 849–854.
36. La Milia, V., S. Di Filippo, M. Crepaldi, L. Del Vecchio, C. Dell'Oro, S. Andrulli, and F. Locatelli, 2005: Mini-peritoneal equilibration test: A simple and fast method to assess free water and small solute transport across the peritoneal membrane. *Kid. Int.,* **68,** 840–846.
37. Axelsson, J., O. Devuyst, L. Nordfors, O. Heimbürger, P. Stenvinkel, and B. Lindholm, 2006: Place of genotyping and phenotyping in understanding and potentially modifying outcomes in peritoneal dialysis patients. *Kid. Int. Suppl.,* **103,** 138–145.
38. Ho-dac-Pannekeet, M. M., B. Atasever, D. G. Struijk, and D. T. Krediet, 1997: Analysis of ultrafiltration failure in peritoneal dialysis patients by means of standard peritoneal permeability analysis. *Perit. Dial. Int.,* **17,** 144–150.
39. Smit, W., P. van Dijk, M. J. Langedijk, N. Schouten, N. van den Berg, D. G. Struijk, and R. T. Krediet, 2003: Peritoneal function and assessment of reference values using a 3.86% glucose solution. *Perit. Dial. Int.,* **23,** 440–449.
40. Kolesnyk, I., M. Noordzij, F. W. Dekker, E. W. Boeschoten, and R. T. Krediet, 2009: A positive effect of AII inhibitors on peritoneal membrane function in long-term PD patients. *Nephrol. Dial. Transplant.,* **24,** 272–277.
41. Kagami, S., W. A. Border, D. E. Miller, and N. A. Noble, 1994: Angiotensin II stimulates extracellular matrix protein synthesis through induction of transforming growth factor-beta expression in rat glomerular mesangial cells. *J. Clin. Invest.,* **93,** 2431–2437.
42. Williams, J. D., N. Topley, K. J. Craig, R. K. Mackenzie, M. Pischetsrieder, C. Lage, and J. Passlick-Deetjen, 2004: The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. Kid. Int., **66,** 408–418.
43. Johnson, D. W., F. G. Brown, M. Clarke, N. Boudville, T. J. Elias, M. W. Foo, B. Jones, H. Kulkarni, R. Langham, D. Ranganathan, and J. Schollum, 2012: The effects of biocompatible compared with standard peritoneal dialysis solutions on peritonitis microbiology, treatment, and outcomes: the balANZ trial. *Perit. Dial. Int.,* **32,** 497–506.
44. Paniagua, R., M. J. Ventura, M. Avila-Díaz, A. Cisneros, M. Vicenté-Martínez, Z. García-González, D. Villanueva, O. Orihuela, G. Alcántara, and D. Amato, 2009:

Icodextrin improves metabolic and fluid management in high and high-average transport diabetic patients. *Perit. Dial. Int.,* **29,** 422–432.
45. Johnson, D. W., M. Arndt, A. O'Shea, R. Watt, J. Hamilton, and K. Vincent, 2001: Icodextrin as salvage therapy in peritoneal dialysis patients with refractory fluid overload. *BMC Nephrol.*, **2,** 2.
46. Davies, S. J., E. A. Brown, N. E. Frandsen, A. S. Rodrigues, A. Rodriguez-Carmona, A. Vychytil, E. Macnamara, A. Ekstrand, A. Tranaeus, and J. C. Divino Filho, 2005: Longitudinal membrane function in functionally anuric patients treated with APD: data from EAPOS on the effects of glucose and icodextrin prescription. *Kid. Int.,* **67,** 1609–1615.
47. Krediet, R. T., 2014: Should peritoneal resting be advised in ultrafiltration failure associated with a fast peritoneal solute transport status? *Perit. Dial. Int.,* **34,** 695–697.
48. De Sousa, E., G. Del Peso, L. Alvarez, S. Ros, A. Mateus, A. Aguilar, R. Selgas, and M. A. Bajo, 2014: Peritoneal Resting with Heparinized Lavage Reverses Peritoneal Type I Membrane Failure. A Comparative Study of the Resting Effects on Normal Membranes. *Perit. Dial. Int.,* **34,** 698–705.
49. Balasubramaniam, G., E. A. Brown, A. Davenport, H. Cairns, B. Cooper, S. L. Fan, K. Farrington, H. Gallagher, P. Harnett, S. Krausze, and S. Steddon, 2009: The Pan-Thames EPS study: treatment and outcomes of encapsulating peritoneal sclerosis. *Nephrol. Dial. Transplant.,* **24,** 3209–3215.
50. Korte, M. R., M. W. Fieren, D. E. Sampimon, H. F. Lingsma, W. Weimar, and M. G. Betjes, 2011: Tamoxifen is associated with lower mortality of encapsulating peritoneal sclerosis: results of the Dutch Multicentre EPS Study. *Nephrol. Dial. Transplant.,* **26,** 691–697.
51. Baranowska-Daca, E., J. Torneli, R. P. Popovich, and J. W. Moncrief, 1995: Use of bethanechol chloride to increase available ultrafiltration in CAPD. *Adv. Perit. Dial.,* **11,** 69–72.
52. Ho-dac-Pannekeet, M. M., N. Schouten, M. J. Langendijk, J. K. Hiralall, D. R. de Waart, D. G. Struijk, and R. T. Krediet, 1996: Peritoneal transport characteristics with glucose polymer based dialysate. *Kid. Int.,* **50,** 979–986.
53. Stoenoiu, M. S., J. Ni, C. Verkaeren, H. Debaix, J. C. Jonas, N. Lameire, J. M. Verbavatz, and O. Devuyst, 2003: Corticosteroids induce expression of aquaporin-1 and increase transcellular water transport in rat peritoneum. *J. Am. Soc. Nephrol.,* **14,** 555–565.
54. Fabbrini, P., M. N. Schilte, M. Zareie, P. M. ter Wee, E. D. Keuning, R. H. Beelen, and J. van den Born, 2009: Celecoxib treatment reduces peritoneal fibrosis and angiogenesis and prevents ultrafiltration failure in experimental peritoneal dialysis. *Nephrol. Dial. Transplant.,* **24,** 3669–3676.
55. Aroeira, L. S., E. Lara-Pezzi, J. Loureiro, A. Aguilera, M. Ramírez-Huesca, G. González-Mateo, M. L. Pérez-Lozano, P. Albar-Vizcaíno, M. A. Bajo, G. del Peso, and J. A. Sánchez-Tomero, 2009: Cyclooxygenase-2 Mediates Dialysate-Induced Alterations of the Peritoneal Membrane. *J. Am. Soc. Nephrol.,* **20,** 582–592.
56. Sandoval, P., J. Loureiro, G. González-Mateo, M. L. Pérez-Lozano, A. Maldonado-Rodríguez, J. A. Sánchez-Tomero, L. Mendoza, B. Santamaría, A.

Ortiz, M. Ruíz-Ortega, and R. Selgas, 2010: PPAR-γ agonist rosiglitazone protects peritoneal membrane from dialysis fluid-induced damage. *Lab. Investig. J. Tech. Methods Pathol.,* **90,** 1517–1532.
57. Kihm, L. P., S. Müller-Krebs, J. Klein, G. Ehrlich, L. Mertes, M. L. Gross, A. Adaikalakoteswari, P. J. Thornalley, H. P. Hammes, P. P. Nawroth, and M. Zeier, 2011: Benfotiamine protects against peritoneal and kidney damage in peritoneal dialysis. *J. Am. Soc. Nephrol.,* **22,** 914–926.
58. Zareie, M., G. J. Tangelder, T. Wee, L. H. Hekking, A. A. van Lambalgen, E. D. Keuning, I. L. Schadee-Eestermans, C. G. Schalkwijk, R. H. Beelen, and J. van den Born, 2005: Beneficial effects of aminoguanidine on peritoneal microcirculation and tissue remodelling in a rat model of PD. *Nephrol. Dial. Transplant.,* **20,** 2783–2792.
59. Lee, Y. K., J. Y. Lee, J. S. Kim, K. B. Won, H. J. Kang, T. J. Jang, W. T. Tak, and J. H. Lee, 2009: The breakdown of preformed peritoneal advanced glycation end products by intraperitoneal alagebrium. *J. Korean Med. Sci.,* **24,** 189–194.
60. Haslinger, B., M. F. Goedde, K. H. Toet, and T. Kooistra, 2002: Simvastatin increases fibrinolytic activity in human peritoneal mesothelial cells independent of cholesterol lowering. *Kid. Int.,* **62,** 1611–1619.
61. Chang, T. I., H. Y. Kang, K. S. Kim, S. H. Lee, B. Y. Nam, J. Paeng, S. Kim, J. T. Park, T. H. Yoo, S. W. Kang, and S. H. Han, 2014: The effect of statin on epithelial-mesenchymal transition in peritoneal mesothelial cells. *PloS One*. **9,** e109628.
62. Coronel, F., S. Cigarran, A. Gomis, B. Rodríguez-Cubillo, J. A. Herrero, P. Delgado, and J. Delgado, 2012: Changes in peritoneal membrane permeability and proteinuria in patients on peritoneal dialysis after treatment with paricalcitol−a preliminary study. *Clin. Nephrol.,* **78,** 93–99.
63. Vargha, R., M. Endemann, K. Kratochwill, A. Riesenhuber, N. Wick, A. M. Krachler, L. Malaga-Dieguez, and C. Aufricht, 2006: Ex vivo reversal of in vivo transdifferentiation in mesothelial cells grown from peritoneal dialysate effluents. *Nephrol. Dial. Transplant.,* **21,** 2943–2947.
64. Li, J. H., H. J. Zhu, X. R. Huang, K. N. Lai, R. J. Johnson, and H. Y. Lan, 2002: Smad7 Inhibits Fibrotic Effect of TGF-β on Renal Tubular Epithelial Cells by Blocking Smad2 Activation. *J. Am. Soc. Nephrol.,* **13,** 1464–1472.
65. Park, S. H., S. Y. Choi, M. H. Kim, E. J. Oh, H. M. Ryu, C. D. Kim, I. S. Kim, and Y. L. Kim, 2008: The TGF-β-induced gene product, βig-h3: its biological implications in peritoneal dialysis. *Nephrol. Dial. Transplant.,* **23,** 126–135.
66. Krediet, R. T., 2013: Cancer antigen 125 as a biomarker in peritoneal dialysis: mesothelial cell health or death? *Perit. Dial. Int.,* **33,** 715–718.
67. Struijk, D. G., 2008: Monitoring of the peritoneal membrane. *NDT Plus,* **1,** 29–35.

Chapter 23

Encapsulating Peritoneal Sclerosis

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Encapsulating Peritoneal Sclerosis

Introduction

Encapsulating peritoneal sclerosis (EPS) is a devastating complication of long term peritoneal dialysis (PD) first reported in 1980. EPS results from chronic inflammation of the peritoneum which is multifactorial in nature. Prolonged PD is the commonest risk factor identified. Several multicentre studies in Japan reported that EPS occurs between 0.8% and 2.8% of all the patients. Reported incidence in Australia is 0.7%. In Europe, the incidence ranges from 0.3 per 1000 in Spain to 3.1 in 1000 in Belgium. It is characterised by chronic malnutrition, acute or subacute intestinal obstruction and ultrafiltration failure (UFF). Diagnosis is confirmed by microscopic/or radiological observation of sclerosis, calcification, peritoneal thickening and encapsulation of the intestine. The mortality rate of patients with EPS is between 25% to 35%.

Risk factors

Duration of PD: This is the most important risk factor for the development of EPS.

In an Australian study, the incidence of EPS increased with duration of dialysis being 1.9, 6.4, 10.8 and 19.4% in patients on PD for more than 2, 5, 6, and 8 years, respectively.

Age of Starting PD: Younger the patient starts PD, the greater the chance for development of EPS. This variable is not related to the duration of dialysis, however the peritoneal mesothelial repair is vigorous in younger patient and results in early development of fibrosis.

Kidney Transplantation: The risk of developing EPS is high after renal transplantation. Calcium neurin inhibitors either cyclosporine or tacrolimus given after transplantation are profibrotic agents which upgrade the synthesis of TGF ß and other profibrotic factors which in turn potentiate the synthesis of matrix. Cessation of PD prevents the removal of inflammatory substances which further enhances the progression to sclerosis.

Bioincompatibility of PD fluids: Hyperosmolality, acidity, high glucose content and glucose degradation products promote EPS formation. These factors enhance the remodelling and fibrosis of peritoneal membrane which enhance the peritoneal permeability that is a forerunner of EPS.

Other PD dependant factors: Like plasticisers, chlorhexidine antibiotics, acetate and lactate buffer can also cause remodelling of membrane.

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Genetic factors: A few genetic abnormality is seen among the EPS population like RAGE-429T/C single nucleotide polymorphisms. eNOS genotype polymorphism is also more frequent.

Peritonitis: Recurrent peritonitis can damage the peritoneal membrane. The enzymatic activity of bacteria can cause degradation of fibrinogen to fibrin which facilitates fibrin deposition. The peritonitis often results in cessation of PD which results in an accumulation of inflammatory substances in the peritoneum. And, also peritonitis acts as a second hit for EPS.

Conversion of PD to haemodialysis (HD): This results in an accumulation of inflammatory substances in the peritoneum.

Pathogenesis of encapsulating peritoneal sclerosis

Role of Inflammatory Factors: The concentration of proinflammatory and profibrotic cytokines is very high in PD effluent which is due to increased synthesis by mesothelial cells and fibroblastic cells. This occurs under the influence of the risk factors in long term PD patients. PD catheter by itself and the bacterial biofilm formed in relation with catheter, low PH, high osmolality, high glucose level, GDP, AGES, promote the synthesis of TGF and PDGF. Synthesis of pro inflammatory cytokines like IL-1, IL6, IL-18, and TNF is upregulated. Bowel ischaemia associated with fibrosis also leads to translocation of bacteria from intestine which increases the inflammation and fibrosis.

Fibrin Deposition and Fibrinolysis: Peritoneal inflammation initiates the fibrous exudation which can be either lysed or remodelled by fibroblasts causing fibrous adhesion formation. Plasmin- plasminogen-plasminogen activator-plasminogen activator inhibitors plays a key role in the metabolism of fibrin. The serum of long term patients on PD contains high levels of plasminogen activator inhibitors 1 and 2 and low levels of plasmin. Mesothelial cells under the influence of profibrotic factors express more plasminogen activator inhibitors. Imbalance between fibrin synthesis and degradation leads to EPS formation.

Epithelial mesanchymal transformation (EMT): Mesothelial cell are unique in expression of both epithelial and mesenchymal markers. The mesothelial cells are the main source of myofibroblasts in long term patients on PD. Under the influence of risk factors, mesothelial cells lose cell to cell contact and apical and basal polarity and invade the basal layer. These cells acquire mesenchymal phenotype, express alpha smooth muscle actin and express and deposit extracellular matrix. Loss of *E Catherinis* is a prerequisite for EOT transformation. The mesothelial markers like ICAM -1 and cytokeratin are present on the myofibroblasts. Proinflammatory and profibrotic cytokines AGES, bioincompatibe dialysate, induce the formation of EMT. EMT is essential for the development of peritoneal fibrosis and EPS. The myofibroblasts synthesise more fibrin and other extracellular matrix.

Growth factors and EPS: Interaction of various growth factors is important for the thickening of sub mesothelial layer and coooning of bowel. The levels of pro neoangiogenic factor vascular endothelial factor level found in the peritoneal effluent directly correlates with the duration of PD. VEGF induces neoangiogenesis, vasculopathy and thickening of membrane. TGF ß is also found to be high in peritoneal effluent which induces the expression of procollagen 1 in mesothelial cells, promotes peritoneal fibrosis and the adhesion of intestines. TGF ß also increases the level of metalloproteinases-2 which is a potential marker of peritoneal injury and progression to EPS. Many other growth factors like HGF, PDGF, CTGF and FGF are involved in the formation of EPS.

Pathology:

Macroscopy: Cocoon like encapsulation of the entire intestines is seen in advanced EPS. Intestinal loops are adherent to one another and are fixed. The visceral peritoneum is fibrous and thickened. The adhesion between parietal and visceral peritoneum is very rare and is seen only in advanced cases. Fibrin deposition, focal bleeding on the peritoneum and varying degrees of bloody ascitis are observed.

Microscopy: Sub mesothelial compact zone is thickened and there is gradual loss of mesothelium (mesothelial denudation). Histologically, membrane consists of fibrinous matrices with homogenous or lamellar appearances. Materials stain red or blue with mason trichrome and tissues are histochemically positive for fibrin. Perivascular bleeding is frequently observed. The enlarged fibroblasts are distributed in increased number in the fibrous tissue. Mononuclear cell infiltration and increased angiogenesis are also observed. Vasculopathy, arterial occlusion, inflammation, tissue and arterial calcification and ossification are also observed

Histological criteria for the diagnosis

1. Fibrin deposition.

2. Fibroblast enlargement.

3. Capillary angiogenesis.

4. Mononuclear infiltration.

5. Presence of several immune histological markers of peritoneal fibroblast activation like MIF, FGF, Bek, Mib-1 and Bcl-2.

Cinical features

EPS in the early stages presents with abdominal symptoms like anorexia, nausea, vomiting, early satiety, abdominal pain and altered bowel habits. In advanced stages patients have features of abdominal obstruction, infection, malnutrition and bowel ischaemia.

Classification of EPS

Nakamoto classified EPS into 4 stages depending upon clinical symptoms

Stage 1: Pre EPS stage is asymptomatic with mild ascitis and no inflammation.

Stage 2: Inflammatory stage patients are symptomatic with nausea and diarrhea due to partial encapsulation of bowel and intestinal swelling mild inflammation with fibrin exudation.

Stage 3: Encapsulation symptoms of bowel obstruction due to the formation of the fibrous cocoon. It can be associated with mild to severe inflammation.

Stage 4: Chronic stage of ileus where absolute bowel obstruction due to encapsulating cocoon is seen. There is no inflammation at this stage.

Diagnosis

Clinical findings, radiological tests and histopathological findings of the diseased tissue are useful for the diagnosis. One should suspect development of EPS in susceptible patients who develop clinical symptoms of intestinal obstruction, inflammation, malnutrition and ultrafiltration failure and high CRP level and low albumin level. Ultrasonography, water soluble contrast studies and CT scanning are helpful in the confirmation of EPS. CT scan findings include peritoneal enhancement, peritoneal thickening, calcification, signs of bowel obstruction and loculated collection. Dynamic cinematographic magnetic resonance scanning with advanced image analysis may be useful in early diagnosis. For the final confirmation, peritonial biopsy is essential and the typical histopathological findings confirm the diagnosis.

Biomarkers for the diagnosis of EPS

CA125-denoting loss of mesothelial cells are decreased in the PD effluent long before the development of EPS. And, also the levels of inflammatory cytokines like IL-6 are increased.

Treatment of EPS

PD should be stopped immedialy after the diagnosis of EPS and PD catheter should also be removed. Most of the patients are malnourished and nutritional support is essential for these patients. Total parenteral nutrition should be started perioperatively and should be continued until the gut function improves.

Medical treatment

Corticosteroids are very effective in the early inflammatory phase of EPS. Steroids suppress inflammation, prevent fibrin deposition and collagen synthesis. It also prevents malnutrition. Steroids prevent the accumulation of ascitis and its

formation. However, in the advanced stage of disease, the clinical response to steroid is very poor.

Tamoxifen is a selective estrogen receptor modulator with antifibrotic properties. Tamoxifen inhibits/modulates the action of TGF ß, blocks EMT, inhibits mesothelial migration, improves fibrinolysis and reduces the levels of VEGF, which in turn reduces the angiogenesis. Tamoxifen is always used in combination with steroids.

Surgery in EPS

In advanced stages of disease, surgery is the only option. Peritonectomy and enterolysis are the types of surgical treatment. Mortality ranges from 19% to 35%. Recurrence after surgery is around 24%. Recent surgery which involves noble plication of intestine (suturing of the intestines to each other to prevent obstruction) along with routine enterolysis reduces the recurrence rate to 12%. Steroids and tamoxifen may be continued after the surgery, as they have a beneficial role in preventing the recurrence. Renal transplantation is another option of treatment. Despite the high risk of developing recurrent disease, chance of survival is much improved with functioning renal transplant.

Prevention

At present, there is no strategy to prevent the development of EPS. Prevention of recurrent peritonitis is also a useful strategy to prevent EPS. The use of more biocompatible dialysate prevents EPS. Use of tamoxifen and angiotensin converting enzyme inhibitors may be helpful in ameliorating EPS. Other options include shifting of patient from PD to HD after 8 years, assessment of the peritoneal membrane function after 8 years and shifting of high transporters to HD. The assessment of CA125 and IL-6 after peritoneal lavage and conversion to HD in appropriate patients is another option.

Conclusion

EPS is a rare and devastating complication of long-term PD. The exact etiology of EPS is still unknown. Prolonged PD is the single most risk factor for the development for EPS. Uremia, inflammation, EMT and loss of fibrinolytic activity are the possible mechanisms of EPS development. CT scan and MRI scan are useful in the diagnosis of EPS. Low levels of CA125 and high IL-6 levels in PD effluent are the early biomarkers of EPS. In the early stages, medical treatment with corticosterods, tamoxifen and nutritional treatment prevents the progression of disease. In the advanced stages, surgical treatment of peritonectomy and enterolysis are required to relieve the bowel obstruction. Peri operative TPN should be continued in the postoperative period until bowel function improves. Corticosteroids and tamoxifen should be given in postoperative period to prevent the recurrence of disease.

References

1. Aguilera, A., M. Yáñez-Mo, R. Selgas, F. Sánchez-Madrid, and M. López-Cabrera, 2005: Epithelial to mesenchymal transition as a triggering factor of peritoneal membrane fibrosis and angiogenesis in peritoneal dialysis patients. *Curr. Opin. Investig. Drugs,* **6,** 262–268.

2. Augustine, T., P. W. Brown, S. D. Davies, A. M. Summers, and M. E. Wilkie, 2009: Encapsulating peritoneal sclerosis: clinical significance and implications. *Nephron. Clin. Pract.*, **111,** 149-154.

3. Baroni, G., A. Schuinski, T. P. deMoraes, F. Meyer, and R. Pecoits-Filho, 2012: Inflammation and the peritoneal membrane: causes and impact on structure and function during peritoneal dialysis. *Mediators Inflamm.*, **2012,** 91-95.

4. Boulanger, E., 2008: Peritoneal and systemic inflammation: the benefits of using biocompatible peritoneal dialysis fluids. *Perit. Dial. Int*., **28,** 28–31.

5. Braun, N., P. Fritz, C. Ulmer, J. Latus, M. Kimmel, D. Biegger, G. Ott, F. Reimold, K. P. Thon, J. Dippon, and S. Segerer, 2012: Histological criteria for encapsulating peritoneal sclerosis—a standardized approach. *PLoSONE* **7,** e48647.

6. Braun, N., F. Reimold, D. Biegger, P. Fritz, M. Kimmel, C. Ulmer, and M. D. Alscher, 2009: Fibrogenic growth factors in encapsulating peritoneal sclerosis. *Nephron. Clin. Pract.*, **113,** 88–95.

7. DeFreitas, D., A. Jordaan, R. Williams, J. Alderdice, J. Curwell, H. Hurst, A. Hutchison, P. E. Brenchley, T. Augustine, and A. M. Summers, 2007: Nutritional management of patients undergoing surgery following diagnosis with encapsulating peritoneal sclerosis. *Perit. Dial. Int.*, **28,** 271–276.

8. DelPeso, G., M. A. Bajo, F. Gil, A. Aguilera, S. Ros, O. Costero, M. J. Castro, and R. Selgas, 2003: Clinical experience with tamoxifenin peritoneal fibrosing syndromes. *Adv. Perit. Dial*., **19,** 32–35.

9. Gandhi, V. C., H. M. Humayun, T. S. Ing, J. T. Daugirdas, V. R. Jablokow, S. Iwatsuki, W. P. Geis, and J. E. Hano, 1980: Sclerotic thickening of the peritoneal membrane in maintenance peritoneal dialysis patients. *Arch. Intern. Med*., **140,** 1201–1203.

10. Habib, S. M., M. G. H. Betjes, M. W. Fieren, E. W. Boeschoten, A. C. Abrahams, W. H. Boer, D. G. Struijk, W. Ruger, C. Krikke, R. Westerhuis, and R. G. de Sévaux, 2011: Management of encapsulating peritoneal sclerosis: a guideline on optima land uniform treatment. *Neth. J. Med*., **69,** 500–507.

11. Hirahara, I., M. Inoue, K. Okuda, Y. Ando, S. Muto, and E. Kusano, 2007: The potential of matrix metalloproteinase-2 as a marker of peritoneal injury, increased solute transport, or progression to encapsulating peritoneal sclerosis

during peritoneal dialysis–a multicentre study in Japan. *Nephrol.Dial. Transplant.* 22, 560–567.

12. Honda, K., K. Nitta, S. Horita, M. Tsukada, M. Itabashi, H. Nihei, T. Akiba, and H. Oda, 2003: Histologic criteria for diagnosing encapsulating peritoneal sclerosis in continuous ambulatory peritoneal dialysis patients. *Adv. Perit. Dial. Conf. Perit. Dial.*, **19,** 169–175.

13. Honda, K., K. Nitta, S. Horita, W. Yumura, and H. Nihei, 1996: Morphological changes in the peritoneal vasculature of patients on CAPD with ultrafiltration failure. *Nephron,* **72,** 171–176.

14. Honda, K., and H. Oda, 2005: Pathology of encapsulating peritoneal sclerosis. *Perit. Dial. Int*., **25,** 19–29.

15. Io, H., C. Hamada, Y. Ro, Y. Ito, I. Hirahara, and Y. Tomino, 2004: Morphologic changes of peritoneum and expression of VEGF in encapsulated peritonea lsclerosis rat models. *Kid. Int.*, **65,** 1927–1936.

16. Junor, B. J., and M. A. McMillan, 1993: Immunosuppression in sclerosing peritonitis. *Adv. Perit. Dial*., **9,** 187–189.

17. Kawaguchi, Y., H. Kawanishi, S. Mujais, N. Topley, and D. G. Oreopoulos, 2000: Encapsulating peritoneal sclerosis: definition, etiology, diagnosis and treatment. International Society for Peritoneal Dialysis AdHoc Committee on Ultrafiltration Management in Peritoneal Dialysis. *Perit. Dial. Int.*, **20,** 43–55.

18. Kawaguchi, Y., A. Saito, H. Kawanishi, M. Nakayama, M. Miyazaki, H. Nakamoto, and H. Tranaeus, 2005: Recommendations on the management of encapsulating peritoneal sclerosis in Japan, 2005: diagnosis, predictive markers, treatment, and preventive measures. *Perit. Dial. Int.*, **25,** 83–95.

19. Kawanishi, H., 2012: Surgical and medical treatments of encapsulation peritoneal sclerosis. *Contrib. Nephrol.,* **177,** 38–47.

20. Kawanishi, H., Y. Kawaguchi, H. Fukui, S. Hara, A. Imada, H. Kubo, M. Kin, M. Nakamoto, S. Ohira, and T. Shoji, 2004: Encapsulating peritoneal sclerosis in Japan: a prospective, controlled, multicenter study. *Am. J. Kid. Dis*., **44,** 729–737.

21. Plummer, M., C. Bromberek, B. Bresnahan, and S. Hariharan, 2002: Expression of TGF-beta and fibrogenic genes in transplant recipients with tacrolimus and cyclosporine nephrotoxicity. *Kid. Int*., **62,** 2257–2263.

22. Kolesnyk, I., F. W. Dekker, M. Noordzij, S. IeCessie, D. G. Struijk, and R. Krediet, 2007: Impact of ACE inhibitors and AII receptor blockers on peritoneal membrane transport characteristics in long-term peritoneal dialysis patients. *Perit. Dial. Int*., **27,** 446–453.

23. Kuriyama, S., and H. Tomonari, 2001: Corticosteroid therapy in encapsulating peritoneal sclerosis. *Nephrol. Dial. Transplant.*, **16,** 1304–1305.

24. Liu, L., C. X. Shi, A. Ghayur, C. Zhang, J. Y. Su, C. M. Hoff, and P. J. Margetts, 2009: Prolonged peritoneal gene expression using a helper-dependent adenovirus. *Perit. Dial. Int*., **29,** 508–516.

25. MandlWeber, S., C. D. Cohen, B. Haslinger, M. Kretzler, and T. Sitter, 2002: Vascular endothelial growth factor production and regulation in human peritoneal mesothelial cells. *Kid. Int*., **61,** 570–578.

26. Masunaga, Y., S. Muto, S. Asakura, T. Akimoto, S. Homma, E. Kusano, and Y. Asano, 2003: Ascites from patients with encapsulating peritoneal sclerosis augments NIH/3T3 fibroblast proliferation. *Ther. Apher. Dial*., **7,** 486–493.

27. Nakayama, M., Y. Kawaguchi, H. Yamada, T. Hasegawa, K. Takazoe, N. Katoh, H. Hayakawa, N. Osaka, H. Yamamoto, A. Ogawa, and H. Kubo, 1997: Immuno histochemical detection of advanced glycosylation end- products in the peritoneum and its possible patho physiological role in CAPD. *Kid. Int*., **51,** 182–186.

28. Rigby, R. J., and C. M. Hawley, 1998: Sclerosing peritonitis: the experience in Australia. *Nephrol. Dial. Transplant*., **13,** 154–159.

29. Ro, Y., C. Hamada, M. Inaba, H. Io, K. Kaneko, and Y. Tomino, 2007: Inhibitory effects of matrix metallo proteinase inhibitor ONO- 4817 on morphological alterations in chlorhexidine gluconate induced peritoneal sclerosis rats. *Nephrol. Dial. Transplant.*, **22,** 2838–2848.

30. Sampimon, D. E., M. R. Korte, D. L. Barreto, A. Vlijm, R. deWaart, D. G. Struijk, and R. T. Krediet, 2010: Early diagnostic markers for encapsulating peritoneal sclerosis: a case-control study. *Perit. Dial. Int*., **30,** 163–169.

31. Sulaiman, H., L. Dawson, G. J. Laurent, G. J. Bellingan, and S. E. Herrick, 2002: Role of lasminogen activators in peritoneal adhesion formation. *Biochem. Soc. Trans*., **30,** 126–131.

32. VanWestrhenen, R., J. Aten, N. Hajji, O. J. deBoer, C. Kunne, D. K. deWaart, and R. T. Krediet, 2007: CyclosporinA induces peritoneal fibrosis and angiogenesis during chronic peritoneal exposure to a glucose based, lactate buffered dialysis solution in the rat. *Blood Purif*., **25,** 466–472.

33. Vlijm, A., J. Stoker, S. Bipat, A. M. Spijkerbower, S. S. Phoa, R. Maes, D. G. Struijk, and R. T. Krediet, 2009 Computed tomographic findings characteristic for encapsulating peritoneal sclerosis: a case-control study. *Perit. Dial. Int*., **29,** 517–522.

34. Williams, J. D., K. J. Craig, C. vonRuhland, N. Topley, and G. T. Williams, 2003: The natural course of peritoneal membrane biology during peritoneal dialysis. *Kid. Int.,* **64,** 43-49.

35. Wong, C. F., S. Beshir, A. Khalil, P. Pai, and R. Ahmad, 2005: Successful treatment of encapsulating peritoneal sclerosis with azathioprine and prednisolone. *Perit. Dial. Int*., **25,** 285–287.

36. Wright, B, A. Summers, J. Fenner, R. Gillott, C. E. Hutchinson, P. A. Spencer, M. Wilkie, H. Hurst, S. Herrick, P. Brenchley, and T. Augustine, 2011: Initial observations using a novel cinemagnetic resonance imaging technique to detect changes in abdominal motion caused by encapsulating peritoneal sclerosis. *Perit. Dial. Int*., **31,** 287–290.

37. Yamamoto, R., Y. Otsuka, M. Nakayama, Y. Maruyama, N. Katoh, M. Ikeda, H. Yamamoto, K. Yokoyama, Y. Kawaguchi, and M. Matsushima, 2005: Risk factors for encapsulating peritoneal sclerosis in patients who have experienced peritoneal dialysis treatment. *Clin. Exp. Nephrol*., **9,** 148–152.

38. Yang, A. H., J. Y. Chen, and J. K. Lin, 2003: Myofibroblastic conversion of mesothelial cells. *Kid. Int*., **63,** 1530–1539.

39. Zweers, M. M., D. G. Struijk, W. Smit, and R. T. Krediet, 2001: Vascular endothelial growth factor in peritoneal dialysis: a longitudinal follow up. *J. Lab. Clin. Med*., **137,** 125–132.

Chapter 24
Sodium Sieving

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Sodium Sieving

Sodium and water retention as well as hypertension are common in peritoneal dialysis (PD) patients and contribute to cardiovascular diseases, which are the leading causes of death in these patients [1]. Restricting the oral sodium intake is frequently not enough, and compliance is often inadequate, to achieve a neutral sodium balance. The removal of sodium and fluid has been identified as a predictor of mortality in PD patients independent of residual renal function and failure to achieve >750 ml of daily ultrafiltration (UF) in anuric patients is associated with increased mortality. The combination of fluid overload along with hypertension can be a major factor for developing cardiovascular disease, the leading cause of death in PD patients. Therefore, sodium removal by dialysis is crucial for peritoneal dialysis (PD) patients.

The pattern of sodium transport in peritoneal dialysis differs from the typical pattern observed for other small solutes such as urea, creatinine, potassium, etc.,for which the dialysate concentration equilibrates with the respective plasma concentration during the exchange. The sodium concentration in most currently used dialysis fluids is already close to, or only slightly lower than the plasma sodium concentration. Thus sodium transport is accomplished almost in an isocratic condition. This situation favors a precise estimation of sieving coefficient (S) because the impact of diffusive transport will be smaller than for other solutes. During PD, sodium is transported by diffusion (due to the concentration gradient between blood and dialysate), by convection (due to ultrafiltration), and by peritoneal absorption (bulk flow of fluid and solutes, comprising of direct lymphatic absorption and absorption to interstitial tissues) [2, 3].

As regards sodium transport from blood to dialysate, convective transport is found to be about two times higher than the diffusive transport for all the three glucose solutions. Convection depends mainly on the rate of ultrafiltration, and therefore it is most rapid at the beginning of the exchange and its rate increases with the initial glucose concentration in dialysis fluid (**Figure 1**). Diffusive transport also increases with the initial glucose concentration because of the increase in sodium concentration gradient, especially in the initial short period of the dwell, due to increased dilution of sodium in dialysis fluid induced by ultrafiltration of water from blood with considerable rejection (sieving) of sodium during this process. The rate of sodium diffusion is almost constant because the changes in sodium gradient during the exchange are rather small except during the initial short period of the dwell.

V. Billa

Concept of Sieving

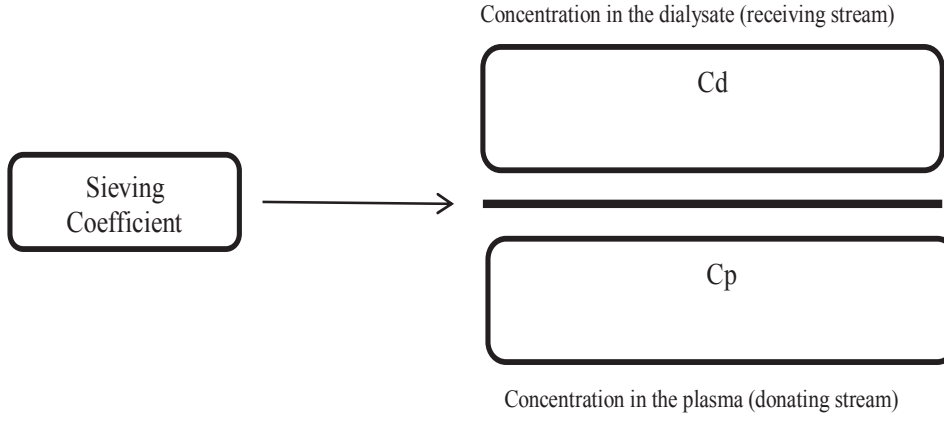

Figure 1: The Concept of Sieving.

Absorption of sodium, together with dialysis fluid is considerably more than the diffusive transport. The net sodium removal would therefore be negative if it was not for the convective transport in the other direction. This dissociation between UF of water and sodium transport is, therefore, of greatest clinical relevance to patients using automated PD (APD) during short dwells that might have clinical consequences [4].

Applied anatomy of the peritoneal membrane

The average surface area of the peritoneal membrane is between 1 and 1.3 m^2 in adults. During PD, it is principally the parietal peritoneum that participates in peritoneal transport. In addition to the capillary surface area, the diffusion length between the dialysate and the mesothelium also plays an important role in the overall transport characteristics of the peritoneum. There are three barriers between the dialysate in the peritoneum and capillary blood: the capillary wall, which is most important; the interstitium; and the mesothelial cell layer. The mesothelial cell layer does not constitute a major barrier to solute or water transport, while the interstitium offers some resistance to solute transport that is mainly restricted to large solutes [5].

The 3-pore model**:** Pores for solute transport: According to the three-pore model of solute transport, the capillary wall consists of a system of pores of three sizes, which are size selective in restricting solute transport:

● Large pores constitute 3% percent of the total number of pores, average radius >150 Å. The radii of the larger pores vary in size.

● Small pores constitute 95%, with an average radius 40 to 50 Å that mediate the transport of lower-molecular-weight solutes. The radii of the smaller pores are constant. The number of small pores limits the transport of these solutes.

● Ultra-small pores constitute 2%, have a 3 to 5 Å radius, and are essentially Aquaporin-1 channels. This is permeable only to water, is present in the endothelial cells of the peritoneal microvasculature as the major water channel. The aquaporin system is responsible for trans-cellular water transport induced by the osmotic gradient created by adding hypertonic dialysate to the peritoneum. On average, it accounts for approximately 40 percent of total capillary ultrafiltration, with the remainder occurring via the para-cellular route between the cells. Unlike aquaporin-mediated transport, which is primarily determined by the osmotic gradient, the small-pore water transport is dependent upon non-osmotic determinants [6].

Applied physiology of the peritoneal membrane

Solutes of interest in peritoneal clearance include, sodium molecular weight (MW) 23, Urea MW 56, creatinine MW 113. For solutes that are much smaller than the membrane pores the movement of solvent carries the solute with it at the same rate, independent of molecular size. For larger solutes, however, movement of solute may be relatively restricted. The magnitude of this restriction can be expressed as the sieving coefficient, which is simply the rate of movement of solute relative to solvent, and is a property of both the membrane and the solute. The transport of low-molecular-weight solutes (e.g. urea and creatinine) across the peritoneum primarily occurs by diffusion. This process is size selective (small solutes diffusing at faster rates than the larger solutes), and the rate is dependent upon the concentration gradient, peritoneal surface area, and peritoneal permeability.

Solute transport = Concentration gradient x Surface area of the Peritoneal membrane x Peritoneal

Membrane permeability

Solute transport = Concentration gradient x MTAC

MTAC (Mass transfer area coefficient) = measures the equilibrium concentrations of two streams across a semipermeable membrane

The MTAC for sodium is 4 mL/min, urea 16, and creatinine is 9, when hypertonic glucose (3.86 percent) is used as a dialysate [7]. Na has a molecular weight of 23 and can easily travel through the small pores.

However, *in vivo* sodium behaves as a larger molecule, probably due to hydration-induced alterations in its configuration and therefore can travel only through the larger pores. The MTAC of sodium is therefore significantly lower. Thus, sodium

behaves as a larger molecule. The molecular radii of Na (0.98A) and Cl (1.81 A) are much smaller than those estimated during PD (2.3A each). It is conceivable that interactions of these ions with water molecules leads to the development of a water shell and cause the development of transport characteristics that suggest a higher molecular weight. The lower MTAC of sodium is likely due to the lower permeability coefficient of Sodium present across the lipid bilayer membrane [5, 8].

In the beginning of the dwell, with a hyperosmolar dialysis solution, the crystalloid osmotic gradient of the PD fluid will have a maximum value. This drives free water transport through the aquaporins into the peritoneal cavity. This causes a dilution of the dialysate sodium, so dialysate sodium concentration goes down. Small pores, however, are influenced by tonicity only to a limited extent. As a consequence, there is an increasing sodium concentration gradient in the second part of the dwell, and this drives diffusive sodium transport over the small pores during this part. Sieving of sodium is defined as the dip in the dialysate concentration of sodium that occurs during the initial phase of a dialysis exchange with a hyperosmolar dialysis solution because of the dissociation between the amounts of water and sodium transport.

Measurement of Sieving Coefficient of sodium

Although sodium is being sieved at the blood side, the Sieving Coefficient is conventionally measured on the dialysate side. Ratio of sodium concentration in the ultrafiltrate and plasma is used the Sieving Coefficient (SC) for sodium.

$$\text{Sieving Coefficient} = \frac{\text{Ultrafiltrate [Na]}}{\text{Plasma [Na]}}$$

The lower the amount of sodium being sieved, the higher is the SC. If SC = 1, then equimolar amounts of Na and H_2O has moved from the Plasma to the Ultrafiltrate i.e both Na and water moved at the same rate from the plasma to the ultrafiltrate, i.e Na diffusion = Ultrafiltration rate

The higher the amount of sodium being sieved, the lower is the SC. If no Na moves from the plasma to the Ultrafiltrate, then the SC is 0. Thus the higher the SC, the greater the convective transport for that solute. Realistically the Sieving coefficient of Sodium is between 0 and 1. The Sieving coefficient of Sodium in the absence of diffusion averages 0.7 [9, 10].

Clinical application of Sodium sieving in Peritoneal Dialysis

In fast transporters, this "second part" starts very fast, whereas in slow transporters, it can take up to an hour (visualized by the sodium dip). So, the deeper the sodium dip, and the later it appears in the time of the dwell, the more there will be sodium sieving in short dwells.[11]

Ultrafiltration and Sodium removal are two distinct processes. Pure water removal is not proportional to sodium removal. Sodium sieving is all about pure water removal. Sieving makes ultrafiltration a less effective form of convective solute transport. However, without sieving, glucose-induced ultrafiltration itself could not occur, as the membrane would not be "semipermeable." In most patients, the sodium concentration in blood and dialysate are similar (132mEq/L), which implies that aquaporin-mediated water transport can be estimated by the amount of sodium sieving, measured as the dip in the D/P sodium. In fast transporters, this starts very fast, whereas in slow transporters, it can take up to an hour.

Realistically the Sieving coefficient of Sodium ranges between 0 and 1. The Sieving coefficient of Sodium in the absence of diffusion averages 0.7 [12]. This hindrance in the removal of sodium compared to the removal of water is not clinically important during CAPD, because the increment in the concentration gradient is counteracted by increased diffusion of sodium. Depending upon the modality employed, sodium sieving can produce dysnatremias in the patient. During short dwells using hypertonic dialysate, as often applied in automated PD, much more water than sodium is removed from the extracellular volume; this can lead to severe hypernatremia [13, 14, 15]. Dialysis solutions that are not hypertonic, for instance because they remove fluid by colloid osmosis, do not induce sodium sieving and will therefore remove water and sodium at similar rates [19].

In comparison, sodium sieving in CAPD can produce hyponatremia. 1) Euvolemic hyponatremia is a result of sodium deficit due to reduced intake or excessive dialytic sodium removal. This phenomenon can be observed in CAPD. 2) Hypervolemic hyponatremia due to a positive balance with electrolyte free water and weight gain. 3) Hypervolemic hyponatremia in malnutrition or in catabolic states, loss of potassium and inorganic phosphates from intracellular compartment with expansion of ECF volume with or without weight loss [16, 17, 18].

Sodium sieving is also dependent upon the concentration of the PD solution used, which influences the amount of Na removed during PD. Both hypotonic and hypertonic CAPD end up removing similar quantities of Sodium although the mechanics of this is different. By increasing the glucose tonicity, there is more UF and hence more sodium sieving. During CAPD with a net ultrafiltration of 1 L/24 h the peritoneal removal of sodium is only 98 mmol/day [19]. Icodextrin containing solutions are characterized by the presence of large glucose polymers as osmotic agent, hence giving rise to a slow but sustained ultrafiltration. This glucose polymer-containing solution induces ultrafiltration according to the principle of colloid osmosis. Based on the three-pore model there will be no sieving of sodium in the initial phase of a dwell with icodextrin and subsequently no change in D/P sodium over time [20]. (**Figure 2**)

For any degree of ultrafiltration sodium removal is better with CAPD as compared to APD status also influences sodium sieving.

Low transporters = Higher ultrafiltration =more sodium sieving = lower D/P sodium

High transporters = Low Ultrafiltration = less sodium sieving = higher D/P sodium

Membrane failure = Low ultrafiltration = less sodium sieving = higher D/P sodium [4]

The modified PET Test can study sodium sieving. This test semi quantitatively evaluates the membranes transport capacity determined by the rate at which the solute reaches equilibrium concentration in the plasma and the dialysate. In addition to the D/P Creatinine and the UF obtained, Sodium sieving which is a reflection of the free water transport in the first hour of the exchange is expressed as D/P Na at 60 mins or by the dip in the dialysate [Na] at 60 minutes (ΔNa).

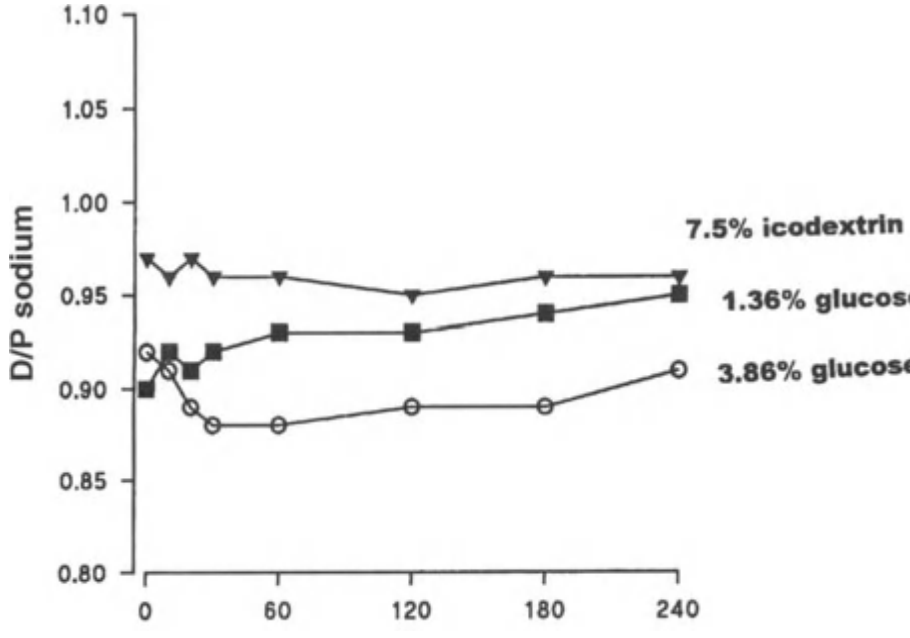

Figure 2: Dialysate/plasma ratio sodium (D/P sodium) during 4-h dwells with glucose 1.36% (•), glucose 3.86% (o) and 7.5% icodextrin.

During the hypertonic dwells with 3.86% glucose a decrease of D/P sodium was observed, indicating sieving of sodium through ultrasmall pores, whereas the icodextrin solution induced no changes in D/P sodium. (Drukker Parsons and Mayer. Replacement of Renal Function by Dialysis. 5th Edition Eds. Waller H. Hörl, Karl M. Koch, Robert M. Lindsay, Claudio Ronco, James F. Winchester (editor-in-chief) Springer).

It is preferable to use ΔNa over D/P Na for a number of reasons: (i) it is not necessary to assay the concentration of sodium in both the dialysate and the plasma (it also means not having to correct for the concentration in the plasmatic water); (ii) peritoneal diffusion of sodium in the first 60 minutes of the PET can be considered negligible (iii) the ΔNa value is more intuitive and more straightforward

A preserved sodium sieving means ΔNa ≥5 mmol/L and in patients with reduced sodium sieving ΔNa <5 mmol/L. A reduction in, or loss of, Na sieving and therefore reduced, zero or even negative ΔNa, is symptomatic of a reduction in, or loss of, free water transport capacity. Reduced or absent free water transport may contribute to reduced UF capacity or UF failure, as it represents approximately 50% of peritoneal UF in the first part of an exchange with a hypertonic solution. In addition, ΔNa alterations can be associated with severe peritoneal membrane damage [18].

Unlike water, the removal of Sodium during PD either by diffusion or by convection is a challenge. Whatever Sodium removal occurs by trans-capillary ultrafiltration and diffusion is counteracted by the uptake of Sodium coupled to peritoneal fluid absorption. The resultant low net removal of Sodium from the body is also a function of the low MTAC of the peritoneal membrane. Reduction in peritoneal absorption would significantly increase the sodium removal and may therefore provide an alternative means of increasing removal of sodium and water, especially in high transport patients and when low glucose solutions are used.

The finding that sodium diffuses as a larger molecule during PD has focused attention on the potential use of ultralow sodium dialysis solutions to improve net ultrafiltration. Favourable results of such a solution in overhydrated CAPD patients has been reported [21] Two studies have been published comparing dialysate with sodium concentration of 100 mmol/L with a commercially available normal sodium dialysis solution [22, 23]. Sodium removal increased about threefold during a 6-h dwell [22], but the low sodium solution induced only marginally better Ultrafiltration. This could be explained by the calculated reflection coefficient of glucose that was slightly higher than the reflection coefficient of sodium [9].

The Sodium Sieving phenomenon prevents the ultrafiltration force to clear Sodium. If Sieving did not exist, then the membrane would not be called semipermeable. Solutes and water would freely travel back and forth across the membrane, dissipating concentration gradients and thus preventing the ability of an osmotic pressure to build up and cause ultrafiltration. Hence PD technology as we know it would not have been possible. Thus Sieving, although it make convection less effective, it makes osmotic pressures more effective and hence ultrafiltration possible.

References

1. Lamiere, N. H., R. Vanholder, and A. Van Loo, 1996: Cardiovascular diseases in peritoneal dialysis patients: the size of the problem. *Kid. Int.,* **50,** 28–36.

2. Leypoldt, J. K., 2002: Solute transport across the peritoneal membrane. *J. Am. Soc. Nephrol.,* **13,** 84–91.

3. Aguirre, R. A., and H. Abensur, 2014: Physiology of fluid and solute transport across the peritoneal membrane. *J. Bras. Nefrol.,* **36**, 74-79.

4. Aanen, M. C., D. Venturoli, and S. J. Davies, 2005: A detailed analysis of sodium removal by peritoneal dialysis: comparison with predictions from the three-pore model of membrane function. *Nephrol. Dial. Transplant.,* **20,** 1192–1200.

5. Misra, M., and R. Khanna, Mechanisms of solute clearance and ultrafiltration in PD. In: Up To Date, Golper, T. A. (Ed).

6. Rippe, B., 1993: A three-pore model of peritoneal transport. *Perit. Dial. Int.,* **13,** 35–38.

7. Heimbürger, O., J. Waniewski, A. Werynski, and B. Lindholm, 1992: A quantitative description of solute and fluid transport during peritoneal dialysis. *Kid. Int.,* **41,** 1320.

8. Wang, T., J. Wstlewslu, O. Heimburger, A. Werynski, and B. Lindholm, 1997: A quantitative analysis of sodium transport and removal during peritoneal dialysis. *Kid. Int.,* **52**, 1609—1616.

9. Krediet, R. T., 2010: The physiology of peritoneal solute transport and ultrafiltration. *Textbook of Peritoneal Dialysis.* Gokal, R., R. Khanna, R. T. Krediet, and K. D. Nolph, Eds. 137–172.

10. Krediet, R. T., Peritoneal anatomy and physiology during peritoneal dialysis. *Replacement of renal function by dialysis.* Horl, W. H., K. M. Koch KM, R. M. Lindsay, C. Ronco, and J. F. Winchester, Eds., 115-157.

11. van den Berg, R., T. Trijntje, Cnossen, J. Constantijn, A. M. Konings, P. Jeroen, P. Kooman, M. Frank, S. van der Sande, M. Karel, and L. Leunissen, 2008: Different treatment options in peritoneal dialysis. *NDT Plus*, **1,** 14-17.

12. Chen, T. W., R. Khanna, H. Moore, Z. J. Twardowski, and K. D. Nolph, 1991: Sieving and reflection coefficients for sodium salts and glucose during peritoneal dialysis in rats. *JASN*, **2,** 1092-1100.

13. K. D. Nolph, J. E Hano, and P. E. Teschan, 1969: Peritoneal sodium transport during hypetonic peritoneal dialysis: Physiologic mechanisms and clinical implications. *Ann. Intern. Med.,* **70**, 931-941.

14. Raja, R. M., R. E. Cantor, C. Boreyko, H. Busheri, M. S. Kramer, and J. L. Rosenbaum, 1972: Sodium transport during ultrafiltration peritoneal dialysis. *Trans. Am. Soc. Artif. Intern. Organs,* **18,** 429-433.

15. Colorobi, A., 1991: Sodium modelling in CAPD. *Contrib. Nephrol.,* **89,** 155-66.

16. Rodriguez-Carmona, A., M. Pérez-Fontán, R. Garca-Naveiro, P. Villaverde, and J. Peteiro, 2004: Compared time profiles of ultrafiltration, sodium removal, and renal function in incident CAPD and automated peritoneal dialysis patients. *Am. J. Kid. Dis.,* **44,** 132-145.

17. Ortega, O., P. Gallar, and A. Carreno, 2001: Peritoneal sodium mass removal in continuous ambulatory peritoneal dialysis and automated peritoneal dialysis: influence on blood pressure control. *Am. J. Nephrol.,* **21**,189–193.

18. Virga, G. A., 2013: Comparison between continuous ambulatory and automated peritoneal dialysis. *J. Nephrol.,* **26,** 140-158.

19. Ho-dac-Pannekeet, M. M., N. Schouten, and M. J. Langedijk, 1996: Peritoneal transport characteristics with glucose polymer based dialysate. *Kid. Int.,* **50,** 979.

20. Rusthoven, E., R. T. Krediet, H. L. Williems, L. A. Monnens, and C. H. Scroder, 2005: Sodium sieving in children. *Perit. Dial. Int.,* **25,** 141–142.

21. Nakayama, M., K. Yokoyama, and H. Kubo, 1996: The effect of u1tra-low sodium dialysate in CAPD. A kinetic and clinical analysis. *Clin. Nephrol.,* **45,** 188-193.

22. Imholz, A. L. T., G. C. M. Koomen, D. G. Struijk, L. Arisz, and R. T. Krediet, 1994: Fluid and solute transport in CAPD patients using ultralow sodium dialysate. *Kid. Int.,* **46,** 333-340.

23. Leypoldt, J. K., Charney, A. K.Cheung, C. L. Naprestek, B. H. Akin, and T. R. Shockley, 1995: Ultrafiltration and solute kinetics using low sodium dialysate. *Kid. Int.,* **48,** 1959-1966.

Chapter 25

Abnormalities of Host Defence Mechanisms during Peritoneal Dialysis

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Abnormalities of Host Defence Mechanisms during Peritoneal Dialysis

Normal Peritoneal Host Defence Mechanisms

Human immunity consists of innate immunity and adaptive immunity. Innate immunity is present since birth and is protective against a wide range of antigens. Antigen exposure in not needed but there is no memory cell formation [1]. The components of innate immunity are cells, chemical mediators and pattern recognition receptors. Adaptive immunity is acquired after exposure and consists of lymphocytes and antibodies [2]. Both the types of immunity exist in the peritoneal cavity as well. However, there are some difference between the peritoneal defence mechanisms and those in the blood. The factors responsible for the specific micro-environment in the peritoneal cavity are not clear.

Cells in peritoneum

Peritoneal cells consist of resident cells in the peritoneum (mesothelial cells, peritoneal macrophages, natural killer cells, antigen presenting cells [APC]) that form a part of innate immunity. Other cells, *i.e.*, neutrophils (PMN) and lymphocytes increase in number during peritonitis by migrating from capillaries. (Adaptive immunity) [3-7].

Peritoneal Macrophages

(PMΦ) arise from bone marrow and are released into circulation as monocytes. These migrate into the peritoneal cavity and become PMΦ [3, 4] Normal peritoneal cavity has 100 ml fluid and contains 5×10^5-10^6/ml PMΦ [3]. Their functions are:

Antigen presentation: Macrophages process the antigen and act as APCs [3, 5] APCs present the antigen together with the major histocompatibility complex (MHC) to T cells, *i.e*., APC with MHC-II present it to CD4 and APC with MHC-I present it to CD8 cells. Co-stimulatory molecules like CD80/86 with B7 are needed for interaction. (**Figure 1**) APCs contribute to the malnutrition-inflammation-atherosclerosis syndrome and may also affect T-cell functions.

M. Sahay

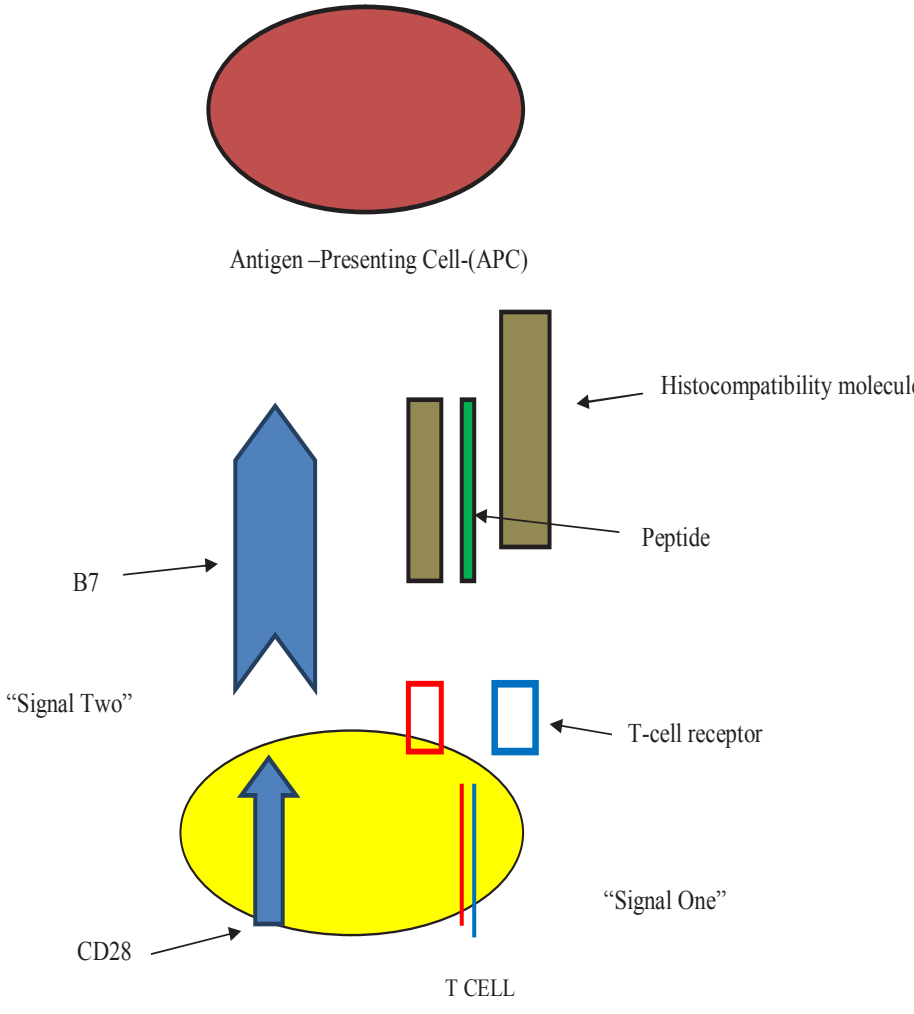

Figure 1: APC and T-Cell Interaction

Phagocytosis by PMΦ involves

• *Recognition and attachment*: Receptors on the surface of PMΦ recognise the pathogen [3, 5]. Opsonization of pathogen promotes phagocytosis. Opsonization is the coating of antigen by substances called opsonins, *e.g.*, IgM, IgG, complement factor C3b, fibronectin, mannose binding lectin, CRP, fibrinogen *etc*. PMΦ have CD11b, CD16, CD64 and CD14 on surface which bind to the opsonins.
• *Engulfment*: the particle is engulfed by phagocyte and a phagosome is formed which fuses with lysosome to form phagolysosome.
• Killing and degradation in the phagolysosome occurs by mainly oxygen dependent mechanisms due to generation of free oxygen radicals. NADPH oxidase in the cell membrane acts on the oxygen molecule to produce superoxide O_2^-. This molecule by spontaneous dismutation forms hydrogen peroxide (H_2O_2). H_2O_2 is converted to OH^- which kills the bacterium (**Figure 2**).

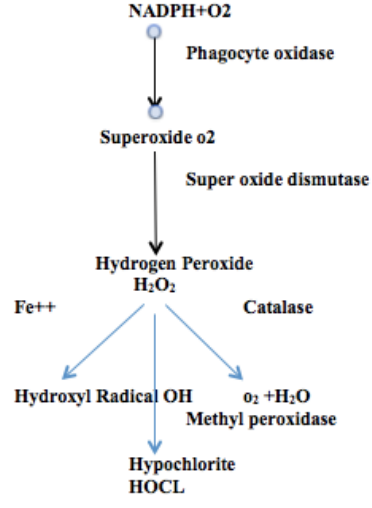

Figure 2: Free Oxygen Radicals

Secretion of cytokines

Based on the types of cytokines produced, PMΦ are of 2 types-

• PMΦ1 are activated by bacterial products and γ-IFN and produce NO and pro-inflammatorycytokine eg. IL-1 and TNF which stimulate leucocytes and peritoneal mesothelial cells.
• PMΦ2 are activated by microbial products and IL-4, 5. These release IL-10 and TGF-β and are anti-inflammatory. (**Table 1a , 1b**)

Table 1a: Cytokines of Innate Immunity

	Sources(s)	**Target(s)**
IL 1	Macrophages, Endothelia, Epithelia	Endothelia (↑coagulation, ↑inflammation), hepatocytes (↑acute phase proteins), hypothalamus (↑fever)
IL 6	Macrophages, Endothelia T lymphocytes	Hepatocytes (↑acute phase proteins), B lymphocytes (↑ proliferation)
IL 10	Macrophages, T lymphocytes	Macrophages, Dendritic cells (↓IL 12)
IL 12	Macrophages, Dendritic cells	Th1 lymphocytes (↑ differentiation),Tc lymphocytes (↑IFN-II Y), NK lymphocytes (↑IF-II Y)
IL 15	Macrophages	NK lymphocytes(↑ proliferation) T lymphocytes(↑ proliferation)
IL 18	Macrophages	NK lymphocytes(↑IFN II Y) T lymphocytes(↑IFN II Y)
IL 23	Macrophages, Dendritic cells	T lymphocytes(↑17)
IL 27	Macrophages, Dendritic cells	Th1 lymphocytesinhibition and/or differentiation) NK lymphocytes(↑IF-II Y)
TNF	Macrophages, T lymphocytes	endothelia(↑coagulation, ↑inflammation) hepatocytes (↑acute phase proteins), neutrophils (↑ activation), hypothalamus(↑fever)
INF-I(α)	Macrophages	All cells (↑ viral immunity, ↑MHC class I), NK lymphocytes (↑activation)
INF-I (β)	Fibroblasts	All cells (↑ viral immunity, ↑MHC class I), NK lymphocytes (↑activation)
INF-I	Under study	All cells (↑ viral immunity, ↑MHC class I), NK lymphocytes (↑activation)
Chemokines	Macrophages, Endothelia, Fibroblasts, Epithelia	Phagocyte (↑mitigation), B lymphocytes (↑mitigation), T lymphocytes (↑mitigation), ↑wound repair

Table 1b: The Cytokines of Adaptive Immunity

	Source(s)	Target(s)
Lymphotoxin	T Lymphocytes	B Lymphocytes (↑ development) T Lymphocytes (↑ development) neutrophils (↑ migration ↑ activation)
IL-2	T Lymphocytes	T Lymphocytes (↑ Survival, ↑ Proliferation,↑ cytokines) B Lymphocytes (↑ Proliferation,↑ antibody production), NK Lymphocytes (↑Proliferation,↑ activation)
IL-4	Th2 Lymphocytes	B Lymphocytes (↑ isotope switch IgE), Th2 Lymphocytes (↑Proliferation, ↑differentiation), macrophages (↓IFN-II ϒ response), Mast cells(↑ proliferation)
IL-5	Th2 Lymphocytes	B Lymphocytes(↑Proliferation,↑ isotope switch IgA) Eosinophils (↑Proliferation,↑ activation)
IL-13	Th2 Lymphocytes NK-T Lymphocytes	B Lymphocytes(↑ isotope switch IgE) macrophages(↑ Mast cells collagen), Fibroblasts (↑ collagen), epithelia (↑ mucus)
IL-17	T Lymphocytes	Endothelia(↑ chemokines), Macrophages (↑ cyto-kines),epithelia(↑ G-CSF and GM-CSF)
INF-ϒ	Th1 Lymphocytes, TC Lymphocytes, NK	B Lymphocytes(↑ isotope switch) Th1 lymphocytes(↑ differentiation), macrophages(↑ activation) various cells (↑ antigen processing and ↑MHC Class I)

Peritoneal Lymphocytes (PL): In normal subjects, 5–10% of peritoneal cells are lymphocytes compared to 20% in blood. T and B lymphocytes aggregate within milky spots in parietal peritoneum, contributing 10% each to the total cell number [3]. T-cells are derived from bone marrow and mature in thymus. T cells are organized perivascularly within the peritoneum [5]. PLs are of following types:

- CD4 +and CD3+ PLs which bind to MHC class II. These cells can be

1. Effector cells

- TH-1 cells which are activated by INFγ and produce IL2. They activate T cells to become cytolytic T cells and also activate macrophages and NK cells.
- TH-2 cells: These are activated by IL-4 and produce IL4, 5, 6, 13. These are anti-inflammatory cytokines. These help in the synthesis of all the antibodies except IgG2b.
- TH-17 cells produce IL17 and recruit monocytes and neutrophils to the site of inflammation.

2. Memory T cells provide memory so that the second exposure to the same antigen results in an amplified response.

- CD8+ T cells- are CD3+ CD8+ and are class I MHC restricted.

1. Cytotoxic: They kill tumor cells and virus infected cells. The majority of the peritoneal CD8+ cells secrete Th1 cytokines, *i.e.*, IL-2, IFN-γ and TFN-α which are cytotoxic. Some peritoneal CD8+ cells secrete IL-4 and IL-5 characteristic of Th2 cells. These Th2-type cells support B cell differentiation and secretion of IgG and IgA, but have no cytotoxic activity.

2. Suppressor T cells regulate immune responses. Th2-type CD8+ cells are present in intestinal Peyer's patches and normal human peritoneum.

CD4/CD8 ratio is 2 in blood and 0.5 in peritoneum, reflecting a decrease in CD4 and an increase in CD8 cells. About 90% of PL-CD4+ cells and 75% of CD8+ cells express the CD45 RO isoform of CD45 characteristic of memory/effector T cells [3].

Natural killer (NK) cells are CD3-lymphocytes. These are enriched in peritoneal cavity (25%) compared to blood (10%). About 80% of the peritoneal CD3– cells are NK cells. Overall, 60% of the peritoneal CD3–/CD8+ cells express the CD8α+β– homodimer (*versus* 2.5% in blood), whereas others express recombination-activating gene RAG-1[8]IL-15 produced by macrophages and stromal cells in response to IFN-γ that attracts NK cells.

B cells Overall, 12% of the peripheral lymphocyte are B cells, whereas only 2.3% of peritoneal lymphocytes are B cells [3].

Mesothelial Cells (HPMC) are the most abundant cells of peritoneal cavity. They are not passive but play an active role in the immune response. They are situated between the peritoneal cavity, containing macrophages and lymphocytes, and the microvasculature and help in recruiting leucocytes from blood to the peritoneum. They are activated by cytokines from macrophage like IFN-γ. HPMC perform following functions:

Secretion of cytokines- IL-1α and IL-1β-IL-1 stimulates prostaglandin (PG) production. PGs stimulate endothelial cells to synthesize vasodilatory molecules and neutrophil chemotactic peptides. More inflammatory cells are recruited [3]. HPMC also produce important proinflammatory cytokine IL-6, chemokines IL-8, MCP-1, RANTES and 6-keto-PGF1α. The mesothelial cells express adhesion molecules ICAM-1 and VCAM-1/2which can be induced by PMΦ-induced cytokines IL-1 and TNF-α [8]. (**Table 2**). HPMC also produce IL-15 which is a potent T cell activator. High levels of IL 15 are detected in the effluent of patients suffering from peritonitis and low levels in non-infected patients. The main TNF receptor expressed on HPMC is TNF-R1 (p55). IL-1 downregulates this receptor

with an accumulation of soluble TNF-R1, because of increased shedding of the receptor.

Function as antigen-presenting cells to T cells, and activate peritoneal helper (CD4) lymphocytes and express HLA-DR molecules. ICAM-1 is the major accessory molecule on HPMC while B7-1 and B7-2 molecules are not detected.

Toll-like-receptors (TLRs) (described below) are expressed on the HPMC. HPMC actively participate in the peritoneal immune response against an invading pathogen [3].

Polymorphonuclear cells (PMNs) are the main cells for host defence. PMNs have many granules in the lysosomes. Primary (azurophilic) granules contain myeloperoxidase, lysozyme, acid hydrolase, elastase, non-specific collagenase, defensin, bactericidal permeability protein, phospholipase. Secondary granules contain lysozyme, lactoferrin, microglobulin, cytochrome B. PMNs perform 2 functions:

Migration: PMNs migrate from capillaries to peritoneum under the influence of chemotaxins from macrophages. There is an expression of adhesion molecules on PMN and the endothelium which facilitate both adhesion to the endothelial surface and transendothelial migration to the site of inflammation (**Table 2**). After crossing the peritoneal capillary wall, the migrating leucocytes also cross the mesothelial cell layer to reach the peritoneum.

Phagocytosis: Neutrophils are one of the main cell types responsible for phagocytosis. In addition to the generation of OH like in macrophages, in PMNs H_2O_2 is also converted by Cl/Myeloperoxidase (MPO) to from hypochlorous acid which is a potent free radical. Also, oxygen independent killing occurs by substances in the azurophilic granules. Priming of PMNs regulates host defence responses. Priming allows enhanced response of PMNs to second exposure to the same stimulus. During priming, there is a transient rise in the intracellular calcium concentrations. Priming allows neutrophils to survive longer as constitutive apoptosis is attenuated [7, 9]

Eosinophils develop from stem cells in response to IL-5.The major chemokine for eosinophils is eotaxin. Eosinophil granules contain major protein (MBP). Eosinophils produce leukotrienes, PAF, peroxidase, eosinophilic cationic proteins and reactive O_2 and have weak phagocytic activity. MBP is bactericidal, toxic to parasites and causes degranulation of mast cells. Eosinophils increase in peritoneum during parasitic or fungal infections or drug allergies.

Basophils circulate in the blood, where as mast cells mature in tissues and are important source of histamine.

Mediators

Important mediators involved in immune reactions are–Preformed-histamine, serotonin, lysosomal enzymes and newly synthesized: PGs, leukotrienes, platelet activating factors, nitric oxide, cytokines (**Table1**) and anti-microbial peptides. These are in the plasma and can diffuse into the peritoneum.

- Histamine is vasodilatory.
- Prostaglandins -Arachidonic acid metabolites are produced from phospholipases in the cell wall and form prostaglandins, of which PGE2 and PGI2 are vasodilatory while PGF2 is vasoconstrictory.
- Leukotrienes and thromboxane (TXA2) are also arachidonic acid metabolites and are vasoconstrictive.
- Platelet activating factor (PAF) from leucocytes causes platelet aggregation and vasodilatation, increased vascular permeability, triggers inflammatory and thrombotic cascades.
- Nitric oxide (NO) is formed by the action of NO synthase from the endothelial cells. NO reacts with oxygen and super oxide and forms peroxynitrate (ONOO), which decomposes to form reactive OH radical. NO inhibits platelets aggregation and serves as an effector of macrophage induced cytotoxicity.
- Cytokines consists of plasma proteins which include interleukins, growth factors. Cytokines IL-1, IL-6, IL-12, and TNF-α are pro-inflammatory. IL-4, 5, IL-10 and TGF-β are anti-inflammatory. (Table 1a and 1b)
- Antimicrobial peptides (defensins, cathelin, probiotics). Defensins are cationic 3 – 5 kDa antimicrobial peptides with a broad spectrum of action against many bacteria. Defensins are present in the normal and damaged peritoneum, but defensin expression may be insufficient in PD patients [10].

Pattern recognition receptors (PRR)

PRR are of three types:

- *Secreted PRR:* These act as opsonins, *e.g.*, mannose-binding lectin is a secreted pattern-recognition receptor specific for microbial carbohydrates. Binding of mannose-binding lectin to bacteria leads to activation of complement cascade and promotes opsonization and phagocytosis [6].
- *Endocytic PRR* are present on the phagocytes and recognise pathogen associated molecular patterns (PAMP). The pathogens are taken up and digested by phagocytes.
- *Signaling pattern-recognition receptors:* These include Toll-like receptors (TLR) [11-14]. (**Figure 3**) TLR recognise various PAMPs, *e.g.*, common pathogenic components, such as lipopolysaccharides (LPSs), peptidoglycans, RNA from viruses, and bacterial oligodeoxynucleotides. They help in the phagocytosis and activation of the complement and cytokines, such as IL-1, IL-6, and TNF-α. TLRs activate nuclear factor B (NF-B) and AP-1.TLRs are involved in maturation of APCs, which have molecules (CD80, CD86) on its surface. TLRs, when exposed to

PAMPs up-regulate expression of these molecules, leading to APC maturation. This mature cell migrates to a draining lymph node and presents antigen to naive T cells, and trigger adaptive immune response [6, 14].

- TLR4 attaches to bacterial LPS in gram negative bacteria except Leptospira.
- Tamm-Horsfall protein activates APCs via a TLR4-dependent mechanism. TLR4 is required on intrinsic renal cells for control of ascending urinary tract infections (UTIs).
- TLR2 reacts with PAMPs in Gram-positive and Gram-negative bacteria.
- TLR11 is found on uroepithelium and prevents UTI.
- TLR3 recognises double stranded viral DNA
- TLR5 recognises bacterial flagellin.

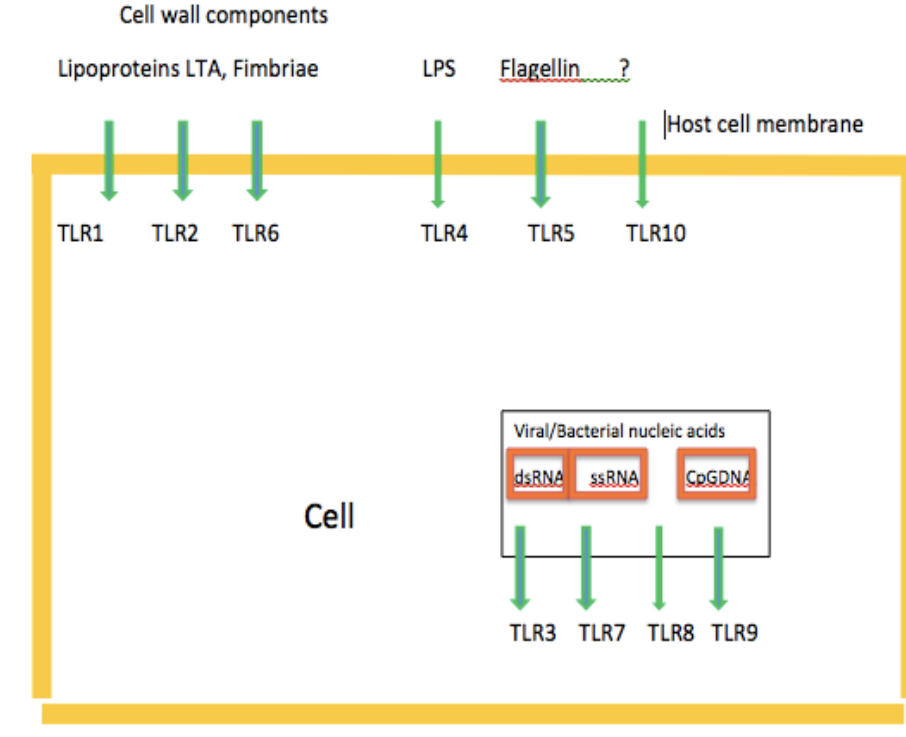

Figure 3: Toll like receptors with their specific antigens

Causes of Immune Dysfuntion in CKD on CAPD

However, in patients with CKD on continuous peritoneal dialysis (CAPD) there is an impairment of host defence mechanisms [3]. This occurs due to

Effects of CAPD

- *Dilution of immune cells:* When the patient is initiated on CAPD, there is an improvement of uremia related factors; however, in CAPD, due to the presence of 2 liters of dialysate in the cavity, the resident macrophages are diluted and their concentration falls to 10^3 to 10^4/ml . Intraperitoneal opsonization is defective in patients on CAPD. The concentration of IgG and C3 are 1/30 and 1/70 of normal. Macrophages and cytokines that are activated during infection are removed during each exchange of dialysis fluids. Thus, even a small bacterial inoculum, as occurs with a touch contamination, can induce peritonitis.
- *Non physiologic fluid:* In addition the composition of earlier peritoneal dialysis fluids is clearly non-physiologic, CAPD fluid consists of dextrose and many have high osmolality. Some fluids have a low pH and high lactate. Continuous exposure of peritoneal cells to these solutions may result in an impairment of the local peritoneal host defence mechanisms [15]. Opsonic activity with a 2.27% glucose-based PD solution is better versus 1.1% amino-acid-based solution as some amino acids from the dialysate inhibit the classical and alternative pathways of complement activation, leading to lower opsonic activity.

Unlike in HD, where there may be back filtration of endotoxins from dialysate and bio-incompatible membranes of the dialyser, there is no issue of membrane incompatibility or endotoxin diffusion [16].

- The indwelling PD catheter produces a breach in the peritoneum.

Bacteria can track along the catheter. The bacteria can directly grown on catheter or may grow in slime layer or biofilms on the catheter. Biofilms protect the bacteria from host defences. Staphylococcus and pseudomonas are notorious for producing biofilms. Biofilms predispose to recurrent/relapsing peritonitis.

Bacteria can enter the peritoneum through luminal route by touch contamination. Bacteria may transmigrate from the bowel or from hematogenous route or rarely in females may come from vagina.
- Exit site infecions (ESI) are common in PD patients. Those with ESIs develop peritonitis more frequently.
- PD interferes with normal mechanisms of lymphatic absorption and thereby impedes the passage of pathogens into the systemic circulation. This defect in normal lymphatic function is most likely a result of mechanical factors associated with the instillation of large volumes of fluid into the abdominal cavity.

Effect of CKD

- *Uremic toxins:* The solutes in CKD that interact negatively with biologic functions are called uremic toxins. Uremic toxins are retained due to a fall in GFR or are generated in the body or introduced into the body *via* intestine. They either exist in free water-soluble form or bind reversibly to serum proteins and are poorly

dialysable [7]. The various toxins and the immune dysfunction caused by them is listed in the table 3.

- Residual renal function, if significant is associated with preserved immune function [19].
- Anemia
- Hyperparathyroidism-Chronic hyperparathyroidism in uremia affects cellular especially PMN functions *via* sustained elevation of their Ca^{2+}. Ca^{2+} is an important second messenger in PMNs and regulates functional responses and modulates apoptosis. Parathyroidectomy lowers, but does not normalize, PMN Ca^{2+} of patients with CKD.
- Resistance to erythropoietin
- Acidosis promotes cellular esp PMN apoptosis [20]
- Inflammation and oxidative stress
- Decreased vitamin D impairs the immune response
- Iron overload- Iron therapy affects leukocyte functions and cytokine production, promote oxidative stress and support bacterial growth. Therefore, iron therapy may play a role in atherosclerosis and infection, especially if there is iron overload.
- Complement factor C5a - delay apoptosis of PMNLs via phosphoinositide-3 kinase and the ERK-signaling pathway [21].
- Malnutrition decreases immune cell number and function.

Table 3: Uremic Toxin

Uremic Toxin	Functional Disturbance
LMW Solutions	
Phenylacetic Acid(PAA)	Macrophages: inducible nitric acid synthase↓ PMNs:Oxidative burst, Phagocytosis and integrin expression ↑apoptosis↓[7]
Dinucleoside phosphates	Leukocytes:oxidative burst↑[7]
Guanidino compounds	Monocytes/macrophages: pro and anti-inflammatory
Indoxyl sulphate	Endothel:E- selectin↑
P-cresyl sulphate	Leukocytes: oxidative burst↑
Homocysteine(Hcy)	ICAM-1↑;damage of DNA and proteins
Methyl glyoxal(MGO)	PMNs: apoptosis↑ oxidative burst↑; Monocytes: apoptosis↑
Middle Molecules, Proteins	
Immunoglobulin Light chains (IgLCs)	PMNs:Chemotaxis↓glucose uptake solution↓, glucose uptake basal↑, apoptosis↓
Retinol Binding protein (RBP)	PMNs:Chemotaxis↓, oxidative burst↓, apoptosis↓
Leptin	PMNs:Chemotaxis↓, oxidative burst↓
Resistin	PMNs:Chemotaxis↓, oxidative burst↓
Tamm-Horsfall protein[THP]	PMNs:(High concentrations) apoptosis↓, Chemotaxis↓, Phagocytosis↑;(Low concentrations) Chemotaxis↑
High Density lipoprotein(HDL)	Loss of anti-inflammatory properties in uremia
Protein Modifications	
Glucose modified proteins[18]	PMNs:Chemotaxis↓ glucose uptake↑, apoptosis↑ [18]
AGE –Modified albumin	Leukocytes:activating pro-atherogenic[126]
AGEs	Macrophages:TNF and IL-1 secretion↑ Monocytes: Chemotaxis↑[128]

Glycated collagen	PMNs:Adhesion↑
Advanced oxidation protein products(AOPPs)	PMNs and monocytes:oxidative burst↑
Oxidizes low density lipoproteins(oxLDLs)	Macrophage activation PMNLs and esionophils: Chemotaxis↑,degranulation ↑; Regulatory T cells:Proteasome activity ↓→cell cycle arrest and apoptosis
Homocysteinylated albumin	Monocytes:adhesion↑

Immune Dysregulation in CKD on CAPD

• Uremic milieu as well as the process of CAPD affects all aspects of immune function. The changes in immune function and their clinical significance are summarised in the **Table 4**.

Immune Dysfunction: Clinical Significance

• CKD is associated with a significant increase in all-cause mortality. The main factors responsible for the increased risk of morbidity and mortality in patients with CKD are cardiovascular disease (CVD) and infections [38, 39]. Both complications are linked to a disturbed immune response.

• Diminished action of immune cells leads to infections. Increased peritonitis is seen. There is a high failure rates for vaccinations against hepatitis B virus, influenza virus, *Clostridium tetani*, or *Corynebacterium diphtheriae* due to alterations in the function of T lymphocytes [40]. There is an increased incidence of blood stream infections and respiratory infections in CKD [41].

• Foot ulcers and amputations are common in the diabetic patients not only due to vasculopathy but also due to osteomyelitis and sepsis. Both pulmonary and extrapulmonary TB is common and the tuberculin skin test is negative in CKD [42]. Increased UTI occurs due to decreased TLR expression.

Overactivation of immune system contributes to inflammation and oxidative stress, malnutrition and CVD [43, 44]. Increased activity of the macrophage scavenger receptors during ESRD enhance oxLDL clearance and foam cell formation, an early step in the atherogenesis [45, 46]. Alterations in the pattern-recognition receptors contribute to hypercytokinemia, which is strongly associated with CVD. Other mechanisms of atherogenesis include up-regulation of fibrinogen, lipoprotein (a), and CRP levels and increase in Th1/Th2 ratio. Paradoxically, decrease in activity of TLR system results in a decreased CVD risk [6, 47]. Uremia causes a change in epigenome [48].

Management of Immune Dysfunction

In patients on CAPD, intraperitoneal IgG may correct the IgG concentration in the peritoneal fluid but is expensive and remains unproven. Opsonic activity can be enhanced by resting the peritoneum with APD [49, 50]. Newer PD fluids that contain glucose polymers (such as icodextrin), amino acids rather than glucose, or fluids that results in fewer glucose degradation products (GDPs) may be relatively less harmful to neutrophil and macrophage function [50-52]. All thepatients on CAPD should be vaccinated. Vaccination has been developed for *Staphylococcus aureus* using 2 capsular polysachharides serotype 5 and 8 and may reduce peritonitis due to *Staphylococcus aureus*. Exogenous interferon is being tried and calcitriol has been shown to increase the phagocytosis and oxygen dependent killing of microbes. An improvement in the PD connectology, twin bag systems, flush before fill techniques have lowered the incidence of peritonitis.

Table 4: Immune dysfunction in CKD on CAPD

	Number	**Function**	**Clinical significance**
Macrophages	Number □ 10^3-10^4 Immature cells 50% □ in CD11b, CD16, CD64 and CD14	Overactive [23,24]/Underactive [25] □ Fc receptor mediated phagocytosis Respiratory burst □ Intracellular killing □ PGE □ IFN-γ , IL-1, IL2 , TNF □ TNF-α □,NF κB□ Vit D to active vit D□ TLR□ Ag presentation □	Increased risk of peritonitis
PMN	Number □(10^3 instead of 10^7 PMNs numbers normal in others	Functions impaired. Abnormal phagocytosis Inappropriate PMN priming-low-grade inflammation and oxidative stress in CKD patients [30]. □in apoptosis - □immune response □apoptotic PMNs by macrophages – inflammation [31].	Imbalance between anti-apoptotic and pro-apoptotic factors [32] Response □due to p-cresol [33].
Ply	No. □20–30% of peritoneal cells. Later number stable Transient □in acute peritonitis Baseline values in 1 mo months. Ply □85% T cells□	CAPD Both Th1 Th2 □ In HD Th1/Th2 ratio □due to □IL-12 □mesothelial production of IL-15 □IFN-γ □IL-4 [34]. □Secretion IFN-γ [3].	Number does not correlate with peritonitis [3]. Response to vaccinations altered
B lymphocytes	□apoptosis B lymphopenia [35]	Function is preserved. IgA, IgG and Ig M concentrations are normal in CKD and dialysis [33].	
Mesothelial cell Cytokines	Number □ Hypercytokinemia □removal rate □Cytokine generation rate [6,	□TLR on mesothelium □Anti-inflammatory cytokines, IL-10 □Pro-inflammatory cytokines, TNF and IL-6.	Peritonitis Increased risk of peritonitis, malnutrition and atherosclerosis and

	36].		cardiovascular disease
Receptors	MBL receptors altered SR-A and CD [36] TLR4 expression	cytokine production [37]	protection against peritonitis [6, 37].

CAPD experience

Hemodialysis (HD) is provided free by the government, however PD is not included in the government scheme. Thus, CAPD is being provided free of cost at our centre for limited number of very sick patients or children who have contraindication to HD. A total of 50 patients underwent CAPD at our centre in 1 year. All were on glucose based therapy. The average age of CAPD patients was 28.72+/-19.8 years. Overall, 32% of the cases were below 18 years of age. There were a total of 53 episodes of peritonitis. A total of 18 patients (36%), did not have even a single episode of peritonitis. Culture negative rate was high, accounting for 30.3% of the total. The most common organism isolated was *Klebsiella pneumoniae* (23%), followed by *E.coli* (14%). There was one episode of tuberculous peritonitis, one episode of Candida sp. peritonitis, both leading to catheter removal and one episode of mucor peritonitis which led to death. The peritonitis rate was 1 episode in 16.55 months. A total of 8% patients developed exit site infection while 8% patients developed tunnel tract infection. These rates are now decreasing due to strict hand hygiene and patient re-training. Culture negative rates are now declining due to improvement in culture technique and incorporation of dedicated microbiologist into the programme.

Stiff catheter PD is being done at our centre in 1000 cases over the last 7 years. The incidence of peritonitis is <3% due to the short duration of therapy, *i. e.,* <72 hours.

References

1. Janeway, C. A. Jr., and R. Medzhitov, 2002: Innate immune recognition. *Annu. Rev. Immunol.,* **20,** 197–216.

2. Medzhitov, R., and C. A. Jr. Janeway, 2000: Innate immunity. *N. Engl. J. Med.,* **343:** 338–344.

3. Rapoport, J., J. Michael, and H. C. Chaimovitz, 1999: The Peritoneal Immune System and Continuous Ambulatory Peritoneal Dialysis. *Nephron.,* **81:** 375–380.

4. Holmes, C. 1994: Peritoneal host defence mechanisms in peritoneal dialysis. *Kid. Int.,* **46,** 58–70.

5. Goldstein, C. S., J. S. Bomalaski, R. B. Zurier, E. G. Neilson, and S. D. Douglas, 1984: Analysis of peritoneal macrophages in continuous ambulatory peritoneal dialysis. *Kid. Int.,* **26,** 733–740.

6. Kato, S., M. Chmielewski, H. Honda, R. Pecoits-Filho, S. Matsuo, Y. Yuzawa, A. Tranaeus, P. Stenvinkel, and B. Lindholm, 2008: Aspects of Immune Dysfunction in End-stage Renal Disease. *Clin. J. Am. Soc. Nephrol.,* **3,** 1526–1533.

7. Cohen, G. and W. H. Hörl, 2012: Immune Dysfunction in Uremia-An Update. *Toxins,* **4,** 962-990.

8. Jonjic, N., G. Peri, S. Bernasconi, F. L. Sciacca, F. Colotta, P. G. Pelicci, L. Lanfrancone, and A. Mantovani, 1992: Expression of adhesion molecules and chemotactic cytokines in cultured human mesothelial cells. *J. Exp. Med.,* **176,** 1165–1174.

9. Shahin, R. D., I. Engberg, L. Hagberg, and C. S. Eden, 1987: Neutrophil recruitment and bacterial clearance correlated with LPS responsiveness in local gram-negative infection. *J. Immunol.,* **138,** 3475–3480.

10. Grupp, A., M. Kimmel, P. Fritz, B. Voggenreiter, H. Stöltzing, U. Kuhlmann, E. F. Stange, T. Mettang, K. Fellermann, and D. M. Alscher, 2007: The expression patterns of peritoneal defensins. *Perit. Dial. Int.,* **27,** 654–662.

11. Czyzyk, J., 2006: The role of Toll-like receptors in the pathogenesis of renal disease. *Semin. Nephrol.,* **26,** 167–172.

12. Texereau, J., J. D. Chiche, W. Taylor, G. Choukroun, B. Comba, and J. P. Mira, 2005: The importance of Toll-like receptor 2 polymorphisms in severe infections. *Clin. Infect. Dis.,* **41,** 408–415.

13. Pasare, C., and R. Medzhitov, 2004: Toll-like receptors: linking innate and adaptive immunity. *Microbes Infect.,* **6,** 1382–1387.

14. Schroder, N. W., and R. R. Schumann, 2005: Single nucleotide polymorphisms of Toll-like receptors and susceptibility to infectious disease. *Lancet Infect. Dis.,* **5,** 156–164.

15. Kazancioglu, R., 2009: Peritoneal defense mechanisms- the effect on new peritoneal dialysis solutions. *Perit. Dial. Int.,* **2,** 198-201.

16. Hernandez, M. R., A. M. Galan, A. Cases, J. Lopez-Pedret, A. Pereira, R. Tonda, J. Bozzo, G. Escolar, and A. Ordinaz, 2004: Biocompatibility of cellulosic

and synthetic membranes assessed by leukocyte activation. *Am. J. Nephrol.,* **24,** 235–241.
17. Cohen, G., M. Rudnicki, R. Deicher, and W. H. Horl, 2003: Immunoglobulin light chains modulate polymorphonuclear leucocyte apoptosis. *Eur. J. Clin. Invest.,* **33,** 669 – 676.
18. Cohen, G., M. Rudnicki, F. Walter, T. Niwa, and W. H. Horl, 2001: Glucose-modified proteins modulate essential functions and apoptosis of polymorphonuclear leukocytes. *J. Am. Soc. Nephrol.,* **12,** 1264 –1271.
19. Pecoits-Filho, R., O. Heimburger, P. Barany, M. Suliman, I. Fehrman-Ekholm, B. Lindholm, and P. Stenvinkel, 2003: Associations between circulating inflammatory markers and residual renal function in CRF patients. *Am. J. Kid. Dis.,* **41,** 1212–1218.
20. Wann, J. G., Y. H. Hsu, C. C. Yang, C. S. Lin, D. W. Tai, J. S. Chen, C. W. Hsiao, and C. F. Chen, 2007: Neutrophils in acidotic haemodialysed patients have lower intracellular pH and inflamed state. *Nephrol. Dial. Transplant.,* **22,** 2613–2622.

21. Perianayagam, M. C., V.S. Balakrishnan, A. J. King, B. J. Pereira, and B. L. Jaber, 2002: C5a delays apoptosis of human neutrophils by a phosphatidylinositol 3-kinase-signaling pathway. *Kid. Int.,* **61,** 456–463.

22. Davies, S. J., J. Suassuna, C. S. Ogg, and J. S. Cameron, 1989: Activation of immunocompetent cells in the peritoneum of patients treated with CAPD. *Kid. Int.,* **36,** 661–668.

23. Peterson, P. K., E. Gaziano, H. J. Suh, M. Devalon, L. Peterson, and W. K. Keane, 1985: Antimicrobial activities of dialysate-elicited and resident human peritoneal macrophages. *Infect. Immun.,* **49,** 212–218.

24. McGregor, S. J., J. H. Brock, J. D. Briggs, and B. J. R. Junor, 1987: Bactericidal activity of peritoneal macrophages from CAPD patients. *Nephrol. Dial. Transplant.,* **2,** 104–108.
25. Carcamo, C., M. Fernandez-Castro, R. Selgas, C. Jimenez, S. Molina, and F. Vara, 1996: Long-term continuous ambulatory peritoneal dialysis reduces the expression of CD11b, CD14 and CD64 on peritoneal macrophages. *Perit. Dial. Int.,* **16,** 582–659.
26. Levy, R., J. Klein, T. Rubinek, M. Alkan, S. Shany, and C. Chaimovitz, 1990: Diversity in peritoneal macrophage response of CAPD patients to 1, 25-dihydroxyvitamin D3. *Kid. Int.,* **37,** 1310–1315.
27. Meuer, S. C., M. Hauer, P. Kurz, K. H. M. zum Buschenfelde, and H. Kohler, 1987: Selective blockade of the antigen-receptor- mediated pathway of T cell activation in patients with impaired primary immune responses. *J. Clin. Invest.,* **80,** 743– 749.
28. Verkade, M. A., C. J. van Druningen, L. M. Vaessen, D. A. Hesselink, W. Weimar, and M. G. Betjes, 2007: Functional impairment of monocyte-derived dendritic cells in patients with severe chronic kidney disease. *Nephrol. Dial.*

Transplant., **22,** 128– 138.
29. Sela, S., R. Shurtz-Swirski, M. Cohen-Mazor, R. Mazor, J. Chezar, G. Shapiro, K. Hassan, G. Shkolnik, R. Geron, and B. Kristal, 2005: Primed peripheral polymorphonuclear leukocyte: a culprit underlying chronic low-grade inflammation and systemic oxidative stress in chronic kidney disease. *J. Am. Soc. Nephrol.,* **16,** 2431–2438.
30. Cendoroglo, M., B. L. Jaber, V. S. Balakrishnan, M. Perianayagam, A. J. King, and B. J. Pereira, 1999: Neutrophil apoptosis and dysfunction in uremia. *J. Am. Soc. Nephrol.,* **10,** 93–100.
31. Glorieux, G., R. Vanholder, and N. Lameire, 2003: Uraemic retention and apoptosis: what is the balance for the inflammatory status in uraemia? *Eur. J. Clin. Invest.,* **33,** 631–634.
32. Donze, H. H., C. Lue, B. A. Julian, W. H. Kutteh, A. Kantele, and J. Mestecky, 1997: Human peritoneal B-1 cells and the influence of continuous ambulatory peritoneal dialysis on peritoneal and peripheral blood mononuclear cell (PBMC) composition and immunoglobulin levels. *Clin. Exp. Immunol.,* **109,** 356–361.
33. Sester, U., M. Sester, M. Hauk, H. Kaul, H. Kohler, and M. Girndt, 2000: T-cell activation follows Th1 rather than Th2 pattern in haemodialysis patients. *Nephrol. Dial. Transplant.,* **15,** 1217– 1223.
34. Fernandez-Fresnedo, G., M. A. Ramos, M. C. Gonzalez-Pardo, A. L. de Francisco, M. Lopez-Hoyos, and M. Arias, 2000: B lymphopenia in uremia is related to an accelerated in vitro apoptosis and dysregulation of Bcl-2. *Nephrol. Dial. Transplant.,* **15,** 502–510.
35. Pecoits-Filho, R., P. Barany, B. Lindholm, O. Heimburger, and P. Stenvinkel, 2002: Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment. *Nephrol. Dial. Transplant.,* **17,** 1684–1688.
36. Ando, M., A. Shibuya, K. Tsuchiya, T. Akiba, and K. Nitta, 2006: Reduced expression of Toll-like receptor 4 contributes to impaired cytokine response of monocytes in uremic patients. *Kid. Int.,* **70,** 358–362.
37. Foley, R. N., P. S. Parfrey, and M. J. Sarnak, 1998: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am. J. Kid. Dis.,* **32,** 112–119.
38. Sarnak, M. J., and B. L. Jaber, 2000: Mortality caused by sepsis in patients with end-stage renal disease compared with the general population. *Kid. Int.,* **58,** 1758–1764.
39. Eleftheriadis, T., G. Antoniadi, V. Liakopoulos, C. Kartsios, and I. Stefanidis, 2007: Disturbances of acquired immunity in hemo- dialysis patients. *Semin. Dial.,* **20,** 440 – 451.
40. Wakasugi, M., K. Kawamura, S. Yamamoto, J. J. Kazama, and I. Narita, 2012: High mortality rate of infectious diseases in dialysis patients: a comparison with the general population in Japan. *Ther. Apher. Dial.,* **16,** 226–231.
41. Soni, R., B. Horowitz, and M. Unruh, 2013: Immunisation in end-stage renal disease: opportunity to improve outcomes. *Semin. Dial.,* **26,** 416–426.

42. Yilmaz, M. I., J. J. Carrero, J. Axelsson, B. Lindholm, and P. Stenvinkel, 2007: Low-grade inflammation in chronic kidney disease patients before the start of renal

replacement therapy: sources and consequences. *Clin. Nephrol.,* **68,** 1–9.

43. Qureshi, A. R., A. Alvestrand, A. Danielsson, J. C. Divino-Filho, A. Gutierrez, B. Lindholm, and J. Bergstrom, 1998: Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. *Kid. Int.,* **53,** 773–782.

44. Stenvinkel, P., P. Barany, O. Heimburger, R. Pecoits-Filho, and B. Lindholm, 2002: Mortality, malnutrition, and atherosclerosis in ESRD: what is the role of interleukin-6? *Kid. Int.,* **80,** 103–108.
45. Stenvinkel, P., 2001: Inflammatory and atherosclerotic interactions in the depleted uremic patient. *Blood Purif.,* **19,** 53–61.
46. Kiechl, S., E. Lorenz, M. Reindl, C. J. Wiedermann, F. Oberhollenzer, E. Bonora, J. Willeit, and D. A. Schwartz, 2002: Toll-like receptor 4 polymorphisms and atherogenesis. *N. Engl. J. Med.,* **347,** 185–192.
47. Kiechl, S., G. Egger, M. Mayr, C. J. Wiedermann, E. Bonora, F. Oberhollenzer, M. Muggeo, Q. Xu, G. Wick, W. Poewe, and J. Willeit, 2001: Chronic infections and the risk of carotid atherosclerosis: prospective results from a large population study. *Circulation,* **103,** 1064–1070.
48. Stenvinkel, P., and T. J. Ekstrom, 2009: Does the uremic milieu affect the epigenotype? *J. Ren. Nutr.*, **19,** 82–85.
49. Williams, J. D., N. Topley, K. J. Craig, R. K. Mackenzie, M. Pischetsrieder, C. Lage, J. Passlick-deetjen, 2004: The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. *Kid. Int.,* **66,** 408–418.
50. Rogachev, B., M. J. Hausmann, R. Yulzari, M. Weiler, C. Holmes, D. Faict, C. Chaimovitz, and A. Douvdevani, 1997: Effect of bicarbonate-based dialysis solutions on intracellular pH (pHi) and TNFα production by peritoneal macrophages. *Perit. Dial. Int.,* **17,** 546-553.
51. ter Wee, P. M., and F. J. van Ittersum, 2007: The new peritoneal dialysis solutions: friends only, or foes in part? *Nat. Clin. Pract. Nephrol.,* **3,** 604–612.
52. Carrero, J. J., M. I. Yilmaz, B. Lindholm, and P. Stenvinkel, 2008: Cytokine dysregulation in chronic kidney disease: how can we treat it? *Blood Purif.,* **26,** 291–299.

Chapter 26

Prevention of Peritonitis in Peritoneal Dialysis

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Prevention of Peritonitis in Peritoneal Dialysis

Introduction

Peritoneal dialysis (PD) is a one of the important though underutilized modality for renal replacement therapy (RRT). Although, PD is a known mode of RRT for more than four decades, it has failed to get popularity due to a variety of reasons. Apart from financial implications of high cost of PD, fear of infection and a false belief of high rates of PD peritonitis had a major negative impact on the growth of PD. Modality choice is also influenced by the negative information provided by hemodialysis (HD) centers, patients on HD and further exaggerated by the nephrologists not in favour of PD, discouraging patients who are considering a switch to the PD modality.

Peritonitis remains the 'Achilles Heel' in the growth of PD and is one of the most dreaded and feared complication.

Although, only 5% of the peritonitis episodes directly related to death within four weeks of the episode of peritonitis; it was indirectly related to about 16-18% of deaths in patients on PD [1] and results in shift to HD in significant number of patients. Peritonitis episode can also lead to structural changes in the peritoneal membrane in up to one-third of patients and if a patient has repeated episodes of peritonitis, it can lead to membrane failure resulting in technique failure and loss of PD. Thus, it is important to prevent the occurrence of peritonitis and to minimize its incidence as much as possible. Although, marked advancement has been made in the treatment of peritonitis, but prevention of peritonitis remains the bugbear for successful PD programme. The International Society for Peritoneal Dialysis (ISPD) had first published guidelines for prevention and treatment of peritonitis in 1983 and revised in 1993, 1996, 2000, 2005, 2010 and 2016 and it is important to follow these guidelines for a successful PD programme.

Incidence of PD peritonitis in India

Due to a lack of the central registry, the exact incidence of peritonitis is India is not fully known. The peritonitis rate reported during earlier days of PD practise in India were very high, up to the tune of 1 episode every 5-6 patients-months [2], but that rate declined over a period of time due to an improvement in technology like switch to double-bag system as well as an improvement in training and overall health status of patients on PD. In an old study from tertiary centre in Chandigarh, India, the peritonitis rate was 0.62 episodes/patient-year [3]. Similarly, in an early study from Lucknow, India, the overall peritonitis rate reported was 0.63 episodes per patient-CAPD year [4], however, in the latest study from same center, the rate of peritonitis has declined to 0.41 episodes per patient year [5]. A study from Chennai has reported an incidence of peritonitis as 1 episode/75 patient-months at

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the beginning and 1 episode/ 30 patient-months who survived in PD for more than 3 years [6]. A recent study from Himachal Pradesh reported rate of peritonitis as 1 episode per 30.6 patient-months or 0.39 episodes per patient-year [7], while in another study from Kolkata in pediatric patients, the rate of peritonitis has been reported as 0.85 per year of PD usage [8]. Another study from South India reported 90 cases of peritonitis over 3 year period with a culture positivity of 50% and half of them were by Gram positive organisms [9]. Moreover, the incidence of peritonitis has been found to be higher in summers [2] at some centers. Similarly, PD peritonitis has been reported to have a higher incidence if they are reported from smaller or peripheral centers as compared to larger centers. Patients living in peripheral areas do not have an access to laboratory facilities, hampering quick sampling for microbiology and culture to identify causative organisms. Similarly, smaller PD programmes do not have nurses or doctors available on call, which results in diagnosis and treatment being delayed until patients can reach the hospital. In many such instances, patients depend exclusively on the clinical coordinators for advice and treatment.

In addition, two unique features used to have been noted about PD-related infections in Indian patients in earlier studies: a high rate of culture-negative cases (culture-positive organisms in only 63-72% of peritonitis episodes) and a predominance of Gram-negative peritonitis (60-66% of all positive cultures) [3,4]. Most common organisms in earlier studies were *E.Coli, Klebsiella pneumoniae, Acinetobacter, Pseudomonas* and *Enterobacter* species. Overall, organisms of the faecal origin were more frequent than those of the skin origin. However, in the latest studies, the incidence of culture negative peritonitis is 8.4-18.2% which is equivalent to that reported in the Western literature [5, 10]. Similarly, in the newer studies, most common organisms are the Gram positive organisms, followed by the Gram negative organisms.

Risk factors for PD peritonitis

Intact peritoneum and the body defence mechanism are the most important defence mechanism for peritonitis. PD peritonitis differs from surgical peritonitis by a low incidence of diffuse sepsis. Patients on PD are at a risk to peritonitis due to the following factors, which are specific to PD:

1. Large number of manual exchanges leading to a higher chance of contamination.
2. Continuous presence of non-physiological solution within the abdominal cavity leads to a defect in the defence mechanism of mesothelium.
3. Altered mesothelial anatomy on long term PD.
4. PD catheter itself acts as a bridge between the sterile and non sterile environment.
5. Defective host defence due to chronic uremic state.

In addition, following are some of the modifiable risk factors for peritonitis [11]:

- Social / environmental- smoking, living distantly from PD unit. pets

- Medical- obesity, depression, hypokalemia, hypoalbuminemia, absence of vitamin D supplementation, invasive interventions (e.g. colonoscopy).
- Dialysis-related- prior HD, PD against patient's choice, training, bioincompatible fluids, wet contamination.
- Infection-related- nasal *Staphylococcus aureus* carrier status, previous exit-site infection.

Contamination is the most common cause of peritonitis. Contamination can be intraluminal, *i.e*., touch contamination or periluminal, *i.e.*, catheter related or from transvisceral migration or from haematogenous spread. Prior to the use of Y system, double-bag system and "flush before fill" technique, spiking was the most common cause of touch contamination [1-4]. All PD peritonitis episodes are potentially preventable. The prevention of PD peritonitis requires a dedicated team effort with patient also as a stake holder. Patient must understand that majority of peritonitis are preventable and they are also responsible for their care and outcome.

Preventive strategies start before the catheter placement with the selection of proper candidate for PD. Strict asepsis during catheter insertion, training and regular retraining with proper monitoring are essential for successful PD programme. Proposed preventive steps are discussed below and summarized in **Table 1**.

Table 1: Risk factors and Preventive strategies for PD peritonitis

Risk Factors	**Organism**	**Preventive Strategy**
Poor Hand Hygiene	Coagulase negative *Staphylococcus, Staphylococcus aureus, Pseudomonas aeruginosa*	Retraining
Not Wearing Mask	*Streptococcus*	Retraining
Nasal SA Carrier	*Staphylococcus aureus*	Intranasal or Tropical Mupirocin
Hand washing	Gram negative	? Gentamycin cream at exit site
Poor Hygiene/Wearing Diapers	Enteric Organisms	Antibiotic Prophylaxis
Connection with the bag	Coagulase negative *Staphylococcus, Staphylococcus aureus*	Retraining / Exchange Device
Exit site infection	Coagulase negative *Staphylococcus, Staphylococcus aureus, Pseudomonas aeruginosa*	Mupirocin or Gentamicin to Exit Site
Uterine Procedures	Enteric Organism	Antibiotic Prophylaxis
Dental Procedure/infections	*Streptococcus*	Dental Care
Colonoscopy	Enteric Bacteria	Antibiotic Prophylaxis
Frequent Antibiotics	Fungus	Antifungal Prophylaxis

Catheter insertion

PD catheter should be placed on an 'in-patient' basis and should be done under all aseptic conditions in an operating room. Patient should take a scrub bath on the day of insertion. All abdominal hairs should be removed and bowel preparation should be done by an overnight laxative.

Preoperative antibiotics

ISPD has recommended use of prophylactic systemic antibiotic prior to catheter insertion and rate this as 1A, *i.e.*, both recommended and that the evidence is of the highest quality. Vancomycin and first generation cephalosporins are the preferred antibiotics. Antibiotics are usually given just before the catheter insertion. Use of pre-implantation prophylactic antibiotic reduces the incidence of catheter exit site colonization, wound infection, early exit site infection and tunnel infection [12, 13]. Double cuffed catheters are preferred over single cuff catheter. Exit site should be directed down-wards and outwards and tunnel should avoid the pressure sites during routine activity. Exit site should be round in shape and should snugly fit to catheter. Sutures at the exit site should be avoided as they help in bacterial colonization. Hematoma formation should be avoided during catheter placement. However, the shape and design of catheter has no implication on preventing peritonitis episode [1]. There is no data on the effectiveness of routine use of intranasal mupirocin to eradication of *Staphylococcus aureus* nasal carriage before catheter insertion. One randomised trial has shown that peritoneoscopic insertion led to lesser episodes of peritonitis [14] but other trials have failed to demonstrate this advantage over conventional insertion technique [15, 16]. Similarly, midline and lateral insertion has no difference in terms of peritonitis rate. Although, early studies show that burying the catheter under skin for initial few days led to lower peritonitis rate, further studies failed to prove it [17].

Exit site care

After catheter placement, exit site dressing should be done by the trained nursing staff under strict aseptic condition. Exit site should be kept dry and patient should avoid taking direct shower or tub bath till wound healing. Minimum handling of the catheter should be done to enhance the healing of exit wound. The catheter should be handled carefully to avoid traction injury to exit site which increases the risk of infection.

After healing of wound, strict hand hygiene practice should be practiced. Hand should be washed with soap and water and alcohol based hand sanitizer can be used prior to doing dialysis exchanges. Wearing face mask is optional. A systemic review had shown that application of povidone iodine for exit site care does not

reduce the incidence of exit site infection compared to simple soap and water or no treatment at all [18]. In a study by Mahajan et al from New Delhi, application of mupirocin ointment at the exit site however, has been shown to be effective in reducing *S. aureus* exit-site infection and possibly peritonitis and thus significantly reduce morbidity, catheter loss, and transfer to HD in patients on PD [19]. Mupirocin resistance has been seen in long term especially with intermittent mupirocin application. Other therapies that have been shown to be effective are tropical gentamicin cream, ciprofloxacin solution and oral rifampicin. However, daily use of oral rifampicin is associated with drug interaction with other co-administered drugs and is also associated with development of rifampicin resistance in 18% of cases [20]. There is a strong association between exit site infection and subsequent peritonitis. Early detection and treatment of exit site infection may prevent a peritonitis episode. ISPD recommends oral antibiotic primarily targeting *Staphylococcus aureus* for 2-3 weeks and removal of catheter for refractory exit site infection.

Connection method and exchange procedure

Use of double bag system with Y connection and use of "flush before fill" technique has drastically reduced the incidence of peritonitis [21]. In the current system, manual spiking has been replaced by non-spiking connection system. In "flush before fill" technique, small volume of PD fluid is drained from new bag to draining system before emptying the peritoneal PD fluid and thus flushing pathogenic organisms at connection site, if any. In automated PD, where spiking is an integral part of connection system, use of assist device for connection should be encouraged. Hand washing and proper drying should be done before performing each exchange to avoid touch contamination. Exchange should be done in a clean and preferably dedicated place. Keeping pet animals should be discouraged. All patients must be taught about the factors associated with contamination, measures to avoid it and proper response to contamination. Usually 2 days of oral antibiotic is given after an episode of contamination and dialysis effluent should be sent for culture. Transfer set should be changed periodically and after each episode of peritonitis.

Training

Proper training of the patient about the technique of dialysis exchange and maintenance of strict hygienic practice is the key to a successful PD programme. There should be separate nursing staff who are specially trained for the purpose of patient education. They should also monitor the PD technique and hand hygiene periodically by home visit or during patient visit to health care centre. Training programme should be on one-to-one basis. Focus of training should be on the basics of performing the dialysis correctly to prevent subsequent infection and on ability to recognize contamination. Nursing staff themselves should update periodically. After initial training, patient also should have retraining sessions at periodic interval and especially after an episode of peritonitis. The training and retraining should be

periodically monitored by the team co-ordinator. Patients should also undergo retraining after an episode of peritonitis, prolonged hospitalization, change in dexterity, vision, or mental acuity and following change to another supplier or a different type of connection.

Prophylactic antibiotic

Prophylactic antibiotics are recommended before endoscopic interventions, colonoscopy, sigmoidoscopy, cystoscopy, hysteroscopy, and hysteroscopy assisted intrauterine device implantation or removal, but not after upper gastrointestinal endoscopy. Intravenous ampicillin plus an aminoglycoside, with or without metronidazole are used before these procedures. Hypokalemia, constipation, and gastroenteritis are found to be associated with a higher rate of peritonitis and prompt treatment of these condition reduces the incidence of peritonitis. Currently, no studies have evaluated antibiotic prophylaxis for dental work to prevent peritonitis in PD patients.

Prophylaxis for fungal peritonitis

Patients who are receiving prolong or repeated course of antibiotics are at high risk for fungal peritonitis. Oral Nystatin or fluconazole during antibiotic course reduces the rate of fungal peritonitis. Study by Kumar *et al* had shown that use of anti-fungal therapy during use of intravenous antibiotics reduces the incidence of fungal peritonitis [22]. They noticed that use of oral flucanozole reduced the incidence of fungal peritonitis at their center from 17.6% to 5%.

Different dialysis solution

With the invention of newer biocompatible dialysis solution, initial studies demonstrated lower risk of peritonitis with these neutral pH and low glucose degradation solution compared with conventional solutions [23]. However, a subsequent meta-analysis by Cho *et al* concluded that the use of pH neutral peritoneal dialysate with reduced GDPs though resulted in greater urine volumes and residual renal function after 12 months, but was not associated with other clinical benefits like reduction in rate of peritonitis [24]. ISPD also does not suggest use of biocompatible neutral pH solution for reduction of peritonitis [1].

Modifiable risk factors

Vitamin D deficiency is very common in patients on PD. Vitamin D supplementation has shown to reduce the incidence of PD peritonitis [25]. Hypoalbuminemia is also a risk factor for peritonitis. Improving serum albumin dietary approach reduces the incidence of peritonitis [26]. Depression has also been shown to be a risk factor for peritonitis. The mechanism is unclear. There is no study showing that treatment for depression lowers the subsequent peritonitis risk. Pets are associated with a higher rate of peritonitis and should always be excluded from the room where exchange being done.

All PD patients should be educated about the importance of regular bowel movement and avoidance of constipation. Some patients may require laxatives for treating constipation. Hypokalemia which can worsen bowel immobility should be promptly treated.

Some other patient related factors which need to be addressed in specific cases include associated co-morbidities, infections elsewhere like pyoderma or diabetic foot, bathing and changing frequency, hand and foot hygiene including nail care, adequacy of PD and training and calibre of person doing the procedure

Care must also be given to the area where PD exchanges are being done. The clinical coordinator should check whether there are designated areas for hand washing, distance between the hand washing area and the performance area, area of performance should be isolated, should be at a distance from toilet, should be free from cobwebs, moist corners, leaking roofs, and should be properly ventilated with an adequate sunshine.

Continuous quality improvement

ISPD recommends that each PD centre should have a continuous quality improvement (CQI) programme in place to reduce peritonitis rates. This is a multidisciplinary approach involving nephrologists, nurses, social workers, and dieticians. Role of the team is to evaluate each episode of peritonitis to find out the etiology and develop solutions. The team also needs to plan interventions such as retraining, changing equipment, applying new protocols for exit-site care, or managing contamination. ISPD also recommends monitoring peritonitis rate by each centre yearly, as a part of CQI. Monitoring programme should include the overall peritonitis rate, peritonitis rates of specific organisms, the percentage of patients per year who are peritonitis-free, and the antimicrobial susceptibilities of the infecting organisms. With this information, interventions can be implemented when peritonitis rates are rising or unacceptably high. The overall peritonitis rate should be no more than 0.5 episodes per year at risk, although the rate may vary from one nation to another.

PD catheter should be removed in cases of refractory peritonitis, relapsing peritonitis, refractory exit site and tunnel infection, fungal peritonitis. In mycobacterial peritonitis and multiple enteric organisms peritonitis, catheter should be removed if not responding to therapy. Timely removal of catheter reduces patient morbidity and mortality and preserves the peritoneum for future dialysis.

Conclusion

PD peritonitis is a common but potentially preventable complication of peritoneal dialysis. Proper preventive steps require a dedicated team effort involving treating physician, PD nurse, clinical co-ordinator as well as the patient. Many a times, the

risk factor for development of PD peritonitis is a trivial but an ignored factor, which if taken care of, can prevent PD peritonitis. Prevention in PD peritonitis will go a long way to boost the growth of peritoneal dialysis as a modality of choice of RRT and will dispel the false sense of fear and anxiety associated with it in the prospective patients.

Chapter 27
Bacterial Peritonitis

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Bacterial Peritonitis

Introduction

Peritonitis is associated with peritoneal inflammation leading to hyperemia and changes in the peritoneal transport causing increased solute transport and ultrafiltarion failure. These changes typically resolve within a month after resolution of peritonitis. Bacteria form a bio film around the catheter within 48 hours of the catheter placement. Peritoneal immune defenses protect against the formation of this bio film. The peak incidence of bacterial peritonitis (BP) takes place during hot and humid months.

This is the most common complication of peritoneal dialysis (PD) therapy accounting 30% of technique failure and a major cause of death in 16% cases. It remains a main hurdle of patient's hesitation to accept this form of renal replacement therapy (RRT), despite the latest newer technique (double bag system connection) has significantly reduced the incidence of peritonitis [1, 2]. Incidence of BP is 0.24-1.66 episode /pt/year. A goal rate of 1 episode per 18 months (0.67/ year) is expected [3]. Exit site infection and tunnel infection eventually leads to peritonitis. [4] The main goal of peritonitis treatment is to resolve inflammation rapidly by eradicating the organism and preserving the function of the peritoneal membrane.

Organism

The most common organisms associated with PD peritonitis reported worldwide are coagulase-negative Staphylococcus spp. (CONS) and *S. aureus* followed by Streptococci, Enterobacteriaceae, non-fermenting Gram-negative bacilli and Gram-positive bacilli. (**Table 1**) Approximately, 20%-35% peritonitis worldwide is culture negative.

Table 1: Microbiological cause of peritonitis

S.epidermidis	30-45%
S.aureus	10-20%
Streptococcal species	5-10%
E.coli	5-10%
Other gram negative species	5%

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Pseudomonas species	5%
Others	<5%
Mycobacteria	<1%
Fungus	<1-10%
Culture negative	5-20%

However, reports from India showed a more Gram negative predominance. *E. coli* was the most common isolate. Organisms of fecal origin were significantly more frequent than those of skin origin [5].

Pathogenesis

The intact peritoneum and the defense mechanism of mesothelium are the most important barrier for the development of peritonitis. In patients on PD, both the protective mechanisms are defective [6].

1. Potential routes of infection are*:* There are several sources of bacterial peritonitis in CAPD

- Intraluminal – improper technique; access to bacteria migration *via* the catheter lumen
- Periluminal – bacteria present on skin surface enter the peritoneal cavity *via* the catheter tract
- Transmural – bacteria of intestinal origin migrate through the bowel wall
- Haematogenous – peritoneum seeded *via* the blood stream
- Transvaginal.

2. Bacteria laden plaque*:* The intraperitoneal portion of the catheter covered with a bacteria laden plaque plays an important role in the pathogenesis of resistant peritonitis.

3. Host defences*:* Peritoneal leucocytes are critical in combating bacteria by phagocytosis. Phagocytic, chemotactic and opsonic activities of neutrophils are decreased in patients on PD. The oxidative metabolism in macrophages is also decreased. Further, advanced glycogen end products in PD fluids inhibit CD8+T cells functions. Uremic environment, hypertonic and acidic pH of conventional PD solution, low calcium in dialysate and low levels of peritoneal IgG are major factors that are responsible for inhibition of immune response activity in patients on CAPD.

4. PD exchange practices: Touch contamination, dropping the tube on floor or table, not wearing a mask during exchange, performing the exchange in atmosphere filled

with dust or animal hair, holes in catheter/ accidental disconnection are some of the practices that lead to peritonitis.

5. Gram negative peritonitis*:* Gram negative organisms originate usually from bowel. An uremic patient has impaired intestinal barrier function that leads to transmural movement of bacteria. Constipation, diarrhea, Gastric acid inhibitors, ischemic colitis, cholecystitis are contributing factors for this.

Risk Factors

Extremes of age, female sex, diabetes, heart failure, pulmonary disease, anemia, low serum albumin level, inadequate education, exit site infection poor nutrition and nasal *Staphylococcus aureus* carrier status are the risk factors for bacterial peritonitis. Other modifiable risk factors are smoking, living distantly from PD centre, obesity, depression etc.

Role of Nasal carriage of Staphylococcus aureas in CAPD peritonitis

Persistent but not intermittent *S.aureus* nasal carriage is the major determinant of CAPD peritonitis. Prevalence of *S. aureus* nasal carriers estimated to be 50%, of which 10-35% carries persistently. Several studies showed eradication of bacteria by prophylactic use of Mupirocin significantly decreased the incidence of peritonitis [7].

Definition

Peritonitis is diagnosed if at least 2 following criteria are present [8]

- Abdominal pain
- Cloudy effluent
- Effluent white cell count >100 white blood cell (WBC)/ml (after a dwell time of at least 2 hours) with > 50% polymorphonuclear cells
- Positive dialysis effluent culture.

Differential diagnosis of abdominal pain in patients on PD includes constipation, renal or billiary colic, peptic ulcer disease, pancreatitis and acute intestinal perforation (**Table 2**). These problems should be ruled out in patients with abdominal pain with clear fluid. Degree of pain is usually less with CoNS and greater with Staphylococcus, Gram negative rods and *S. aureus* organism. Gram stain of PD fluids should be done mainly to define presence of yeast

Dialysate culture method

Correct microbiological culture method is of great importance to minimize culture negative peritonitis and to guide therapy efficiently. The yield of PD fluid culture is enhanced by inoculating the fluid directly into rapid blood culture bottle kits. (Centrifuging 50 ml of PD fluid at 3000g for 15 min, followed by resuspension of sediment in 3-5 ml supernatant and inoculation on solid/standard blood culture

media) The specimen should send (whole bag or minimum 100 ml effluent fluid) immediately to laboratory (within 6 hours). In 75 % cases, microbiological diagnosis is established in < 3 days. If cultures remain negative after 3-5 days of incubation, then PD fluid should be sent for repeat cell count, differential count, fungal, Mycobacteria culture. Several novel diagnostic techniques are available but none superior to the conventional techniques

Table 2: Cinical Presentation [9]

Symptoms	**Percentage**
Abdominal pain	95
Nausea and vomiting	30
Fever	30
Chills	20
Constipation or diarrhea	15
Signs	
Cloudy peritoneal fluid	99
Abdominal tenderness	80
Rebound tenderness	10-50
Increased temperature	33
Blood leucocytosis	25
CRP	100

Important Terminology of peritonitis

Recurrent: An episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism

Relapsing: An episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or one sterile episode

Repeat: An episode that occurs more than 4 weeks after completion of therapy of a prior episode with the same organism

Catheter-related peritonitis: Peritonitis in conjunction with an exit site or tunnel infection with the same organism.

Management

International society of peritoneal dialysis (ISPD) recommends to initiate empirical antibiotic therapy as soon as possible after appropriate microbial solution have been obtained. For Gram positive organisms, suggest to use vancomycin or first generation cephalosporin and for Gram negative to use aminoglycosides or ceftazidime [10]. Cefepime can be used for both Gram positive and Gram negative organisms [11]. No evidence for loss of RRF was observed in short term use of aminoglycosides [12].

Dosage of Antibiotics

Intraperitoneal (IP) is the preferred route of administration unless the patient has features of systemic sepsis. IP vancomycin is administered intermittently and the serum vancomycin level be kept above 15μg/ml at the interval of every 4-5 days. IP aminoglycosides is administered as daily intermittent dosing. IP cephalosporin be administered either continuously (in each exchange) or on a daily intermittent basis.

Adjunctive Treatments

Heparin 500 U/L should be used to prevent catheter occlusion by fibrin. The pain can be reduced by 1 or 2 rapid exchanges [13].

Urokinase is a plasminogen activator with fibrinolytic properties, a preferred thrombolytic agent for IP use because it does not provoke an immune response and is not associated with peritonitis like syndrome. About 60000 IU is diluted in 20 ml normal saline. The solution is infused in the catheter lumen and the peritoneal cavity after draining out the PD fluid. Catheter is clamped for 2 hours before dialysis resumed. If symptoms persist, instillation procedure can be repeated 2 days later. Urokinase used to penetrate the bio film layer and allow antibiotics to act on bacterial harbored on the catheter [14]. In a retrospective study, IP Urokinase and oral rifampicin showed catheter salvage in 64% cases of persisting CoNS [15]. **Figures 1, 2, 3, 4, 5 and 6** gives various treatment methods.

Subsequent management of peritonitis

Patients who responded showed a considerable clinical improvement within 48 hours of initiation of the treatment. If no improvement is observed after 48 hrs, cultures should be repeated.

Treatment Algorithms **[8]**

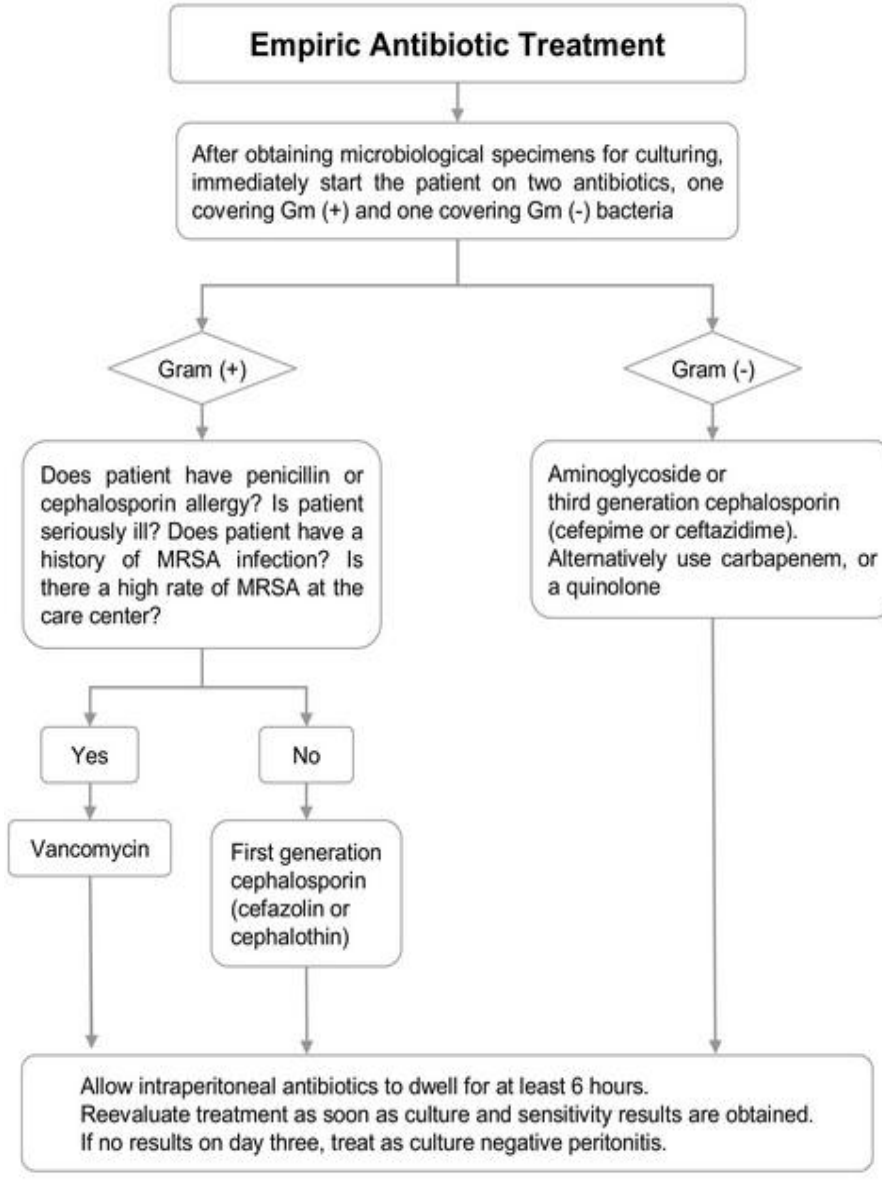

Figure 1: Empirical Antibiotic Treatment

Low transporters = Higher ultrafiltration =more sodium sieving = lower D/P sodium

High transporters = Low Ultrafiltration = less sodium sieving = higher D/P sodium

Membrane failure = Low ultrafiltration = less sodium sieving = higher D/P sodium [4]

The modified PET Test can study sodium sieving. This test semi quantitatively evaluates the membranes transport capacity determined by the rate at which the solute reaches equilibrium concentration in the plasma and the dialysate. In addition to the D/P Creatinine and the UF obtained, Sodium sieving which is a reflection of the free water transport in the first hour of the exchange is expressed as D/P Na at 60 mins or by the dip in the dialysate [Na] at 60 minutes (ΔNa).

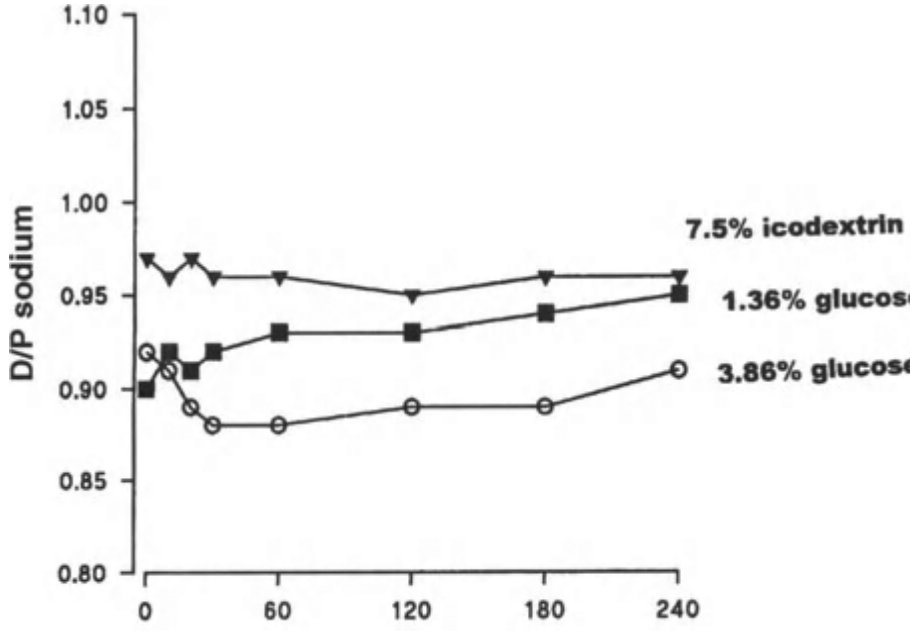

Figure 2: Dialysate/plasma ratio sodium (D/P sodium) during 4-h dwells with glucose 1.36% (•), glucose 3.86% (o) and 7.5% icodextrin.

During the hypertonic dwells with 3.86% glucose a decrease of D/P sodium was observed, indicating sieving of sodium through ultrasmall pores, whereas the icodextrin solution induced no changes in D/P sodium. (Drukker Parsons and Mayer. Replacement of Renal Function by Dialysis. 5th Edition Eds. Waller H. Hörl, Karl M. Koch, Robert M. Lindsay, Claudio Ronco, James F. Winchester (editor-in-chief) Springer).

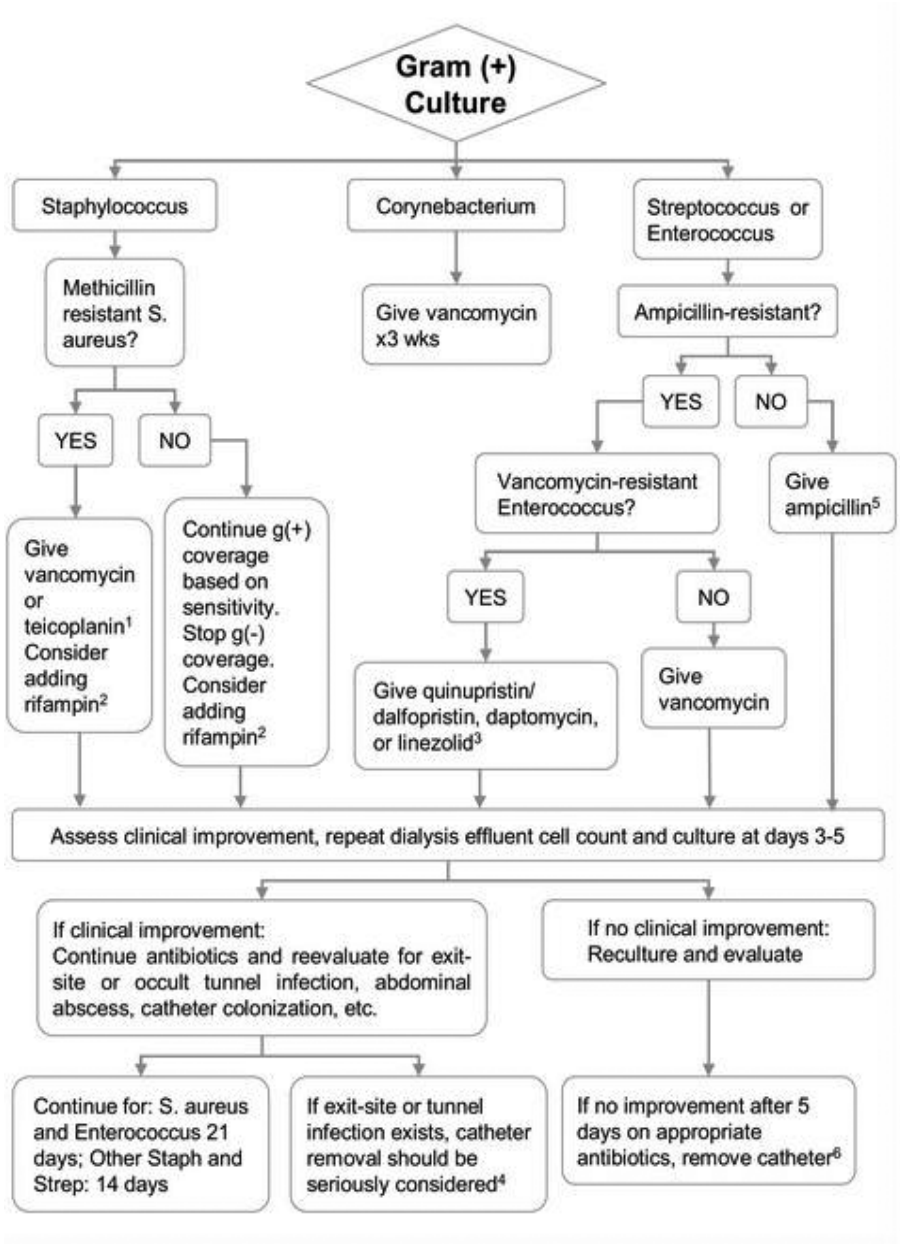

Figure 3: Gram positive culture method

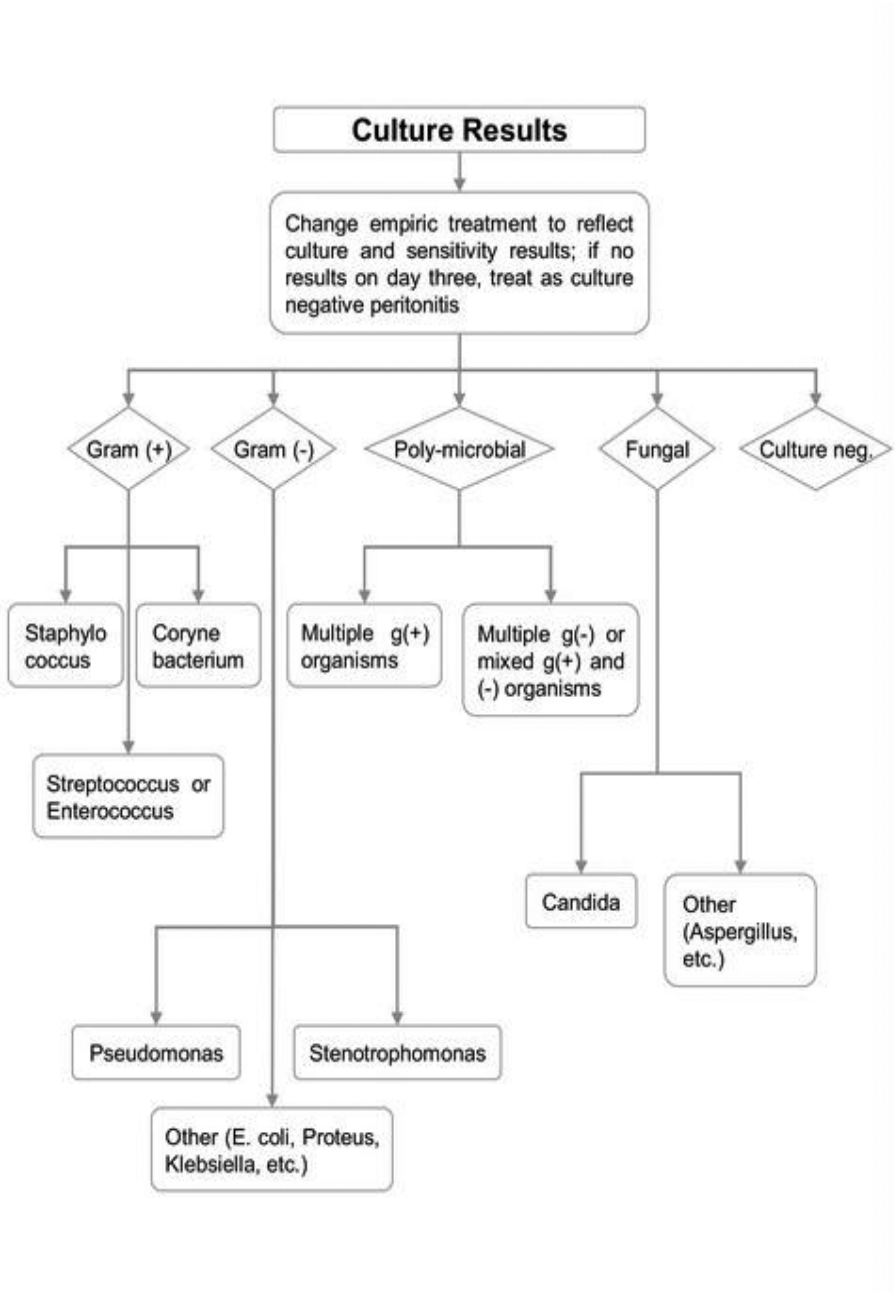

Figure 4: Culture results.

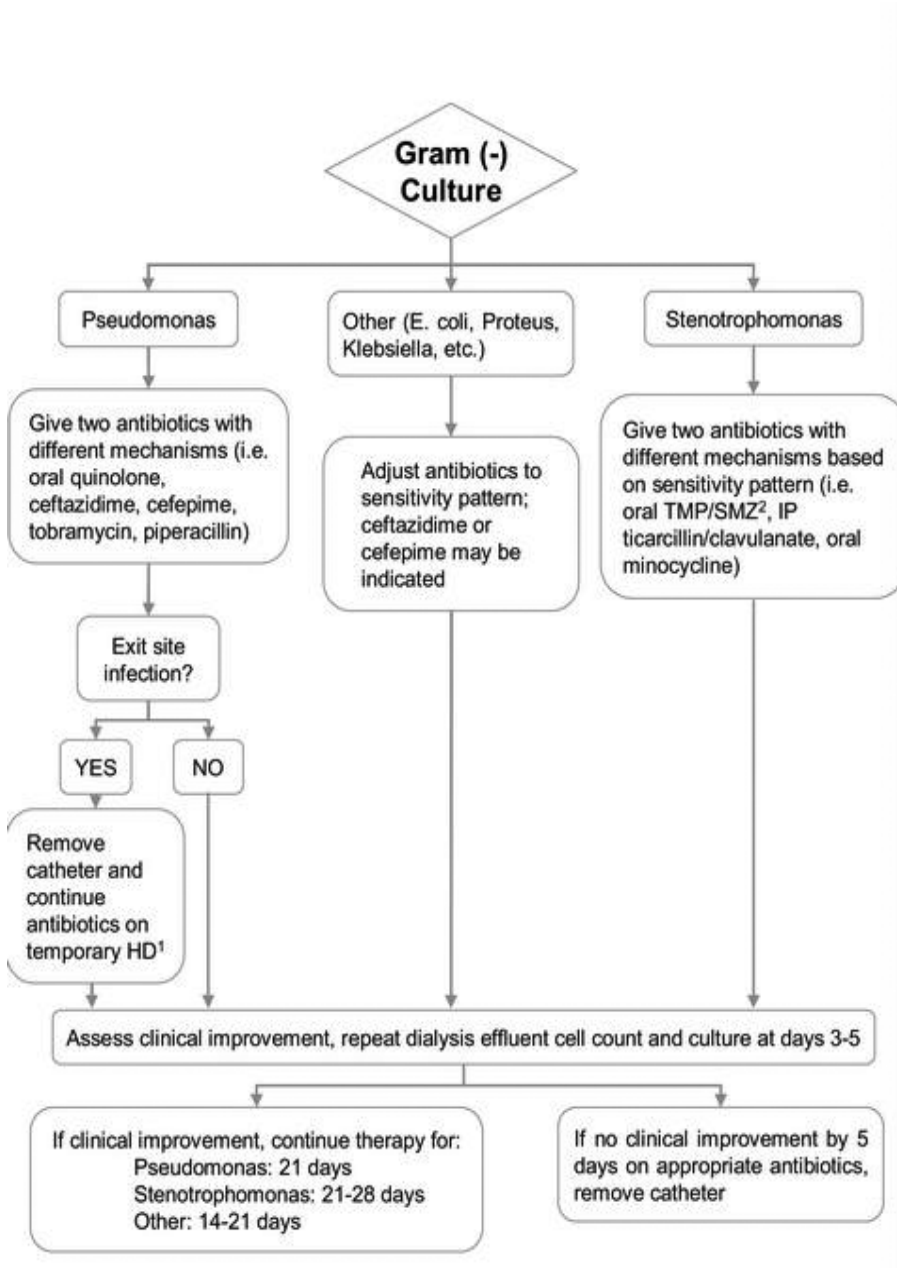

Figure 5: Gram negative culture method.

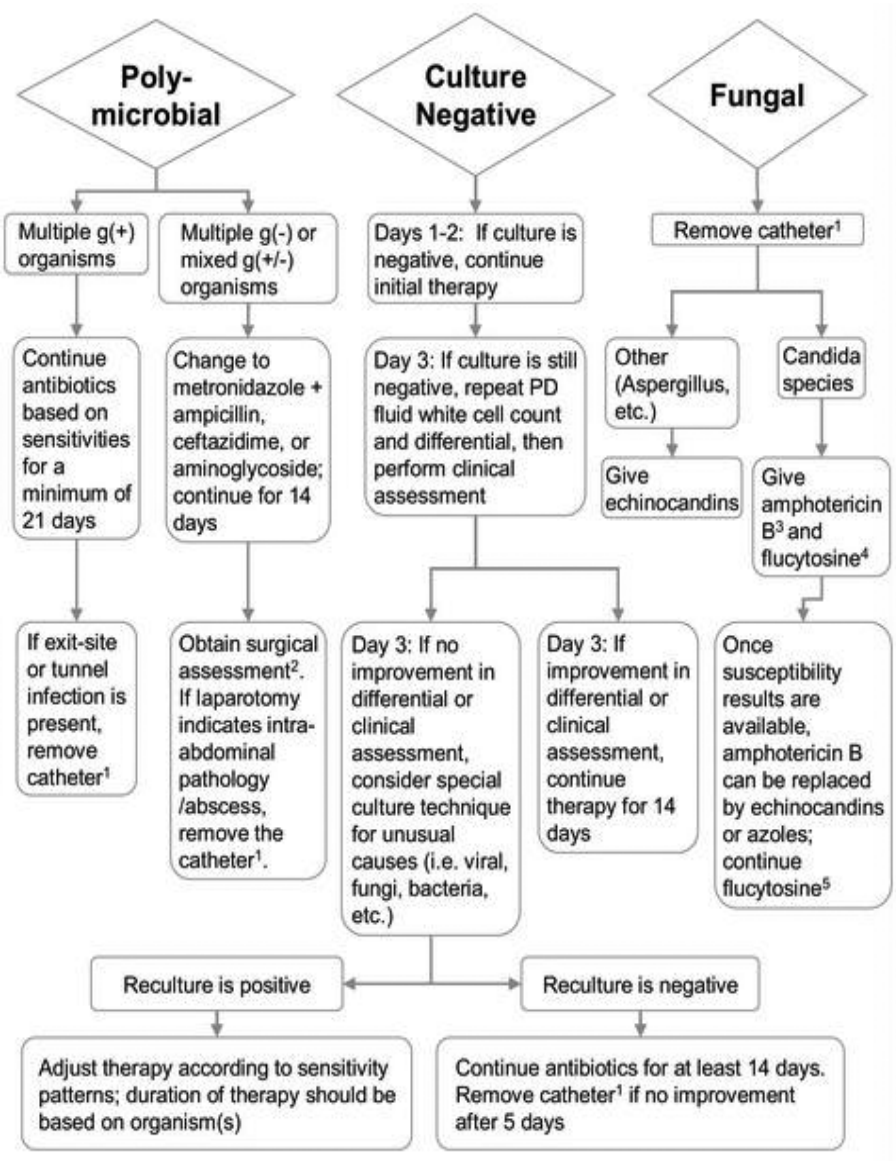

Figure 6: Other organisms: duration of treatment.

Enterococcus species

Enterococcal peritonitis is one of the serious complications of PD, which is usually associated with polymicrobial peritonitis (PMP). Older age, renovascular disease, chronic lung disease, gastrointestinal pathology and coronary disease are risk

factors of PMP. There is an increase risk of catheter loss, change to HD and death [4]. This should be treated for 3 weeks with IP Vancomycin. ISPD suggests adding IP Aminoglycosides for severe Enterococcal peritonitis. For Vancomycin-resistant Enterococcus (VRE), suggested treatment is IP ampicillin for 3 weeks if the organism is susceptible or with alternative antibiotics (linezolid, quinupristin/dalfopristin, daptomycin or teicoplanin, based on antimicrobial susceptibilities) if the organism is ampicillin –resistant. Catheter removal should be done within 1 week of refractory peritonitis [16].

Streptococcal species

Streptococcal peritonitis must be treated with appropriate antibiotics, such as IP ampicillin, for 2 weeks and *S. aureus* for 3 weeks [17].

Corynebacterium peritonitis

It originates from natural flora of skin. Relapse or repeat episodes, catheter removal, permanent HD transfer and death are common ISPD recommends 3 week course of IP vancomycin [18, 19].

Pseudomonas peritonitis

This should be treated with two antibiotics with different mechanisms of action and to which the organism is sensitive (e.g. IP gentamycin or oral ciprofloxacin with IP ceftazidime or cefepime) for 3 weeks. It usually leads to higher rates of catheter removal and permanent HD transfer [20].

Polymicrobial Peritonitis

Streptococcal infection has become less common owing to the improved techniques. Gram negative and PMP infection have become proportionately more common. PMP originates from gastrointestinal pathology. A large study from Australia showed that PMP accounts for 10% of all peritonitis. Most common isolated organism is 1) *Staph epidermidis* and other coagulase negative Staphylococcus, 2) Klebsiella and Enterococci, 3) *E coli* and Klebsiella, least is *E coli* and Streptococcus species. Further, both Gram positive and Gram negative organisms in 41%, pure Gram negative in 22% and mixed Gram positive and Gram negative, fungal organisms were isolated in 13% isolates. The patient is treated with metronidazole in conjunction with IP vancomycin and either IP aminoglycoside or IP ceftazidime for a minimum period of 3 weeks. Surgical evaluation should be obtained immediately when there is no prompt clinical response. Relapse (10%), hospitalisation (83%), catheter removal (43%) and permanent HD transfer (38%) are the most common outcomes. Oral antibiotics metronidazole, amoxicillin and ciprofloxacilin can be used as second and third regime [21].

Culture-Negative Peritonitis*:* If the culture- negative peritonitis is resolving at day 3, ISPD suggests discontinuation of aminoglycoside therapy and continuing treatment with gram-positive coverage (e.g. first-generation cephalosporin or vancomycin) for 2 weeks.

Role of the Type of PD catheter related Interventions in bacterial peritonitis

A systemic review showed that disconnect (double bag and Y – connection) are superior to conventional spike (or luer lock) connect system in prevention of peritonitis. Y-set and twin – bag system does "flush before fill" maneuver which reduces inadvertent peritoneal microbial contamination. No other catheter related interventions such as surgical versus lap insertion technique, different catheter design, APD *vs.* CAPD, single *vs.* double cuff have any significant beneficial effect. However, it was observed that straight catheter has survival benefit over coiled catheter [22].

Re-insertion of a new catheter is attempted after a PD catheter is removed for refractory/relapsing peritonitis. It should be performed at least 2 weeks after the catheter removal and complete resolution of peritoneal symptoms. After severe episode of peritonitis, 50% of patients potentially return to PD [23].

Predictors of outcome in bacterial peritonitis [24]

- Exit site infection
- >5days PD effluent cell count > $100\times10^{\wedge6}$/L prior use of antibiotics
- Serum total protein level
- Pseudomonas Peritonitis

Predictive value of cell count

On day 3, WBC count in PD effluent fluid can predict outcomes of peritonitis. A study from Hong Kong had observed a cut off PD white cell count of 1090/mm^3 on day 3 carried a 9 fold increased risk for treatment failure. When PD cell count exceeds 100/mm^3 for 5 days, treatment failure is significantly higher [25].

Prevention of peritonitis in peritoneal dialysis

Prevention of peritonitis is the major challenge in patients on PD. Intensive patient training with careful attention to their home environment is critical in achieving good PD outcome. Newer measure like double bag, Y connection, flushing before fill, avoiding spike have relatively decreased the incidence of peritonitis.

Less bio incompatible solution with neutral ph and low glucose degradation product have shown beneficial effects on cell viability and increase peritoneal host defense but without any difference in peritonitis risk.

1. Training Programmes [8]

- PD training should be conducted by the nursing staff with appropriate qualifications and experience.
- A home visit by a PD nurse/technician is often useful in detecting problems with exchange technique, adherence to the protocols, and other environmental and behavior issues which increases the risk of peritonitis.
- Each PD centre must have a continuous quality improvement (CQI) programme in place to reduce peritonitis rates.

2. Precautions during catheter implantation [26]

- Implantation should be done by an experienced operator in the operation theatre.
- Tenkhoff catheter is commonly used.
- ISPD does not recommend any specific catheter design for prevention of peritonitis.
- The patient should bath with soap and water in the morning
- The abdominal hair shaving and betadine dressing must be done by the previous evening.
- Determine the site of implantation with exit site directing downward
- Prophylactive antibiotics must be given intravenously prior to the implantation.
- Avoid trauma/ hematoma. The exit site should be made round shaped and the tissue should fit around the catheter

3. Exit-Site Care

- Over time, the exit site and the nasal colonization with pathogenic organisms can lead to exit-site infections and peritonitis. For patients with *S. aureus* colonization, the exit-site prophylaxis with application of daily mupirocin or gentamicin cream reduces clinical infection with this organism. Antibiotic prophylaxis before gastrointestinal, gynecologic, or dental procedures may help to reduce the risk of peritonitis [27].
- Dressing should be done using the sterile technique.
- The exit site should be kept dry.
- Catheter should always be kept immobile.
- Prompt treatment of the exit-site or catheter tunnel infection must be needed to reduce subsequent peritonitis risk.

4. Touch contamination should be avoided by appropriate hand washing and by keeping the hands dry before performing the exchange.

5. Avoid constipation.

Some strategies to decrease *S. aureus* infection are:

- To use Rifampicin 600/day for 5 days every 3 months.

- TMP-SMX (single strength) thrice weekly.

- Mupirocin ointment at nasal nares twice daily for 5 days each month.

NIMS experiences

A total of 556 patients with ESRD underwent CAPD during the last 13 years. The incidence of bacterial peritonitis was 1 episode in 41.2 months. The causes of peritonitis were *Pseudomonas aeruginosa* (*n* = 32), *Escherichia coli* (*n* = 26), *Acinetobacter baumannii* (*n* = 14), *Klebsiella pneumoniae* (*n* = 15), *Staphylococcus aureus* (*n* = 23), coagulase-negative *Staphylococcus* (*n* = 11), and *Enterococcus faecalis* (*n* = 10). Infection with *P. aeruginosa* was a found to have a significant influence on catheter removal; the catheter was removed in 25 patients (37.31%) and retained in 7 (10.93%; *p* = 0.0025; relative risk: 1.842; 95% CI: 1.373 to 2.470). There were 17 episodes of relapsing peritonitis. The causative organisms were *A. baumannii* (*n* = 4), *P. aeruginosa* (*n* = 3), and *E. faecalis* (*n* = 1); the remaining episodes were culture-negative (*n* = 9). The significant risk factors for removal of the catheter were relapsing peritonitis (*p* = 0.0080), presentation more than 48 hours after onset of peritonitis (p< 0.0001), treatment given by a local doctor (*p* = 0.0047), loose stools (p< 0.0001), paralytic ileus (*p* = 0.0011), hypotension (p< 0.0003), serum albumin less than 3.0 g/dL (p< 0.002), and peritonitis caused by *P. aeruginosa* (*p* = 0.0120). On multivariate analysis hypotension, loose stools, and paralytic ileus were identified as risk factors. Of the 131 episodes of bacterial peritonitis, 67 episodes (51.1%) resulted in removal of the Tenckhoff catheter because of refractory peritonitis. Peritonitis was treated effectively in 64 patients (48.9%) [28].

Conclusion

CAPD should be offered to an ESRD patient who accepts the treatment after understanding the procedure in details. Repeated training and frequent home visit by a trained nurse or technician are the pillars for the success of this programme. Empirical treatment with antibiotic should start immediately on the suspicion of peritonitis. The catheter placement should not be done haphazardly. The standard protocol must be followed. Never hesitate to remove the catheter on time when it is indicated to prevent further damage to the peritoneum and loss of the patient.

References

1. Hsieh, Y. P., C. C. Chang, Y. K. Wen, P. F. Chiu, and Y. Yang, 2014: Predictors of peritonitis and the impact of peritonitis on clinical outcomes of continuous ambulatory peritoneal dialysis patients in taiwan—10 years' experience in a single centre. *Perit. Dial. Int.*, **34,** 85–94.
2. Boudville, N., A. Kemp, P. Clayton, W. Lim, S. V. Badve, C. M. Hawley, S. P. McDonald, K. J. Wiggins, K. M. Bannister, F. G. Brown, and D. W. Johnson, 2012: Recent peritonitis associates with mortality among patients treated with peritoneal dialysis. *J. Am. Soc. Nephrol.,* **23,** 1398–1405.
3. Fang, W., Z. Ni, and J. Qian, 2014: Key factors for a high-quality peritoneal dialysis programme — the role of the PD team and continuous quality improvement. *PDI,* **34,** 35–42.
4. Akoh, J. A., 2012: Peritoneal Dialysis Associated Infections: An Update On Diagnosis And Management. *World J. Nephrol.,* **1,** 106-122.
5. Prasad, N., 2003: Outcome Of Gram-Positive And Gram-Negative Peritonitis In Patients On Continuous Ambulatory Peritoneal Dialysis: A Single-Center Experience. Perit. Dial. Int., **23,** 144-147.
6. Burkart, J. M., Up To Date Sept., 2011
7. Nouwen, J. L., M. W. Fieren, S. Snijders, H. A. Verbrugh, and A. Van Belkum, 2005: Persistent (Not Intermittent) Nasal Carriage of Staphylococcus aureus is the Determinant Of CPD-Related Infections. *Kid. Int.,* **67,** 1084–1092.
8. Li, P. K. T., C. C. Szeto, B. Piraino, J. de Arteaga, S. Fan, A. E. Figueiredo, D. N. Fish, E. Goffin, Y. L. Kim, W. Salzer, and D. G. Struijk, 2016: ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. *Perit. Dial. Int.,* **36,** 481–508.
9. Daugirdas, J. T., P. T. Blake, Eds., 2007: Hand Book of Dialysis. Lippincott, Williams and Wilkins, Philadelphia, pp 419.
10. Lui, S. L., S. W. Cheng, and F. Ng, 2005: Cefazolin plus Netilmicin versus Cefazolin Plus Ceftazidime For Treating CAPD Peritonitis: Effect On Residual Renal Function. *Kid. Int.,* **68,** 2375–2380.
11. Wong, K. M., Y. H. Chan, C. Y. Cheung, W. L. Chak, K. S. Choi, S. H. Leung, J. Leung, K. F. Chau, D. N. Tsang, and C. S. Li, 2001: Cefepime Versus Vancomycin Plus Netilmicin Therapy For Continuous Ambulatory Peritoneal Dialysis-Associated Peritonitis. *Am. J. Kid. Dis.,* **38,** 127-131.
12. Badve, S. V., C. M. Hawley, S. P. McDonald, F. G. Brown, N. C. Boudville, K. J. Wiggins, K. M. Bannister, and D. W. Johnson, 2012: Use Of Aminoglycosides For Peritoneal Dialysis-Associated Peritonitis Does Not Affect Residual Renal Function. *Nephrol. Dial. Transplant.,* **27,** 381–387.
13. Ejlersen, E., and L. Brandi, 1991: Is Initial (24 Hours) Lavage Necessary In Treatment Of CAPD Peritonitis? *Perit. Dial. Int.,* **11,** 38-42.
14. Tong, M. K., K. T. Leung, Y. P. Siu, K. F. Lee, H. K. Lee, C. Y. Yung, T. H. Kwan, and T. C. Au, 2005: Use Of Intraperitoneal Urokinase For Resistant Bacterial Peritonitis In Continuous Ambulatory Peritoneal Dialysis. *J. Nephrol.,* **18,** 204-208.

15. Demoulin, N., and E. Goffin, 2009: Intraperitoneal Urokinase and Oral Rifampicin for Persisting Asymptomatic Dialysate Infection Following Acute Coagulase negative Staphylococcus Peritonitis. *Perit. Dial. Int.,* **29,** 548–553.
16. Edey, M., C. M. Hawley, S. P. McDonald, F. G. Brown, J. B. Rosman, K. J. Wiggins, K. M. Bannister, and D. W. Johnson, 2010: Enterococcal Peritonitis In Australian Peritoneal Dialysis Patients: Predictors, Treatment And Outcomes In 116 Cases. *Nephrol. Dial. Transplant.,* **25,** 1272-1278.
17. Shukla, A., Z. Abreu, and J. M. Bargman, 2006: Streptococcal PD peritonitis—a 10-year review of one centre's experience. *Nephrol. Dial. Transplant.,* **21,** 3545–3549.
18. Barraclough, K., C. M. Hawley, S. P. McDonald, F. G. Brown, J. B. Rosman, K. J. Wiggins, K. M. Bannister, and D. W. Johnson, 2009: Corynebacterium Peritonitis In Australian Peritoneal Dialysis Patients: Predictors, Treatment And Outcomes In 82 Cases. *NDT,* **24,** 3834–3839.
19. Szeto, C. C., K. M. Chow, K. Y. Chung, B. Ching-Har Kwan, C. B. Leung, and P. K. T. Li, 2005: The Clinical Course Of Peritoneal Dialysis-Related Peritonitis Caused By Corynebacterium Species. *Nephrol. Dial. Transplant.,* **20:** 2793–2796.
20. Siva, B., C. M. Hawley, S. P. McDonald, F. G. Brown, J. B. Rosman, K. J. Wiggins, K. M. Bannister, and D. W. Johnson, 2009: Pseudomonas Peritonitis In Australia: Predictors, Treatment, And Outcomes In 191 Cases. *Clin. J. Am. Soc. Nephrol.,* **4,** 957–964.
21. Barraclough, K., C. M. Hawley, S. P. McDonald, F. G. Brown, J. B. Rosman, K. J. Wiggins, K. M. Bannister, and D. W. Johnson, 2009: Polymicrobial Peritonitis In Peritoneal Dialysis Patients In Australia: Predictors, Treatment, And Outcomes. *Am. J. Kid. Dis.,* **55,** 121-131.
22. Strippoli, G. F., A. Tong, D. Johnson, F. P. Schena, and J. C. Craig, 2004: Catheter-Related Interventions To Prevent Peritonitis In Peritoneal Dialysis: A Systematic Review Of Randomized, Controlled Trials. *J. Am. Soc. Nephrol.,* **15,** 2735-2746.
23. Szeto, C. C., K. M. Chow, T. Y. Wong, C. B. Leung, A. Y. Wang, S. F. Lui, and P. K. Li, 2002: Feasibility Of Resuming Peritoneal Dialysis After Severe Peritonitis And Tenckhoff Catheter Removal. *J. Am. Soc. Nephrol.,* **13,** 1040–1045.
24. Kofteridis, D. P., A. Valachis, K. Perakis, S. Maraki, E. Daphnis, and G. Samonis, 2010: Peritoneal Dialysis-Associated Peritonitis: Clinical Features And Predictors Of Outcome. *Int. J. Infect. Dis.,* **14,** 489-493.
25. Chow, K. M., C. C. Szeto, K. K. Cheung, C. B. Leung, S. S. Wong, M. C. Law, Y. W. Ho, and P. K. T. Li, 2006: Predictive Value Of Dialysate Cell Counts In Peritonitis Complicating Peritoneal Dialysis. *Clin. J. Am. Soc. Nephrol.,* **1,** 768 – 773.
26. Abraham, G., T. Thiagarajan, and M. Mathew, 2005: Prevention Of Peritoneal Dialysis Related Infections As A Means To Prevent Dropout. *Indian J. Nephrol.,* **15,** 10-13.
27. Segal, J. H., and J. M. Messana, 2013: Prevention of Peritonitis in Peritoneal Dialysis. *Semin. Dial.,* **26,** 494-502.

28. Ram, R., 2014: Risk Factors That Determine Removal of the Catheter in Bacterial Peritonitis in Peritoneal Dialysis. *Perit. Dial. Int.,* **34,** 239–243.

Chapter 28

Peritonitis: Mycobacterium tuberculosis

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Peritonitis - Mycobacterium tuberculosis

Introduction

Tuberculosis (TB) is a disease caused by the Mycobacteria. The lungs are the major site for *Mycobacterium tuberculosis* infection, but it can also affect other parts of the body.

Tuberculosis is an important cause of morbidity and mortality worldwide. Host resistance to *Mycobacterium tuberculosis* infection is mediated by cell-mediated immunity. Chronic kidney disease (CKD) is associated with a large number of immune system disorders including impaired cellular immunity. The incidence of tuberculosis in end stage renal disease (ESRD) is higher than in the general population.

Peritoneal dialysis (PD) is one of the treatment options for patients with ESRD. Although the rate of peritonitis has decreased in parallel to the advances in PD technology, peritonitis remains a leading complication of PD [1-3]. The most common infectious complication of PD is bacterial peritonitis. Dialysis patients are at higher risk of acquiring mycobacterial infections than the general population. Due to various reasons, peritoneal TB carries an important significance among patients on PD. The incidence of tuberculous peritonitis is higher in Asia than elsewhere [3].

The first patient of *Mycobacterium tuberculosis*-complicated continuous ambulatory peritoneal dialysis (CAPD) was reported in 1980. Talwani and Horvath reviewed and published a study on 52 patients with PD and peritoneal TB in 2000 and Akpolat analysed 98 patients in 2009 [4, 5]. In 2013, Ram and colleagues published a series from India [6]. The International Society for Peritoneal Dialysis (ISPD) guidelines about PD related infections briefly discuss main issues about peritoneal TB [1-3]. The aim of this chapter is to discuss the main problems seen in daily practice regarding peritoneal TB among patients on continuous ambulatory peritoneal dialysis (CAPD).

In an Indian study published in 2013, the prevalence of tuberculous peritonitis was reported as 2.6 % (11 patients with tuberculous peritonitis out of 414 patients on CAPD) [6]. Such a high prevalence is expected because *M. tuberculosis* is endemic in our area. Liu *et al,* from Hong Kong reported 14 patients with tuberculous peritonitis in 790 patients on CAPD [7]. The prevalence was 1.7 %. In another study, 3 of 92 (3.2%) patients on CAPD were reported to have tuberculous peritonitis [8].

Main Problems Seen In Daily Practice [Akpolat, 2009]

The important issues seen in daily practice are:

1. What are the clinical findings of peritoneal TB?

2. Is the cell count of peritoneal fluid helpful in the differential diagnosis?

3. Is tuberculin test helpful in the diagnosis?

4. What are the diagnostic methods?

5. Differential diagnosis.

6. The presence of extraperitoneal TB.

7. Medical treatment of peritoneal TB.

8. Treatment delay.

9. Is removal of the catheter necessary?

10. Outcome.

Clinical Findings

Fever, abdominal pain, and cloudy fluid are the most common presenting symptoms. Ultrafiltration failure (UFF), anorexia, nausea, vomiting, diarrhea, weight loss, generalized weakness, and paraplegia are other nonspecific symptoms related to peritoneal TB. All these clinical findings can be seen in bacterial peritonitis as well, therefore, the clinical findings of peritoneal TB are indistinguishable from bacterial peritonitis.

Cell Count of Peritoneal Fluid The peritoneal dialysate cell count should not be solely used to differentiate tuberculous peritonitis from other forms of peritonitis. The initial articles have emphasised on lymphocyte dominance in the peritoneal fluid [9, 10, 11]. However, in the recent two reviews, 76 % and 65 % of patients had neutrophilia in the peritoneal fluid. In our patients, the differential cell count varied from initial neutrophil dominance to later lymphocytic dominance as the duration of peritonitis progressed [4, 5]. There was a report of initial predominance of neutrophils but subsequent lymphocyte dominance, in 6 of 11 patients. It was thus suggested that differential cell count variation is dependent on the rapidity of diagnosis [12]. This leads to two inferences—patients with neutrophilic 'sterile' peritonitis with no response to antibacterial medications should also be investigated for tuberculosis, and predominance of lymphocytic peritonitis should immediately trigger the suspicion for tuberculous peritonitis [13].

Tuberculin Test The predictive value of the tuberculin test in the diagnosis of tuberculosis is not clear in CAPD patients. Anergia is common in patients with ESRD and a negative tuberculin test does not exclude TB diagnosis in patients on CAPD.

Diagnosis

Tuberculosis is an infrequent cause of peritonitis but can be difficult to diagnose. There are many methods that are useful in the diagnosis. Each method has advantages, disadvantages and limitations (**Table 1**). Since negative results have not been mentioned in some of the studies/case reports, it is hard to determine the sensitivity of the diagnostic methods. The usefulness of the diagnostic methods is mainly based on the experience of tuberculosis in nonuremic patients. The diagnosis was done by response to empirical antituberculosis treatment in some patients [5].

Table 1. Main advantages/disadvantages of diagnostic methods

Method	Advantage/disadvantage
Culture	Needs time, shorter in fluid medium.
Smear	Early diagnosis, low sensitivity.
Biopsy	Invasive (generally minimal)
PCR	Early diagnosis, Common false positive and negative result, expensive.

We used 18F-fluorodeoxyglucose positron emission tomography/computerized tomography (18F- FDG PET/CT) scan to help in diagnosis of tuberculous peritonitis in five patients [14]. The first patient was a 35-year-old male with diabetes and hypertension who underwent PD catheter insertion approximately 18 months ago ESRD. He was on automated peritoneal dialysis (APD). He presented with the complaint of fever of one week duration. The fever was of low grade, intermittent, associated with evening rise of temperature and had not subsided with antipyretics. There was a history of abdomen pain and cloudy dialysate of 4 days duration. On admission, the patient had pallor and no palpable lymph nodes. His abdomen was tender. Dialysate was cloudy on the day of admission. There was no evidence of exit site or tunnel infection. He was started on intraperitoneal antibiotics after sending specimens for investigations. The dialysate total leucocyte cell count on the first 3 days was 420, 320 and 280 cells/μL. The differential count was 85% lymphocytes on day 1, and 100% lymphocytes on days 2 and 3. Gram and Ziehl-Neelsen stains of dialysate fluid revealed no organisms. Cultures of dialysate and PCR for tuberculosis sent on days 1 and 3 yielded negative results. With a suspicion of tuberculosis, 18F-FDG PET/CT scan was performed. It revealed metabolically active pre- tracheal, paratracheal and pre-vascular lymphadenopathy (**Figure 1**). The cytology of the pre-tracheal lymph node showed caseating

granuloma. Within 24 hours of start of anti-tuberculous treatment there was clearing of the dialysate. The total leucocyte count decreased from 100 to 10 cells/μL by day 7. After 4 weeks, the culture of the dialysate sent on the day of admission had shown Mycobacteria tuberculosis on the Lowenstein Jensen medium.

Differential Diagnosis

The clinical and laboratory findings of peritoneal TB are nonspecific and the diagnosis requires a high index of suspicion. The hardest case has culture negative peritonitis or culture positive peritonitis resistant to appropriate antibiotics without any additional clues of tuberculosis. Bacterial peritonitis can coexist. In the Indian study two of patients of eleven patients of tuberculous peritonitis, there was an episode of antecedent bacterial peritonitis, and one of them had simultaneous fungal peritonitis [6]. In one of the two reviews, 14 of the 52 (28 %) patients suffered from concomitant and/or antecedent bacterial peritonitis [5]. Hence, tuberculous peritonitis should also be considered in bacterial peritonitis not responding to antibiotics [15].Acid-fast bacilli smear is also positive in nontuberculous Mycobacterium peritonitis and should be considered in the differential diagnosis [16].

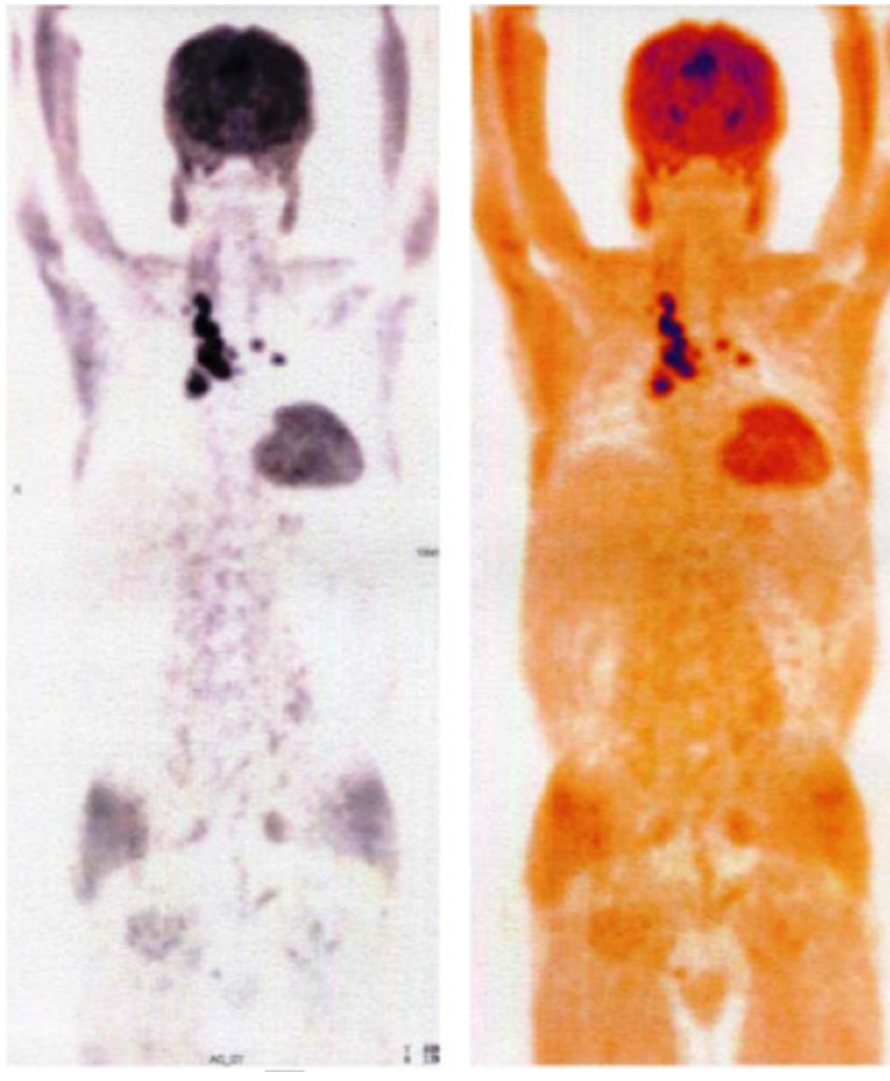

Figure 1: Metabolically active pre- tracheal, para-tracheal and pre-vascular lymphadenopathy (Modified from [14]).

Extraperitoneal TB

Peritoneal TB may be a part of the disseminated disease, miliary tuberculosis.

Extraperitoneal TB was present in 20% of the patients [4, 5, 14, 17].

Treatment

The treatment protocol is mainly based on the treatment of extraperitoneal tuberculosis in ESRD and general protocols for treatment of TB. The 2005 ISPD guideline recommended four drugs: rifampin, isoniazid, pyrazinamide, and ofloxacin and avoided ethambutol [2, 3].

At our institute, the tuberculous peritonitis was treated with the four drug regimen, which includes isoniazid (5 mg/kg/ day), rifampin (10 mg/kg/day), pyrazinamide (10 mg/ kg/day), and ofloxacin (15 mg/kg/day) for 3 months followed by 3 drugs for 6 months and 2 drugs till 18 months. No isoniazid secondary prophylaxis was given. Pyridoxine is given in the doses of 80 to 120 mg per day. It is to avoid not only peripheral neuropathy due to isoniazid but also to prevent isoniazid cerebellitis. The increased sensitivity of the dialysis population to isoniazid neurotoxicity is predominantly due to inhibition the activation of pyridoxine to pyridoxal 5-phosphate (PLP) by isoniazid metabolites. In addition, there is a rapid clearance of PLP by haemodialysis (HD), resulting in a severe deficiency of this active metabolite [18]. In patients on PD with high transporter membrane characteristic, the clearance of PLP may be profound [19].

The ISPD PD-related infections recommendations 2010 update retained avoidance of ethambutol. The rationale of ethambutol avoidance is the risk of optic neuritis with irreversible visual loss [3]. However, the use of ethambutol for the treatment TB in patients with ESRD is a controversial issue [20, 21]. The data about antituberculosis treatment was available in 60 of the 98 cases in Akpolat's review [5]. All regimens included at least three drugs (isoniazid, rifampin, pyrazinamide). Quinolones or ethambutol was the fourth agent in most of the cases in this review.

Treatment Delay

Tuberculosis is an infrequent cause of peritonitis, and it can be difficult to diagnose. Early diagnosis and timely initiation of antituberculosis drugs is the key to the management of peritoneal TB. The average interval between presentation with disease and diagnosis and initiation of treatment was about mean: 6.7 weeks; median: 5 weeks and 6.8 weeks [4, 5]. In our study for the whole cohort, the duration after which the antituberculous therapy was started was 15.1 ± 11.6 days (range: 2–28 days) [6]. Only in 4 of 11 patients, the anti-tuberculous therapy was started within 5 days of onset of symptoms of peritonitis. There was a treatment delay of 22.1 ± 8.2 days in the remaining 7 patients. Of these, two expired due to reasons related to peritonitis, one each suffered from ultrafiltration failure and adhesions and three survived without any complication. In one of the reviews, the treatment delay was identified as a significant factor for mortality in patients with tuberculous peritonitis [4].

Catheter Removal

However, the decision of the removal of CAPD catheter in tuberculous peritonitis is not as clear-cut as in fungal peritonitis [22]. The ISPD guideline about peritonitis had mentioned 'Catheter removal appears to be necessary in all patients' in 2000 [1]. Approach to the catheter removal has changed in the ISPD guideline 2016 as 'Catheter removal may also be considered for Mycobacterial peritonitis' [23].

This contentious issue can only be resolved, if it is known that the removal of catheter is indeed going to be effective (**Table 2**). **Table 2** is based on the results of all the reports of published tuberculous peritonitis. There was no significant difference in the patient survival between patients for whom CAPD catheter was removed or retained. It should be noted that patient characteristics, delay in diagnosis, and anti-tuberculous treatment were not investigated (**Table 1)**. The continuation of CAPD might be possible in tuberculous peritonitis, especially if the diagnosis is made early and appropriate therapy is initiated without delay. The response to anti-tuberculosis treatment should be monitored by serial measurement of white cell count in the peritoneal dialysate. In one study 24 of 25 patients of tuberculous peritonitis in CAPD, in which exact data of individual patients were not given, the mortality rate before the completion of anti-tuberculous treatment for tuberculous peritonitis was about 30 %. Most of the deaths were not directly related to the underlying tuberculous peritonitis. Among patients who completed anti-tuberculosis treatment, about 75 % were successfully maintained on CAPD. The deaths due to tuberculous peritonitis in CAPD have occurred at a median duration of 31.5 days after the start of anti-tuberculous therapy. Recurrent peritonitis and septicaemia and progressive deterioration accounted for three deaths each. Congestive heart failure and ileus were the other causes. Therefore, while the patient is on anti-tuberculous treatment, the catheter might have to be removed immediately, once any of these complications.

Table 2: Removal of Catheter in Tuberculous Peritonitis; Data from the Patients of All the Reports of Tuberculous Peritonitis in CAPD

	CAPD catheter removed	**CAPD catheter retained**
Total number of patients	61	56
Deaths due to tuberculous peritonitis	9	4
Number of patients survived	38	43
Unclear reports of patients either survived or expired	5	1
Unrelated deaths	6	7
Cause of death unclear	3	1

P value calculated for number deaths *versus* number of patients survived in groups with catheter removed and retained is 0.2314 [13].

In all the patients in whom CAPD catheter was not removed and anti-tuberculous therapy was given (**Table 3**), the responses to the anti-tuberculous therapy were different—prompt toseveral weeks [4, 5, 8, 25-38]. In one patient, the peritoneal fluid was clear, and there were no cells before starting antituberculous therapy. The systemic response with normalisation of body temperature was observed in 36 hours [33].

Outcome

The mortality is high in tuberculosis. Talwani and Horvath reported a mortality rate of 25 % at 9 months after diagnosis, and 8 of the 13 fatalities were related to peritoneal tuberculosis. The only statistically significant variable predicting death due to tuberculosis was treatment delay [4]. Therefore, early diagnosis is very important.

In conclusion, the clinical and laboratory findings of peritoneal TB are nonspecific and the diagnosis requires a high index of suspicion. The hardest case has culture negative peritonitis or culture positive peritonitis resistant to appropriate antibiotics without any additional clues of tuberculosis. The sensitivity of smear and culture can be enhanced by centrifuging 50-150 ml of the dialysate sample. Fluid culture medium decreases the required time for growth of mycobacteria. Laparoscopy with biopsy should be considered at an early stage when peritoneal tuberculosis is suspected.

Table 3: Response to Anti-Tuberculous Therapy

Reference	Number of patients	Duration to response to anti-tuberculous therapy (verbatim reproduced from the reference) and other remarks
27	3 out of 92 CAPD patients	Patients required temporary HD for inflow pain, one for one month, another for six weeks. In the third, AFB could not be cultured from peritoneal fluid after two weeks of anti-tuberculous therapy. But this patient withdrew from all the treatment.
28	1	2 weeks for the peritoneal fluid cell count to reduce to 89 cells/μL
29	1	Improvement in abdominal pain, fever, cell count within several weeks
24	1	The patient responded promptly to the antituberculous therapy.
30	1	The response to treatment was promptly
31	1	After 15 days his peritoneal fluid cell count was decreased and his symptoms were relieved.
32	3	All showed clinical improvement within two weeks.
2	1	Peritoneal fluid was clear and no cells were identified, before treatment. There was an immediate response to treatment, with normalization of body temperature at 36 hours.
7	6 out of 10	The signs and symptoms of tuberculous peritonitis subsided within 7 days after initiation of anti-tuberculous treatment in the majority of the patients.
8	1	Alluded to a patient cured without catheter removal
27	5 out of 8	Not mentioned
28	3 out of 10	Not mentioned
29	1 out of 2	Not mentioned
30	1	Not mentioned
31	1	Not mentioned
2	1	Not mentioned

References

1. Keane, W. F., G. R. Bailie, E. Boeschoten, R. Gokal, T. A. Golper, C. J. Holmes, Y. Kawaguchi, B. Piraino, M. Riella, and S. Vas, 2000: Adult peritoneal dialysis-related peritonitis treatment recommendations: 2000 update. *Perit. Dial. Int.,* **20,** 396-411.

2. Piraino, B., G. R. Bailie, J. Bernardini, E. Boeschoten, A. Gupta, C. Holmes, E. J. Kuijper, P. K. Li, W. C. Lye, S. Mujais, and D. L. Paterson, 2005: Peritoneal dialysis-related infections recommendations: 2005 update. *Perit. Dial. Int.,* **25,** 107-131.

3. Li, P. K. T., C. C. Szeto, B. Piraino, J. Bernardini, A. E. Figueiredo, A. Gupta, D. W. Johnson, E. J. Kuijper, W. C. Lye, W. Salzer, and F. Schaefer, 2010: Peritoneal dialysis-related infections recommendations: 2010 update. *Perit. Dial. Int.,* **30,** 393-423.

4. Talwani, R., and J. A. Horvath, 2000: Tuberculous peritonitis in patients undergoing continuous ambulatory peritoneal dialysis: case report and review. *Clin. Infect. Dis.,* **31,** 70-75.

5. Akpolat, T., 2009: Tuberculous peritonitis. *Perit. Dial. Int.,* **29,** 166-169

6. Ram, R., G. Swarnalatha, T. Akpolat, and K. V. Dakshinamurty, 2013: Mycobacterium tuberculous peritonitis in CAPD patients: a report of 11 patients and review of literature. *Int. Urol. Nephrol.,* **45,** 1129–1135

7. Lui, S. L., S. Tang, F. K. Li, B. Y. Choy, T. M. Chan, W. K. Lo, and K. N. Lai, 2001: Tuberculosis infection in Chinese patients undergoing continuous ambulatory peritoneal dialysis. *Am. J. Kid. Dis.,* **38,** 1055–1060.

8. McKerrow, K. J., and T. J. Neale, 1983: Tuberculous peritonitis in chronic renal failure managed by continuous ambulatory peritoneal dialysis. *Aust. NZ J. Med.,* **13,** 343–347.

9. Khanna, R., S. S. Fenton, D. C. Cattran, D. Thomson, M. Deitel, and D. G. Oreopoulos, 1980: Tuberculosis peritonitis in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). *Perit. Dial. Bull.,* **1,** 10–12.

10. O'Connor, J., and M. MacCornick, 1981: Tuberculosis peritonitis in patients on CAPD—the importance of lymphocytesin the peritoneal fluid. *Perit. Dial. Bull.,* **1,** 106.

11. Vas, S. I., 1994: Renaissance of tuberculosis in 1990s: lessons for the nephrologist. *Perit. Dial. Int.,* **14,** 209–214.

12. Herrera, C. M., R. M. Delgado, A. G. Riscos, V. C. Chaves, J. R. Castilla, M. M. Guerrero, and J. M. Aguilar, 1997: Mycobacterium tuberculosis as a cause of

peritonitis in a patient undergoing continuous ambulatory peritoneal dialysis. *Nephron,* **76,** 118.

13. Mousson, C., A. Bonnin, M. Dumas, D. Chevet, and G. Rifle, 1993: Peritoneal tuberculosis and continuous ambulatory peritoneal dialysis. *Nephrol.,* **14,** 139–142.

14. Mogili, H. K., S. L. Boju, R. G. Mantri, and T. C. Kalawat, 2017: Tuberculous peritonitis diagnosed with the help of 18 F-FDG PET/CT scan. *Nephrol.,* **22,** 334-335.

15. Prakash, K. C., 1999: Tuberculous peritonitis. *Perit. Dial. Int.,* **19,** 283-285.

16. Song, Y., J. Wu, H. Yan, and J. Chen, 2012: Peritoneal dialysis-associated nontuberculous mycobacterium peritonitis: a systematic review of reported cases. *Nephrol. Dial. Transplant.,* **27**, 1639–1644.

17. Chau, T. N., V. K. Leung, S. Wong, S. T. Law, W. H. Chan, I. S. Luk, S. H. Lam, and Y. W. Ho, 2007: Diagnostic challenges of tuberculosis peritonitis in patients with and without end-stage renal failure. *Clin. Infect. Dis.,* **45**, 141-146.

18. Tan, M., O. Alkan, S. Karaca, B. G. Karakurum, and Y. Z. Demdroglu, 2009: Cerebellitis due to antituberculosis therapy in a patient with chronic renal failure. *Fırat. Tıp. Dergisi.,* **14,** 290–292.

19. Chaitanya, V., B. Sangeetha, M. H. Reddy, A. C. V. Kumar, R. Ram, and V. Sivakumar, 2016: Isoniazid cerebellitis in a peritoneal dialysis patient. *Nephrol.,* **21,** 442**.**

20. Bhowmik, D., S. Mahajan, and M. Bora, 2011: Concerns Regarding the ISPD Guidelines/Recommendations for Peritonitis Due to Mycobacteria. *Perit. Dial. Int.,* **31,** 363-364.

21. Szeto, C. C., and P. K. Li, 2011: Concerns Regarding the ISPD Guidelines/Recommendations for Peritonitis Due to Mycobacteria--Response to Bhowmik et al. *Perit. Dial. Int.,* **31**, 365.

22. Ram, R., G. Swarnalatha, P. Neela, and K. V. Dakshinamurty, 2008: Fungal peritonitis in CAPD patients: a single centre experience in India. *Nephron. Clin. Pract.,* **110,** 207–212.

23. Li, P. K., C. C. Szeto, B. Piraino, J. de Arteaga, S. Fan, A. E. Figueiredo, D. N. Fish, E. Goffin, Y. L. Kim, W. Salzer, D. G. Struijk, I. Teitelbaum, and D. W. Johnson, 2016: ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. *Perit. Dial. Int.,* **36,** 481-508.

24. Lui, S. L., T. M. Chan, K. N. Lai, and W. K. Lo, 2007: Tuberculous and fungal peritonitis in patients undergoing continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **27,** 263–266.

25. Mion, C. M., A. Slingeger, and B. Canaud, 1986: Peritonitis. *Continuous ambulatory peritoneal dialysis.* Gokal, R., Ed. Churchill Living stone, New York, 163–217.

26. Malik, G. H., A. S. Al-Harbi, S. Al-Mohaya, M. Kechrid, M. S. Sheita, and Q. Azhari, 2003: Tuberculous peritonitis in patients on chronic peritoneal dialysis: case reports. *Saudi J. Kid. Dis. Transpl.,* **14,** 65–69.

27. Mousson, C., A. Bonnin, M. Dumas, D. Chevet, and G. Rifle, 1993: Peritoneal tuberculosis and continuous ambulatory peritoneal dialysis. *Nephrol.,* **14,** 139–142.

28. Baumgartner, D. D., V. E. Arterbery, A. J. Hale, R. K. Gupta, and S. F. Bradley, 1989: Peritoneal dialysis-associated tuberculous peritonitis in an intravenous drug user with acquired immunodeficiency syndrome. *Am. J. Kid. Dis.,* 14, 154–157.

29. Mallat, S. G., and J. M. Brensilver, 1989: Tuberculous peritonitis in a CAPD patient cured with catheter removal: case report, review of literature and guidelines for treatment and diagnosis. *Am. J. Kid. Dis.,* **13,** 154–157.

30. Canbakan, B., I. Ergun, Y. Ekmekci, K. Ates, and O. Karatan, 2007: Pulmonary and peritoneal tuberculosis in a CAPD patient. *Int. Urol. Nephrol.,* **39,** 975–978.

31. Sahin, G., N. Kiraz, I. Sahin, M. Soydan, and Y. Akgun, 2004: Tuberculous peritonitis in a case receiving continuous ambulatory peritoneal dialysis (CAPD) treatment. *Annals Clin. Microbiol. Antimicrob.,* **3,** 19.

32. Tan, D., P. A. Fein, A. Jorden, and M. M. Avram, 1991: Successful treatment of tuberculous peritonitis while maintaining patient on CAPD. *Adv. Perit. Dial.,* **7,** 102–104.

33. Ogutmen, B., S. Tuglular, H. Al Ahdab, E. Akoglu, and C. Ozener, 2003: Tuberculosis peritonitis with clear fluid accompanying systemic disseminated tuberculosis in a CAPD patient. *Perit. Dial. Int.,* **23,** 95–96.

34. Liu, S. L., C. Y. Lo, B. Y. Choy, T. M. Chan, W. K. Lo, and I. K. P. Cheng, 1996: Optimal treatment and long-term outcome of tuberculous peritonitis complicating continuous ambulatory peritoneal dialysis. *Am. J. Kid. Dis.,* **28,** 747–751.

35. Quantrill, S. J., M. A. Woodhead, C. E. Bell, A. J. Hutchison, and R. Gokal, 2001: Peritoneal tuberculosis in patients receiving continuous ambulatory peritoneal dialysis. *Nephrol. Dial. Transpl.,* **16,** 1024–1027.

36. Karayaylali, I., N. Seyrek, T. Akpolat, K. Ates, C. Ozener, M. E. Yilmaz, C. Utas, M. Yavuz, F. Akcicek, T. Arinsoy, R. Ataman, S. Bozfakioglu, T. Camsari, and F. Ersoy, 2003: The prevalence and clinical features of tuberculous peritonitis in CAPD patients in Turkey, report of ten cases from multicenters. *Ren. Fail.,* **25,** 819–827.

37. Dogukan, A., S. Cinar, H. Taskapan, O. Ozcan, O. Oymak, and C. Utas, 1998: Mycobacterium tuberculosis as a cause of peritonitis in a patient undergoing continuous ambulatory dialysis. *Turk. Nefrol. Diyal. Transplant. Derg.*, **4,** 217–219.

38. Lui, S. L., M. F. Lam, K. C. Tse, and W. K. Lo, 2002: Reactivation of systemic lupus erythematosus in a dialysis patient after tuberculous peritonitis. *Lupus,* **11,** 49–51.

Chapter 29

Peritonitis: Nontuberculous Mycobacteria

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Peritonitis: Nontuberculous Mycobacteria

Mycobacterial peritonitis may be due to either *Mycobacterium tuberculosis* or nontuberculous mycobacteria (NTM) [1-4]. The majority of peritonitis cases are caused by *M. tuberculosis* [1, 2]. NTMs are defined as Mycobacterium species other than *M. tuberculosis* and *M. leprae* [3, 5]. These pathogens are a group of environmental organisms that are ubiquitous in soil, dust and water as well as much of the natural environment. In addition, municipal water supplies and tap water can harbor these organisms and pose a threat to exposed PD patients. They have also been found to colonize medical equipment, such as endoscopes and surgical solutions [3, 5, 6]. NTMs are less virulent than M. tuberculosis [3, 5]. Although NTM infections remain uncommon, emerging data indicate that a majority of cases are reported in PD patients [4, 7-11].

It is important that clinicians maintain a high level of suspicion for NTM peritonitis when PD-associated peritonitis cases are culture negative or are refractory to standard antibiotic treatment. The failure to consider mycobacterial infection in the differential diagnosis of peritonitis may lead to delayed diagnosis and treatment. The largest series of NTM peritonitis in PD patients was described in a very recent paper by Renaud *et al*, [4].

NTM peritonitis occurs in all the age groups (5–82 years old) and equally in both the genders. More than half of the patients (57.9%) were reported were from the USA, followed by Asia (26.3%) and Europe (10.5%). This was surprising, because most PD-associated *M. tuberculosis* peritonitis was of Asian origin, and only 15% of *M. tuberculosis* peritonitis was reported in the USA [1-3]. The distribution differences among these countries were probably caused by the publication bias or differences in accurate diagnoses. Patients with ESRD have a relative defect in cell-mediated immunity, which may contribute to NTM infections [12, 57]. Although, the immune mechanisms of the peritoneal cavity have not been clearly described, some studies have demonstrated that PD may hinder both phagocytic and lymphocytic activity in the peritoneal fluid, which allows infection by a smaller inoculum of microorganisms [12, 13]. Most NTM peritonitis patients have an autoimmune disease (e.g. SLE). Although these patients use corticosteroids or immunosuppressants to control their underlying diseases, most reports did not document the use of these drugs in their patients. These drugs suppress the anti-NMT activity of the host immune cells and increase the susceptibility to NMT infection. Diabetes, which is known to include depressed antibacterial immunity, was an important cause of ESRD in our reviewed patients. Therefore, this metabolic disease is also a suspected risk factor for NTM peritonitis. HIV/ AIDS patients are more susceptible to infection with NTM [14]. Overall, most of the PD patients with NTM peritonitis were immunosuppressed, which may partially explain the high rate of bacterial peritonitis or the concomitant bacterial/fungal infections present in the NTM peritonitis patients. The patients reported in a review [15] demonstrated that

the time from symptoms/signs onset to diagnosis and initiation of appropriate treatment averaged 4 weeks. Early diagnosis of NTM peritonitis in PD patients is very difficult because the symptoms and signs are indistinguishable from bacterial peritonitis and tuberculous peritonitis [1, 2]. Peritoneal signs of NTM peritonitis are diverse and range from insidious or subtle presentations to frank symptoms [4, 10]. The most common symptoms are fever, abdominal pain and cloudy fluid. Most patients present with one or more of these symptoms as initial complaint(s). Poor appetite, weakness, nausea, vomiting and weight loss are other non-specific complaints related to peritoneal NTM [4, 10]. Though, these clinical findings are indistinguishable from the symptoms present in bacterial peritonitis and tuberculous peritonitis, in our study, only fever was found to be significantly associated with peritonitis due to NTM peritonitis when compared to bacterial peritonitis [1, 2]. An index of suspicion for NTM peritonitis would be an episode of peritonitis appearing early after placement of the catheter.

The cell count or its differential in PD fluid and peripheral blood are also variable and cannot be used to differentiate between NTM peritonitis and peritonitis caused by *M. tuberculosis* or other bacteria [1, 2]. Therefore, it is not possible for physicians to determine the pathogen(s) using clinical findings before culture outcomes are available. Because acid fast negative bacteria are the most common pathogens in peritonitis almost all of the reported patients received empiric antibacterial therapy before NTMs were identified [7]. It should be emphasized that in 'culture-negative' peritonitis cases and in patients where empiric antibacterial therapy has failed, physicians should actively evaluate peritoneal fluid for uncommon pathogens, such as mycobacteria, fungi and Nocardia.

Rapidly growing NMT commonly requires a minimum of 3–5 days to produce any visible growth. Although a smear of acid-fast bacilli from peritoneal effluent should be performed for rapid detection of mycobacteria, smear negative disease is not uncommon (33.3%). Furthermore, this method will not distinguish between NTMs and *M. tuberculosis*. Although a positive result can indicate that a patient is infected by a Mycobacterium species, this test is not necessary for acute diagnosis of NTM infection. Identification of NTMs at the species level is important because antibacterial susceptibility to anti-microbial drugs is often closely predicted from characterization of isolated mycobacterial species. NTMs have been traditionally grouped into four broad categories according to the Runyon system [3, 5]. In this system, NTMs are divided by growth rates and pigment production [3, 5]. Although this classification is important for identification of mycobacteria, more rapid detection methods are available, such as high-performance liquid chromatography, the sequencing of 16S ribosomal RNA and commercially available molecular probes [3, 5]. The leading causes of NTM peritonitis in PD patients are the rapidly growing *M. fortuitum* and *M. chelonae*. In contrast, only a small number of patients are caused by the slowly growing *Mycobacterium avium*, which is the predominant pathogen that causes pulmonary NTM disease [5, 16, 17]. (**Table 1**) These differences in prevalence may be due to differing growing niches of the NTM species.

Table 1: Reported isolates from 57 cases of PD-associated NTM infections identified in a PubMed search from inception through April 2011 [15]

Isolates	Frequency	Percent (%)
Mycobacterium abscessus	5	8.8
Mycobacterium avium complex	6	10.5
Mycobacterium chelonae	8	14.0
M. chelonae – M. abscessus	1	1.8
Mycobacterium fortuitum	22	38.6
Mycobacterium gastri	1	1.8
Mycobacterium gordonae	3	5.3
Mycobacterium heckeshornense	1	1.8
Mycobacterium kansasii	3	5.3
Mycobacterium phlei	1	1.8
Mycobacterium porcinum	1	1.8
Mycobacterium rhodesiae	1	1.8
Mycobacterium simiae	1	1.8
Mycobacterium smegmatis	1	1.8
Mycobacterium triviale	1	1.8
Mycobacterium xenopi	1	1.8
Total	**57**	**100.0**

In a recent review of 41 articles, 57 patients of PD-associated NTM peritonitis were reported [15]. In this review, only patients of NTM peritonitis among PD patients who were confirmed by culture of the peritoneal fluid were included. At least 21 articles were excluded in this review, as NTM was not identified to the species level.

Removal of the PD catheter before the completion of therapy was performed in a majority of the patients with NTM peritonitis. The most frequent cause of catheter

removal was failure to respond to antibiotic chemotherapy. Clinical features often improved rapidly after catheter removal.

NTM are relatively slow-growing, chronic infections that evolve over a period of weeks to years, not hours to days. Empirical therapy is not usually started. This, therefore, results in removal of the PD catheter in a majority of the patients with NTM peritonitis. Clinical features often improved rapidly after catheter removal.

MAC infection often requires complex multidrug therapy. It includes a macrolide (clarithromycin or azithromycin), ethambutol, and a rifamycin (rifampin or rifabutin). The duration of therapy is prolonged, generally for 12 months after culture conversion, typically for a total of at least 18 months. Other drugs with activity against MAC include aminoglycosides, fluoroquinolones, and clofazimine.

M. kansasii is effectively treated with isoniazid (300 mg/day), rifampin (600 mg/day), and ethambutol (15 mg/kg/day). Treatment should continue until cultures have been negative for at least 1 year. Other drugs with very high activity against *M. kansasii* include clarithromycin, fluoroquinolones, and aminoglycosides.

Rapidly growing mycobacteria pose special therapeutic problems. Extrapulmonary disease in an immune competent host is usually due to inoculation (e.g., surgery, injections, trauma) or line infection and is often treated successfully with a macrolide and another drug (based on in vitro susceptibility), along with removal of the offending focus. By comparison, *M. abscessus,* is extremely difficult to cure, although repeated courses of treatment are usually effective in reducing the infectious burden and symptoms. Therapy generally includes a macrolide along with an intravenous agent such as amikacin, a carbapenem, cefoxitin, or tigecycline. Other oral agents used according to in vitro susceptibility testing and tolerance include fluoroquinolones, doxycycline, or linezolid.

References

1. Akpolat, T., 2009: Tuberculous peritonitis. *Perit. Dial. Int.,* **29,** 166–169.

2. Talwani, R., and J. A. Horvath, 2000: Tuberculous peritonitis in patients undergoing continuous ambulatory peritoneal dialysis: case report and review. *Clin. Infect. Dis.,* **31,** 70–75. 3. Griffith, D. E., T. Aksamit, B. A. Brown-Elliott, A. Catanzaro, C. Daley, F. Gordin, S. M. Holland, R. Horsburgh, G. Huitt, M. F. Iademarco, M. Iseman, K. Olivier, S. Ruoss, C. F. von Reyn, R. J. Wallace Jr, and K. Winthrop, 2007: An official ATS/ IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am. J. Respir. Crit. Care Med.,* **175,** 367–416.

4. Renaud, C. J., S. Subramanian, P. A. Tambyah, and E. J. Lee, 2011: The clinical course of rapidly growing nontuberculous mycobacterial peritoneal dialysis infections in Asians: a case series and literature review. *Nephrol.,* **16,** 174–179.

5. Jarzembowski, J, A., and M. B. Young, 2008: Nontuberculous mycobacterial infections. *Arch. Pathol. Lab. Med.*, **132,** 1333–1341.

6. Falkinham, J. O., C. D. Norton, and M. W. Le Chevallier, 2001: Factors influencing numbers of *Mycobacterium avium, Mycobacterium intracellulare*, and other Mycobacteria in drinking water distribution systems. *Appl. Environ. Microbiol.,* **67,** 1225–1231.

7. Li, P. K., C. C. Szeto, B. Piraino, J. Bernardini, A. E. Figueiredo, A. Gupta, D. W. Johnson, E. J. Kuijper, W. C. Lye, W. Salzer, F. Schaefer, and D. G. Struijk, 2010: Peritoneal dialysis-related infections recommendations: 2010 update. *Perit. Dial. Int.,* **30,** 393–423.

8. Mactier, R., 2009: Peritonitis is still the achilles' heel of peritoneal dialysis. *Perit. Dial. Int.,* **29,** 262–266.

9. Pulliam, J. P., D. D. Vernon, S. R. Alexander, A. I. Hartstein, and T. A. Golper, 1983: Nontuberculous mycobacterial peritonitis associated with continuous ambulatory peritoneal dialysis. *Am. J. Kid. Dis.,* **2,** 610–614.

10. Rho, M., F. Bia, and U. C. Brewster, 2007: Nontuberculous mycobacterial peritonitis in peritoneal dialysis patients. *Semin. Dial.,* **20,** 271–276.11. Ram, R., G. D. Naidu, G. Swarnalatha, and K. V. Dakshinamurty, 2013: Peritonitis due to nontuberculous mycobacterium. *Ind. J. Nephrol.,* **23,** 464–465.

12. Rubin, J., Lin, L. M., R. Lewis, J. Cruse, and J. D. Bower, 1983: Host defense mechanisms in continuous ambulatory peritoneal dialysis. *Clin. Nephrol.,* **20,** 140–144.

13. Kazancioglu, R., 2009: Peritoneal defense mechanisms—the effects of new peritoneal dialysis solutions. *Perit. Dial. Int.,* **29,** 198–201.

14. Jones, D., and D. V. Havlir, 2002: Nontuberculous mycobacteria in the HIV infected patient. *Clin. Chest Med.,* **23,** 665–674.

15. Song, Y., J. Wu, H. Yan, and J. Chen, 2012: Peritoneal dialysis-associated nontuberculous mycobacterium peritonitis: a systematic review of reported cases. *Nephrol. Dial. Transplant.,* **27,** 1639–1644.

16. Cook, J. L., 2010: Nontuberculous mycobacteria: opportunistic environmental pathogens for predisposed hosts. *Br. Med. Bull.,* **96,** 45–59.

17. Parrish, S. C., J. Myers, and A. Lazarus, 2008: Nontuberculous mycobacterial pulmonary infections in Non-HIV patients. *Postgrad. Med.,* **120,** 78–86.

Chapter 30

Culture Negative Peritonitis

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Culture Negative Peritonitis

Patient summary

A 50-year old gentleman, a known case of diabetic chronic kidney disease (CKD) on CAPD for past 14 months residing in Gaya, Bihar called his parent PD (Peritoneal Dialysis) unit in Delhi complaining of pain in abdomen and fever for the past 2 days and noticing cloudy effluent for past 1 day. He was advised to immediately send the most recent drain bag to a local laboratory for microscopic, Gram stain and culture examination and subsequently started on intra-peritoneal Vancomycin (1 gm every 5 days) and Amikacin (125 mg daily) as per the center protocol. The PD fluid microscopy revealed a TLC of 2800/$mm^3$with 90% polymorphs while Gram stain and culture were non-contributory. He reported no significant benefit in symptoms and came to the parent unit after 2 days where PD fluid TLC was 1200/mm^3 with 70% polymorphs while Gram stain and culture were still non-contributory. In this review, we present the available evidence of CNP, epidemiology, diagnostic modalities, reasons and treatment protocol with suggestions regarding the modifications needed in therapy in India.

Introduction

Peritonitis is a significant cause of morbidity and mortality in continuous ambulatory peritoneal dialysis (CAPD) patients [1].Gram-positive organisms are the typical cause of culture positive PD-related peritonitis in various parts of the world [2-5]. On the contrary, Gram-negative organisms are more common than Gram-positive organisms in India [6-8].

Nevertheless, diverse clinical and technical reasons can account for a negative dialysate culture as well [9-11]. The literature for the clinical outcomes and treatment for CNP is even more inconsistent, as very few studies have been conducted and most of them are older reports with many of them being either from single centers or retrospective [10-13].

Epidemiology

Since the late 1980s, there is a definite decrease in CAPD peritonitis, but, the infection remains a significant cause of morbidity and mortality in the patients with CAPD. If the causes of peritonitis and treatment protocols to diminish the risk of infection are closely watched, very low rates of peritonitis is feasible [14]. Among various organisms causing CAPD peritonitis, Gram-positive organisms, in particular, coagulase negative staphylococci (CoNS) appear to be the most common [2-5, 10].

Although, a wide spectrum of organisms can give rise to CAPD peritonitis, culture can be negative, ranging from 12% to 64.7% in various parts of the world [10, 12, 13, 15]. This difference in incidence rates may most likely result from varied reasons including different culture techniques, varied definitions of peritonitis and prior antibiotic therapy in these reports. International Society of Peritoneal Dialysis (ISPD) guidelines have clearly stated that CNP should never account for greater than 20% of peritonitis episodes [16, 17]. In India, the rate of CNP was also found to be as widely varying from 18.2% to 64.7% as reported elsewhere [6, 15, 18, 19]. At our center, between 2004-2010, we found that 43% of our peritonitis were culture negative. Although we have no formal subsequent data, we believe that though the culture positive rates have improved for patients presenting initially to us, the overall rates have remained unchanged.

CNP risk is not uniformly spread across the CAPD programmes. In a study by Szeto *et al*. from Hong Kong, during a follow-up of patients from 1995 to 2001, a total of 1182 episodes of peritonitis were found, among which 212 episodes seen in 149 patients were CNP [10]. A multicentre study done by Network 9 between 1991 and 1992, found CNP in 14% of peritonitis episodes (103 out of 630 episodes) and when repeat cultures were done in 33 subjects, 35% grew isolates. There was no significant difference in the clinical features between CNP and culture positive peritonitis [11]. In another multicentre study from Iran registry from 1995 to 2006, CNP was found in 55.4% of a total 391 episodes of peritonitis. But, this study excluded patients with both culture positive and culture negative episodes; hence the exact incidence can't be assessed [12].

The largest study on CNP to date comes from Australia; wherein CNP was recorded in 12% of all the peritonitis episodes in 8% of all the patients, among a cohort of 4675 CAPD patients with a follow up of 6002 patient-years. The rates of total peritonitis and CNP were 0.60 and 0.07 episodes/patient-year of treatment, respectively. Even in this study, there was a wide variation with rates ranging from 0 to 50% in 66 centers, with 12% of centers having rates >20%. Although, univariate analysis revealed that the treatment at a smaller centre, high body mass index and younger patients were more likely to have CNP, multivariate analysis failed to prove any significant association [13].

An observational study from India, which included 244 patients with peritonitis from 21 centers between 2010 and 2011, reported 64.7% of samples as culture negative. Gram-negative organisms (47.8%) were the predominant organisms followed by Gram-positive in 36.7%, fungal in 13.3% and *Mycobacterium tuberculosis* in 2.2% of the samples [15]. On the other hand, Gupta *et al*. found CNP in 50% of the peritonitis episodes from a center in South India and also observed that Gram-positive organisms were more common than that of Gram-negative infections in contrary to the studies from North India [6-8, 19]. Considering the predominance of Gram-negative organisms of faecal origin in most Indian studies, poor hand hygiene and peculiar prevailing habit of hand cleansing after defaecation might be the factors responsible for facilitating transfer of faecal

flora to the hand which in turn may later lead to touch contamination [19, 20]. Moreover, many centers don't perform special cultures routinely, adding upto the higher rate of CNP [19]. Reduction in the rate of CNP can be achieved only by making improvement in the microbiological culture technique, which was found in a study from a single centre in North India. CNP episodes had decreased from 36.9% to 18.2% from 2003 to 2011 after making the necessary modifications in the culture techniques [6, 18]. Implementation of proper patient counseling, training of medical personnel and avoiding antibiotic usage prior to culture have reduced the ratio of CNP from 40.5% in 2004 to 18.8% in 2010 in a Turkish center [21].

Although, CNP was considered to have a benign outcome in many studies, which may not be reflecting the scenario in all programmes, it is considered an important contributor for CAPD failure in terms of transfer to hemodialysis and mortality, which we will see in subsequent discussion.

Clinical features of Peritonitis

Diagnosis of CNP should be made when all the following features are present [22].

1. Clinical features such as abdominal pain, cloudy effluent or both
2. Dialysis effluent white cell count > 100/μL (after a dwell time of at least 2 hours), with > 50% polymorphonuclear; and
3. Negative dialysis effluent culture at 72 hours*

*In case of culture being negative, other non-inflammatory conditions should also be considered but the empirical antibiotic therapy for peritonitis should be given until the correct diagnosis is made.

Other differential diagnosis of cloudy effluent

Less often certain inflammatory non-infectious conditions may cause sterile peritonitis which has to be ruled out [23-26].

1. Chemical peritonitis like exposure to drugs like Amphotericin B, Vancomycin, exposure to Icodextrin dialysate fluid, or contamination of dialysate with endotoxin or acetaldehyde.
2. Dihydropyridiine and non-dihydropyridine calcium channel blockers (see the inside of the cover page for the figures).
3. Eosinophilic peritonitis (allergic reaction or exposure to air/ drugs such as Vancomycin, Gentamycin, Streptokinase, *etc.*).
4. Hemoperitoneum (catheter related trauma, strenuous exercise, rupture of poly cystic liver cyst, primary malignancies or metastases).
5. Chylous effluent.
6. Specimen taken from "dry" abdomen.

Diagnosis

1. Peritoneal Fluid Cell Count

According to the ISPD guidelines, peritonitis is present if total leucocyte count in the dialysate effluent >100/mm^3 with at least 50% being polymorphonuclear cells. If the specimen is taken from a short dwell, the percentage of PMN cells >50% can be considered a reliable marker, even if, the total WBC count is less than 100/mm^3 [16].

2. Peritoneal Fluid Culture Methods

An appropriate method of culturing PD effluent is the most important step in decreasing CNP. In some centers that specialize in advanced culture techniques, less than 10% rate of CNP can be achieved. Identification of the organism and subsequent antibiotic sensitivities not only help in guiding the treatment but can also often indicate the possible source of infection. The most important initial step is sending the whole dialysate to the laboratory for analysis and culture; these samples should be processed immediately. But if there is an unavoidable delay, then it can be stored at 4°C for a maximum of 6 hours.

There are various methods of improving the culture yield as follows

1. Inoculating the fluid directly into rapid blood-culture bottle kits at bedside (e.g. BACTEC, Kent, UK; Septi-Chek, Roche Diagnostics) [27, 28].
2. Centrifuging 50 ml of the dialysate at 3000 G for 15 minutes and suspending the pellet in 3-5 ml of supernatant fluid after the discarding the rest
3. The lysis centrifugation technique [10, 29].
4. The combination of water lysis, Tween-80 blood agar and Triton-X treatment of the PD effluent is also a sensitive culture method [30]. Further, the specimen should be processed within 6 hours. If delay is inevitable, the culture bottles must be incubated at 37°C. The resuspended pellet can be directly plated on blood and Mckonkey agar and incubated for 48 hours under aerobic, anaerobic and microphilic conditions.

Reasons for CNP

The following are the possible factors which may be responsible for the culture negative results in case of CAPD peritonitis [10, 13, 20, 21].

1. Inappropriate sampling technique.
2. Incorrect culture methods and media used.
3. Unavailability of transport and storage.
4. Insufficient amount of dialysate processed.
5. Non-availability of laboratories.
6. Antibiotic therapy within 30 days.
7. Lack of qualified microbiologist in peripheral laboratories.
8. Low bacterial count in the sample.
9. Slow growing organisms or organisms needing special culture techniques.

Szeto *et al.* found that CNP rate was lower if the dialysate cultures were performed by trained renal nurse when compared with those who have not been trained (11.6%

vs. 56.5%). Recent antibiotic usage within 30 days was found in 26.4-50% of the patients with CNP [9, 10].

In a retrospective analysis by Chen *et al*. after changing culture method to inoculation of centrifuged 50 ml effluent into blood culture bottles instead of inoculating 10 ml of dialysate, CNP rate reduced from 35.7% to 20.7% [22].
If the symptoms and total leukocyte count in PD effluent don't improve after 3 days of treatment, then PD effluent should be sent for repeat cell count, differential count and special culture techniques for isolation of unusual organisms such as Mycobacteria, Nocardia, fungus, Legionella or other fastidious bacteria, Campylobacter species, Urea plasma species, Mycoplasma, or Enterovirus may have to be considered. In addition, subculture on media with aerobic, anaerobic, and microaerophilic incubation conditions for a further 3 – 4 days may help to identify slow-growing fastidious bacteria and yeasts that are undetectable in some automated culture systems [16, 17].

Newer Techniques

Many newer diagnostic techniques have been explored for the early diagnosis of peritonitis. These includes

1. Leukocyte esterase reagent strips [31].
2. Polymerase chain reaction (PCR) for bacterial-derived DNA fragments [32, 33].
3. 16S rRNA gene sequencing [34].
4. Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) [35].
5. Pathogen-specific "immune fingerprints" [36].

But, none of them have proved to be superior to conventional techniques in detecting culture positive peritonitis. But, some of them may be a considerable help in diagnosing CNP as low bacterial load may be one of the reasons for culture negativity. Moreover, some organisms may require special culture techniques for isolation which may not be available or done in all cases.
In a study from Korea, PCR was useful in identifying CNP as PCR assay detected 30 of the 39 culture-negative samples and false-positive rates (10%) were relatively rare and comparable with culture. But, they were not helpful in cases of culture positive peritonitis as only 75/95 grew the same organisms and there was discrepancy in the others. Among 32 patients on antibiotic therapy, 17 samples (53.1%) were positive by PCR assay, whereas only 5 (15.6%) were positive by culture. Thus, they appear to be more useful in patients receiving antibiotic therapy which may also contribute to CNP [32].
Isolation of bacterial DNA followed by sequencing and varying cytokine response in peritoneal dialysis effluent may help in identifying organisms in CNP. Prasad *et al,* in his study, showed that 100% of 30 the CNP samples showed bacteria specific DNAs where as normal patient's dialysate samples didn't show any bacteria specific DNA. Among CNP, Gram-negative bacteria was seen in 53.33% samples and Gram-positive in 13.33% while remaining 33.33% were positive for both Gram-positive and Gram-negative bacteria [37].

Another novel technique, pathogen-specific "immune fingerprints", may also be useful in differentiating CNP from Gram-positive and Gram-negative peritonitis. Culture-positive patients had relatively higher peritoneal levels of IL-1β, IL-2, IL-6, IL-10, IL-22 and TNF-α than in patients with CNP which may indicative of less severe inflammation in case of CNP. But, only two cytokines IL-1β (<4.1 pg/ml) and IL-10 (<23.3 pg/ml) resulted in a relatively higher sensitivity (79%) and specificity (97%) aiding in the accurate diagnosis of CNP [36]. Similarly, in another study from India, it was found that the increased regulatory cytokine IL-10 both in PD fluid as well as systemically may be indicative of Gram-negative peritonitis and greater TNF-α response may be indicative of infection with Gram-positive organisms [36].

Integration of MALDI-TOF MS with an automated blood culture system may allow early diagnosis of peritonitis in case of culture positive peritonitis but they don't have a role in case of negative cultures [35]. Thus, these novel techniques may be useful in cases of CNP although most of these studies are from relatively small samples. Further, large scale studies have to be undertaken in future, before any concrete guidelines regarding their usage can be advocated. At present, the ISPD guidelines don't recommend using any novel techniques for diagnosing a case of CAPD peritonitis [17].

Outcomes of CNP

The outcome of CNP was considered to be benign but this outcome can't be generalized in light of some evidences suggesting the contrary. Bunke *et al*. indicated that initial CNP had a more benign outcome in terms of catheter loss rate accounting for only half as that of culture positive peritonitis [11]. Fahim *et al*. also found a more favourable outcome for CNP when compared with culture positive peritonitis in terms of cure (77% *vs*. 66%), or death (1 vs 2.5%) which were statistically significant. Multivariate analysis also suggested a significantly lower risk of hospitalisation (odds ratio [OR], 0.38; 95% confidence interval [CI], 0.27-0.52), catheter removal (OR, 0.54; 95% CI, 0.38-0.75) and permanent hemodialysis transfer (OR, 0.48; 95% CI, 0.33-0.70).Both culture negative and culture positive episodes (14% *vs*. 14%; P=0.9) had similar relapse rate [13]. In the study conducted by Chen *et al,* older age, abdominal pain and need for salvage therapy were the prime factors related with augmented risk for relapse and treatment failure in CNP cases [22].

In contrast, Szeto *et al*, identified that only 67.5% of CNP had a primary response and only 37.7% had a complete cure. This may be due to the fact that the complete cure in this study was defined as the complete resolution of peritonitis without peritoneal catheter removal, salvage antibiotic therapy, or relapse within 120 days, instead of 30 days as suggested in ISPD guidelines. Moreover, catheter removal was not done as suggested by the ISPD guidelines, if there was no response after 5 days and instead salvage treatment was given [10]. Hence, early removal of catheter should be seriously considered, if there is no response to therapy, particularly for

the patients with recent antibiotic usage. There was no difference in terms of relapse, catheter loss or mortality between culture positive and culture negative cases in the Turkish study [21].

In an observation study done by Abraham *et al*, from India, the outcomes were similar in both the culture positive and culture negative peritonitis patients. Overall, 68.2% of the culture positive cases and 71.1% culture negative patients were completely cured. Besides, 20% and 18.8% patients were transferred to either hemodialysis or underwent renal transplantation, and the mortality was 9.4% and 3.8% in culture positive and culture negative group, respectively [15]. Our impression is that the outcome of CNP depends upon the cause of culture negative results as factors such as improper culture techniques, unavailability of trained personnel or required technical infrastructure may have similar outcomes to that of culture positive cases whereas low bacterial load if was the cause of CNP may have a more benign outcome. But, antibiotic resistance may further complicate this already complex scenario. Hence, further large scale prospective studies on CNP with standardized definitions, proper protocols for culture, usage of novel diagnostic methods and similar treatment protocols are needed for throwing some light on the knowledge gap that we are currently having regarding the outcomes and management of CNP.

Treatment of CNP

According to the ISPD guidelines, the initial empirical therapy should cover both Gram-positive and Gram-negative and they should be center specific [17]. The recommendations include coverage of Gram-positive by either Vancomycin or a first generation cephalosporin and Gram-negative organisms by a third-generation cephalosporin or an aminoglycoside. But once the culture is negative, the guidelines suggest treatment based on improvement of symptoms within 3 days. If the symptoms improve within three days, it suggests discontinuation of aminoglycoside therapy and continuing only Gram-positive coverage for a total duration of 2 weeks.

If the symptoms and WBC count in PD effluent after 3 days don't improve, then special culture techniques as previously mentioned may have to be considered. Many CNP episodes were considered to be probably caused by Gram-positive organisms. If the patient improves clinically, initial therapy should be continued and the duration of therapy should be 2 weeks if the effluent clears promptly [10, 11, 13].

Fahim *et al*, showed that the patients experienced higher rates of catheter removal (25% *vs*. 10%; P<0.001) and permanent hemodialysis transfer (17% *vs*. 9%; P=0.06) if the aminoglycoside was discontinued, when compared with those who were continued on it, even though there were no significant differences between the 2 groups with respect to relapse (17% *vs*. 12%; P= 0.3) and death (1.1% *vs*. 1.1% ;P= 0.9) [13].

There is a predominance of infections with Gram-negative organisms in India, with newer diagnostic modality PCR followed by sequencing also suggesting the possibility of predominantly Gram-negative or mixed infections in CNP. The studies have also shown that the outcome of Gram-negative peritonitis was worse compared with Gram-positive peritonitis. We thus suggest that the empirical treatment should probably be continued with both Gram-positive and Gram-negative coverage for a prolonged duration of 3 weeks as done routinely for severe infections [18, 37, 38]. On the contrary, if there is no response even after 5 days of empirical antibiotics, the catheter should be removed as recommended in the ISPD guidelines.

Various protocols are followed in different centers. The most frequently used combinations of antibiotics in CNP were Vancomycin plus aminoglycoside, a first generation cephalosporin plus aminoglycoside, and a third-generation cephalosporin plus an aminoglycoside [11]. In the study by Chen *et al*, nearly 90% of patients received the regimen with Cefamezine and Gentamycin, and 7 protocols were used in the study by Szeto *et al*, [10, 22]. But, there was no significant difference in the rate of peritonitis resolution between various regimens in these studies. Antibiotic-resistant bacteria are increasingly emerging as a major public health problem. Currently, resistance to aminoglycoside and third generation cephalosporinare is much more frequently encountered [6, 18, 39-41]. Almost all the studies from India looking at the sensitivity pattern have shown a very high resistance of Gram-negative bacteria to cephalosporins and quinolones with intermediate resistance to aminoglycosides and minimal to carbapenems [18, 19, 42]. Hence, the choice of empiric antibiotic therapy should be modified based on the active surveillance of the prevalence of organisms and their susceptibility pattern in the particular center. We suggest the following modification to the current ISPD guideline on culture negative peritonitis (**Figure 1**).

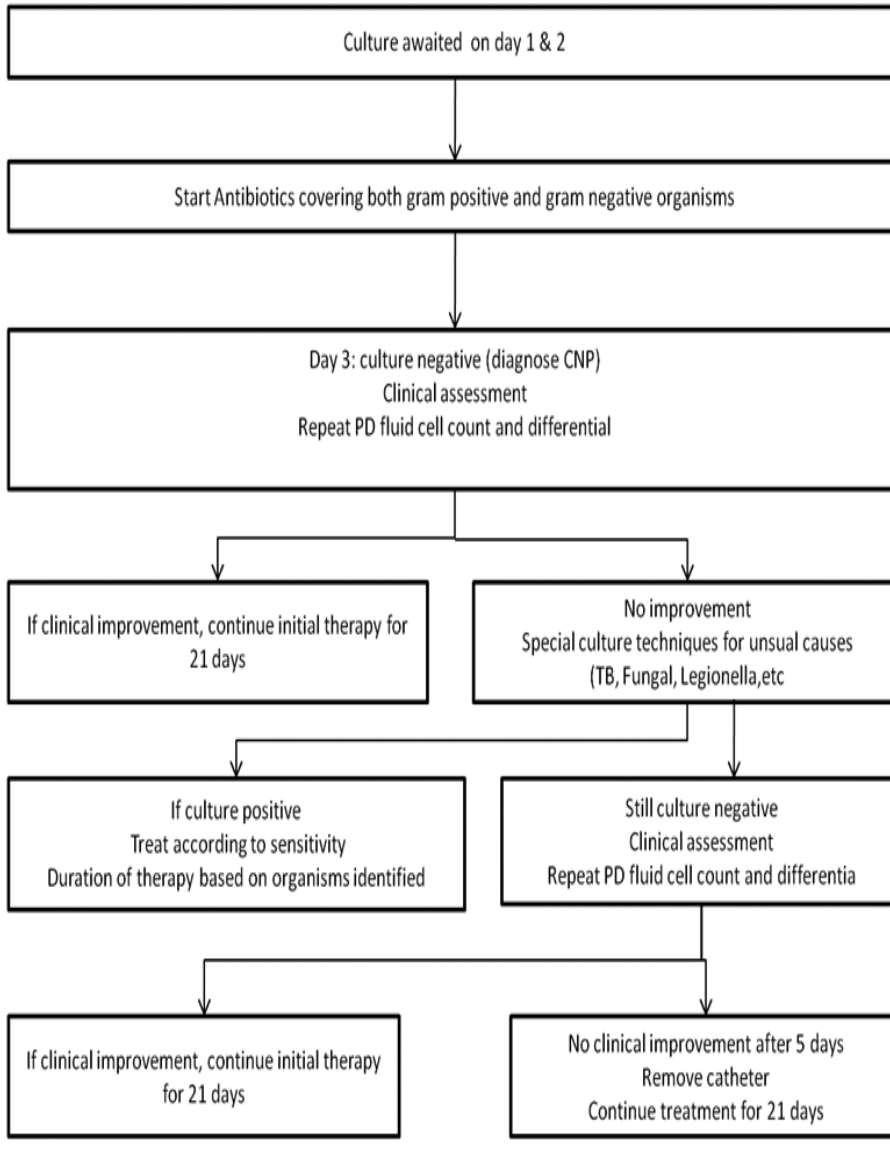

Figure 1: Treatment algorithm for Culture Negative peritonitis

In the index case, Injection Meropenem 1 gm daily was added intra-peritoneally and daily peritoneal TLC were monitored. The patient showed clinical response with intra-peritoneal TLC dropping to zero on day 5. The total therapy was continued for 21 days.

Conclusion

CNP is still a common cause of peritonitis in patients with CAPD and it causes both an increase in morbidity and mortality. The real incidence of CNP is difficult to ascertain, as it is hampered by the paucity of literature and wide variations in its reported incidence. Patient counseling, periodic training of medical personnel about sample collection and proper culture techniques and avoidance of antibiotics prior to culture may help in decreasing the rate of CNP. CNP may not be a benign entity in comparison with culture positive peritonitis in a resource poor country like India. Even if there is rapid clinical improvement with empiric antibiotics, both Gram-positive and Gram-negative coverage should be continued for a minimum of 3 weeks. If there is no improvement within 5 days, removal of catheter should be seriously considered and look out for other organisms requiring special culture techniques should be done. Antibiotic treatment protocols should be periodically revisited with active surveillance of prevalence of organisms and their sensitivity pattern. Novel diagnostic techniques such as PCR and pathogen-specific "immune fingerprints" may prove to be useful in the diagnosis of CNP although they can't be recommended routinely, except for research purposes at the present juncture.

References

1. Piraino, B., 1998: Peritonitis as a complication of peritoneal dialysis. *J. Am. Soc. Nephrol.,* **9,** 1956–1964.

2. von Graevenitz, A., and D. Amsterdam, 1992: Microbiological aspects of peritonitis associated with continuous ambulatory peritoneal dialysis. *Clin. Microbiol. Rev.,* **5,** 36–48.

3. Wakeel, J. A., H. Abu-Aisha, A. H. Mitwalli, S. O. Huraib, N. Memon, and A. S. Marzouk, 1998: Peritonitis in Patients on CAPD at King Khalid University Hospital: Less Infection-rate with More Center-experience. *Saudi J. Kid. Dis. Transplant.*, **1,** 12.

4. Flournoy, D. J., F. A. Perryman, and S. M. Qadri, 1983: Growth of bacterial clinical isolates in continuous ambulatory peritoneal dialysis fluid. *Perit. Dial. Int.,* **3,** 144–145.

5. Spencer, R. C., 1988: Infections in continuous ambulatory peritoneal dialysis. *J. Med. Microbiol.,* **27,** 1–9.

6. Prasad, N., A. Gupta, R. K. Sharma, K. N. Prasad, S. Gulati, and A. P. Sharma, 2003: Outcome of Gram-positive and Gram-negative peritonitis in patients on continuous ambulatory peritoneal dialysis: a single-center experience. *Perit. Dial. Int. J. Int. Soc. Perit. Dial.*, **23,** 144-147.

7. Sharma, R. K., J. Kumar, A. Gupta, S. Gulati, 2003: Peritoneal infection in acute intermittent peritoneal dialysis. *Ren. Fail.*, **25,** 975–980.

8. Jha, V., 2008: Peritoneal Dialysis in India: Current Status and Challenges. *Perit. Dial. Int.,* **28,** 36–41.

9. Sewell, D. L., T. A. Golper, P. B. Hulman, C. M. Thomas, L. M. West, W. Y. Kubey, and C. J. Homes, 1990: Comparison of large volume culture to other methods for isolation of microorganisms from dialysate. *Perit. Dial. Int. J. Int. Soc. Perit. Dial.,* **10,** 49–52.

10. Szeto, C. C., T. Y. H. Wong, K. M. Chow, C. B. Leung, and P. K. T. Li, 2003: The clinical course of culture-negative peritonitis complicating peritoneal dialysis. *Am. J. Kid. Dis.,* **42,** 567–574.

11. Bunke, M., M. E. Brier, and T. A. Golper, 1994: Culture-negative CAPD peritonitis: the Network 9 Study. *Adv. Perit. Dial. Conf. Perit. Dial.,* **10,** 74–78.

12. Najafi, I., S. Ossareh, M. Hosseini, M. R. Ganji, M, Naghibi, K. Makhdoomi, M. R. Ardalan, N. Nouri-Majalan, J. Azmandian, H. Sanadgol, S. Seirafian, and S. Atabak, 2011: Epidemiology of culture-negative peritonitis in Iranian patients on continuous ambulatory peritoneal dialysis. *Iran J. Kid. Dis.*, **5,** 332-337.

13. Fahim, M., C. M. Hawley, S. P. McDonald, F. G. Brown, J. B. Rosman, K. J. Wiggins, K. M. Bannister, and D. W. Johnson, 2010: Culture-Negative Peritonitis in Peritoneal Dialysis Patients in Australia: Predictors, Treatment, and Outcomes in 435 Cases. *Am. J. Kid. Dis.,* **55,** 690–697.

14. Bender, F. H., J. Bernardini, and B. Piraino, 2006: Prevention of infectious complications in peritoneal dialysis: best demonstrated practices. *Kid. Int.*, **70,** 44–54.

15. Abraham, G., and A. Gupta, 2016: Microbiology, Clinical Spectrum and Outcome of Peritonitis in Patients Undergoing Peritoneal Dialysis in India: Results from a Multicentric, Observational Study. *J. Trop. Dis.,* **4**.

16. Li, P.K. T, C. C.Szeto, B. Piraino, J. Bernardini, A. E. Figueiredo, A. Gupta, D. W. Johnson, E. J. Kuijper, W. C. Lye, W. Salzer, F. Schaefer, and D. G. Struijk, 2010: Peritoneal dialysis-related infections recommendations: 2010 update. *Perit. Dial. Int*., **30,** 393–423.

17. Li, P.K. T, C. C.Szeto, B. Piraino, J. Bernardini, A. E. Figueiredo, A. Gupta, D. W. Johnson, E. J. Kuijper, W. C. Lye, W. Salzer, F. Schaefer, and D. G. Struijk, 2016: ISPD Peritonitis Recommendations: 2016 Update on Prevention and Treatment. *Perit. Dial. Int.,* **36,** 481–508.

18. Prasad, K. N., K. Singh, A. Rizwan, P. Mishra, D. Tiwari, N. Prasad, and A. Gupta, 2014: Microbiology and outcomes of peritonitis in northern India. *Perit. Dial. Int. J. Int. Soc. Perit. Dial*., **34,** 188–194.

19. Gupta, S., S. Muralidharan, Gokulnath, and H. Srinivasa, 2011: Epidemiology of culture isolates from peritoneal dialysis peritonitis patients in southern India using an automated blood culture system to culture peritoneal dialysate. *Nephrol.,* **16,** 63–67.

20. Prasad, K. N., 2011: Challenges In PD Microbiology: Culture Negativity and Antimicrobial Susceptibility. *Ind. J. Perit. Dial*., **21,** 22–26.

21. Kocyigit, I., A. Unal, D. Karademir, S. Bahcebasi, M. H. Sipahioglu, B. Tokgoz, O. Oymak, and C. Utas, 2012: Improvement in Culture-Negative Peritoneal Dialysis-Related Peritonitis: A Single Center's Experience. *Perit. Dial. Int. J. Int. Soc. Perit. Dial., 32,* 476–478.

22. Chen, K. H., C. T. Chang, S. M. Weng, C. C. Yu, J. T. Fang, J. Y. Huang, C. W. Yang, and C. C. Hung, 2007: Culture-Negative Peritonitis: A Fifteen-Year Review. *Ren. Fail*., **29,** 177–181.

23. Touré, F., S. Lavaud, M. Mohajer, F. Lavaud, E. Canivet, P. Nguyen, J. Chanard, and P. Pieu, 2004: Icodextrin-induced peritonitis: Study of five cases and comparison with bacterial peritonitis. *Kid. Int*., **65,** 654–660.

24. ManGram, A. J., L. K. Archibald, M. Hupert, J. I. Tokars, L. C. Silver, P. Brennan, M. Arduino, S. Peterson, S. Parks, A. Raymond, M. Mccullough, M. Jones, A. Wasserstein, S. Kobrin, and W. R. Jarvis, 1998: Outbreak of sterile peritonitis among continuous cycling peritoneal dialysis patients. *Kid. Int.*, **54,** 1367–1371.

25. Boer, W. H., P. F. Vos, and M. W. Fieren, 2003: Culture-negative peritonitis associated with the use of icodextrin-containing dialysate in twelve patients treated with peritoneal dialysis. *Perit. Dial. Int.,* **23,** 33–38.

26. Tuncer, M., M. Sarikaya, T. Sezer, S. Ozcan, G. Süleymanlar, G. Yakupoğlu, and F. F. Ersoy, 2000: Chemical peritonitis associated with high dialysate acetaldehyde concentrations. *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. - Eur. Ren. Assoc.*, **15,** 2037–2040.

27. Azap, O. K., F. Timurkaynak, S. Sezer, U. Çağır, G. Yapar, H. Arslan, and N. Ozdemir, 2006: Value of Automatized Blood Culture Systems in the Diagnosis of Continuous Ambulatory Peritoneal Dialysis Peritonitis. *Transplant. Proc.*, **38,** 411–412.

28. Alfa, M. J., P. Degagne, N.Olson, and G. K. Harding, 1997: Improved detection of bacterial growth in continuous ambulatory peritoneal dialysis effluent by use of BacT/Alert FAN bottles. *J. Clin. Microbiol.,* **35,** 862–866.

29. Chow, K. M., V. C. Y. Chow, C. C. Szeto, M. C. Law, C. B. Leung and P. K. T. Li, 2007: Continuous Ambulatory Peritoneal Dialysis Peritonitis: Broth Inoculation Culture versus Water Lysis Method. *Nephron. Clin. Pract.,* **105,** 121–125.

30. Iyer, R. N., A. K. Reddy, S. Gande, and A. Aiyangar, 2014: Evaluation of different culture methods for the diagnosis of peritonitis in patients on continuous ambulatory peritoneal dialysis. *Clin. Microbiol. Infect.*, **20,** 294–296.

31. Park, S.J., J. Y. Lee, W. T. Tak, and J. H. Lee, 2005: Using reagent strips for rapid diagnosis of peritonitis in peritoneal dialysis patients. *Adv. Perit. Dial. Conf. Perit. Dial.,* **21,** 69–71.

32. Yoo, T. H., K. H. Chang, D. R. Ryu, J. S. Kim, H. Y. Choi, H. C. Park, S. W. Kang, K. H. Choi, J. M. Kim, S. K. Ha, D. S. Han, H.Y. Lee, 2006: Usefulness of 23S rRNA Amplification by PCR in the Detection of Bacteria in CAPD Peritonitis. *Am. J. Nephrol.,* **26,** 115–120.

33. Johnson, G., M. Wilks, S. Warwick, M. R. Millar, S. L. Fan, 2006: Comparative study of diagnosis of PD peritonitis by quantitative polymerase chain reaction for bacterial DNA vs culture methods. *J. Nephrol.,* **19,** 45.

34. Ahmadi, S. H., V. Neela, R. A. Hamat, B. L. Goh, A. N. Syafinaz, 2013: Rapid detection and identification of pathogens in patients with continuous ambulatory

peritoneal dialysis (CAPD) associated peritonitis by 16s rRNA gene sequencing. *Trop. Biomed.,* **30,** 602–607.

35. Lin, W. H., J. C. Hwang, C. C. Tseng, Y. T. Chang, A. B. Wu, J. J. Yan, J. J. Wu, and M. C. Wang, 2016: Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry Accelerates Pathogen Identification and May Confer Benefit in the Outcome of Peritoneal Dialysis-Related Peritonitis. *J. Clin. Microbiol.*, **54,** 1381–1383.

36. Lin, C.Y., G. W. Roberts, A. Kift-Morgan, K. L. Donovan, N. Topley, and M. Eberl, 2013: Pathogen-Specific Local Immune Fingerprints Diagnose Bacterial Infection in Peritoneal Dialysis Patients. *J. Am. Soc. Nephrol.,* **24,** 2002–2009.

37. Prasad, N., K. Singh, A. Gupta, and K. N. Prasad, 2016: Isolation of bacterial DNA followed by sequencing and differing cytokine response in peritoneal dialysis effluent help in identifying bacteria in culture negative peritonitis: bacterial DNA in culture negative peritonitis. *Nephrol.* (Available from: http://doi.wiley.com/10.1111/nep.12969).

38. Troidle, L., N. Gorban-Brennan, A. Kliger, and F. Finkelstein, 1998: Differing outcomes of Gram-positive and Gram-negative peritonitis. *Am. J. Kidney Dis.*, **32,** 623–628.

39. Kim, D. K., T. H. Yoo, D. R. Ryu, Z. G. Xu, H. J. Kim, K. H. Choi, H. Y. Lee, D. S. Hang, and S. W. Kang, 2004: Changes in causative organisms and their antimicrobial susceptibilities in CAPD peritonitis: a single center's experience over one decade. *Perit Dial Int.,* **24,** 424–432.

40. Barretti, P., D. Pereira, M. A. Brasil, M. de L. Cunha, J. Caramori, and A. Montelli, 2009: Evolution of Gram-Negative Bacilli Susceptibility in Peritoneal Dialysis-Related Peritonitis in Brazil: a Single Center's Experience Over Nine Years. *Perit. Dial. Int.,* **2,** 230–233.

41. Szeto, C. C., and K. M. Chow, 2007: Gram-Negative Peritonitis—the Achilles Heel of Peritoneal Dialysis? *Perit. Dial. Int.,* **27,** 267–271.

42. Keithi-Reddy, S. R., K. L. Gupta, V. Jha, K. Sud, S. K. Singh. H. S. Kohli, and V. Sakhuja, 2007: Spectrum and sensitivity pattern of Gram-negative organisms causing CAPD peritonitis in India.*Perit. Dial. Int.,* **27,** 205-207.

Chapter 31
Fungal Peritonitis

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Fungal Peritonitis

Introduction

Fungal peritonitis (FP) is a rare but serious complication of chronic peritoneal dialysis (PD), associated with high morbidity and mortality. The incidence of FP reported worldwide varies between 2-15% [1]. The Indian studies report a slightly higher incidence. Studies from different institutes from India reported incidence of 16.2%, 17.6%, and 10.7% [2, 4]. A study from a tertiary care institute in South India reported the burden of fungal peritonitis to be 23.9% [5]. A latest prospective study at a tertiary-care hospital in North India reported incidence of 13.9% [6].

FP carries higher morbidity and mortality compared to bacterial peritonitis. FP is associated with loss of peritoneal membrane function because of peritoneal adhesions, sclerosis, and irreversible membrane damage leading to significant risk of technique failure. Upto 40% patients are unable to resume PD requiring conversion to hemodialysis according to a study [7]. The mortality rate varies from15% to 50% [8].

Organisms

FP is commonly caused by yeasts with *Candidia* species accounting to 70% – 90%. Filamentous fungi such as *Aspergillus*, *Penicillium* are less commonly reported.

Historically, *C. albicans* is more commonly reported than non albicans candida but recent reports suggest increased incidence of non albicans *Candida*. *C. parapsilosis* is increasingly recognised as a common cause of FP [9]. Prasad *et al*, reported Candida species accounted for 89.3% of episodes of FP while dematiaceous fungi accounted for 10.7% of episodes [4].

Among Candida species, non-albicans *Candida* species were more common (53.6% vs 35.7%) than *C. albicans.* Indumathi *et al,* in a study from South India reported *Candida albicans* more common than non albicans *Candida* [2]. In a recent report from a Tertiary care Institute in South India, authors reported all patients of fungal peritonitis were caused by filamentous fungi. Peritonitis caused by rare fungal species is increasingly reported [10].

Risk factors

The most commonly reported risk factors for FP in PD patients are prolonged use of antibiotics and previous bacterial peritonitis. Antibiotics by killing normal flora, promote fungal colonization of the intestinal or genitourinary tract with subsequent transmigration of organisms into the peritoneal cavity. Other reported risk factors are malnutrition, and an immunosuppressed state like HIV. Low serum albumin has

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been reported as a risk factor in a study from a tertiary care institute in South India. Goldie *et al*, studied antibiotic usage in patients who developed FP and found that 65% of patients had received broad-spectrum antibiotics within 1 month, 74% in 3 months, and 97% in 6 months preceding an episode of FP [11]. Prasad *et al*, showed antibiotics usage in 94% of patients who developed FP complicating bacterial peritonitis and in 61% of patients with de novo peritonitis [4].

Clinical features

Clinical features are similar to those of bacterial peritonitis. Signs and symptoms include cloudy dialysate, fever, abdominal pain, nausea, diarrhea and constipation, poor dialysate outflow. In a study from a tertiary care Institute from South India all FP patients had complained of abdominal pain, 77% patients reported vomiting, 74% reported fever, 19% had loose stools and16% had constipation [5]. 90% patients had cloudy peritoneal fluid at the time of presentation.

Diagnosis

The diagnosis of FP is difficult .The diagnostic criteria for fungal peritonitis included PD effluent cell count of 100 or more WBCs per microlitre, differential count of more than 50% polymorphonuclear cells and isolation of the fungus on Gram stain and/or culture. Gram stain of peritoneal fluid can be useful in an early diagnosis of *Candida peritonitis*. Calcofluor stain is useful for identification of other fungi.

The culture technique involves centrifugation of a 50-ml of peritoneal fluid at 3,000 g for 15 min [12]. The supernatant was decanted and the pellet was resuspended in 3–5 ml sterile saline and inoculated in Sabourard's glucose agar and brain heart infusion agar, in addition to standard blood culture media for aerobic and anaerobic organisms. Growth of fungi in cultures is slow, may take several days to weeks, significantly delaying the diagnosis.

Latest diagnostic methods

The growth of fungus in culture may take several weeks delaying the diagnosis. Newer diagnostic methods based on Antibody detection (Immunodiffusion, Counter immunoelectrophoresis, complementfixation, Indirect flouresecent Ab, ELISA, RIA) and antigen detection (WCA, LPA, PHA) can help in early diagnosis. Latest diagnostic methods are PCR based utilising DNA and RNA sequencing.

Prophylaxis

Exposure to antibiotics is an important risk factor for subsequent FP. Antifungal prophylaxis has been tried during period of antibiotics usage to prevent the occurrence of antibiotic-related fungal peritonitis. Various studies have examined the use of either oral nystatin or fluconazole as prophylaxis during antibiotic

therapy [13-19]. Results have been conflicting with some studies showing benefit. Guidelines from International Society for Peritoneal Dialysis (ISPD) PD-related infections (2005 update) recommend that fungal prophylaxis during antibiotic therapy may be beneficial in programmes with high FP rates [20]. Kumar *et al*, showed use of prophylactic antifungal agent significantly reduced the incidence of FP and concluded that fluconazole when used as a prophylactic agent in the setting of bacterial peritonitis significantly reduces the incidence of subsequent FP in CAPD patients (14% vs 5%) P = 0.04 [3].

In a retrospective review, Prabhu *et al,* examined the incidence of FP in a cohort of 115 patients, who had received antibiotics for bacterial peritonitis and received a co-prescription of fluconazole, 50 mg/day for the duration of antibiotic therapy [21]. They observed very low rates of both bacterial peritonitis and FP, and prophylaxis with low-dose fluconazole seemed to confer protection against antibiotic-related fungal peritonitis. The study did not report any adverse effects with the use of fluconazole for prophylaxis.

Management

Treatment consists of early catheter removal once diagnosis of FP is confirmed along with antifungal agents.

Catheter Removal: Catheter should be removed promptly once FP is diagnosed. There is a consensus that the catheter should be removed early, because fungi can colonize it by forming a biofilm along the catheter surface. Current ISPD treatment recommendations for adults include catheter removal immediately after fungi are identified by microscopy or culture. Some suggest early removal allowing vigorous peritoneal lavage with antimycotics until the returning dialysate effluent becomes clear [22].

Antifungal Therapy: The treatment should be started early and often empirically. For initial therapy, the ISPD guidelines recommend administration of amphotericin B combined with flucytosine, which can be replaced by newer agents, according to species identification [22]. Chemical peritonitis and pain has been reported with IP amphotericin. Intravenous amphotericin administration has poor peritoneal penetration .It is practically not used nowadays. Flucytosine is not widely available. Regular monitoring of serum concentration is necessary with flucytosine to avoid bone marrow toxicity. Some centers prefer to start therapy with fluconazole, either alone or in combination with flucytosine.

For Candida species, fluconazole should be started immediately after diagnosis. Flucytosine should be added, depending upon local reports of fluconazole resistance and drug availability. For non-Candida species, a combination of antifungals should be started. Amphotericin B plus flucytosine or fluconazole (if flucytosine is not available) should be started as initial therapy until the culture results are available with susceptibilities.

Fluconazole or voriconazole may replace amphotericin B, based on the species identification and MIC values. Itraconazole or voriconazole, depending on their availability, are alternatives to amphotericin B when filamentous fungi have been cultured. Anti-fungal agents should be continued for at least 2 weeks after catheter removal.

Catheter Reinsertion

Reinsertion should be made after 4 – 6 weeks. ISPD guidelines suggest that if re-insertion of a new catheter is attempted after a PD catheter is removed for refractory, relapsing, or fungal peritonitis, it be performed at least 2 weeks after catheter removal and complete resolution of peritoneal symptoms. Re-insertion of a new catheter should be done by laparoscopic or mini-laparotomy approach so that adhesion can be directly visualized. Ram *et al,* reported 7 cases of successful reinsertion of PD catheter following removal for FP. The authors reported third time insertion of catheter in one case [23].

Table 1: Intraperitoneal and systemic antibiotic dosing recommendations for treatment of Fungal Peritonitis [Li *et al*, 2016]

Drugs	Dosage	
Intraperitoneal Antibiotic Dosing		
	Intermittent (1 exchange daily)	Continuous (all exchanges)
Fluconazole	IP 200 mg every 24 to 48 hours	no data
Voriconazole	IP 2.5 mg/kg daily	no data
Systemic Antibiotic Dosing		
Amphotericin	IV test dose 1 mg; starting dose 0.1mg/kg/day over 6 hours; increased to target dose 0.75–1.0 mg/kg/day over 4 days	
Caspofungin	IV 70 mg loading, then 50 mg daily	
Fluconazole	oral 200 mg loading, then 50–100 mg daily	
Flucytosine	oral 1 gm/day	
Posaconazole	IV 400 mg every 12 hours	
Voriconazole	oral 200 mg every 12 hours	

Conclusions

The clinical features of FP are similar to Bacterial peritonitis and cell count cannot differentiate FP from bacterial peritonitis. High index of suspicion is required. Fungal peritonitis should be considered in diagnosis of culture negative peritonitis especially occuring within 3 months of bacterial peritonitis. A prophylactic antifungal agent should be considered for use during every BP and also during systemic antibiotic treatment. The Tenckhoff catheter should be removed as early as possible, preferably within 24 h of the diagnosis. Reinsertion can be attempted after complete resolution of symptoms.

References

1. Wang, A. Y., A. W. Yu, P. K. Li, P. K. Lam, C. B. Leung, K. N. Lai, and S. F. Lui, 2000: Factors predicting outcome of fungal peritonitis in peritoneal dialysis: analysis of a 9-year experience of fungal peritonitis in a single center. *Am. J. Kid. Dis.,* **36,** 1183–1192.

2. Indhumathi, E., V. Chandrasekaran, D. Jagadeswaran, M. Varadarajan, G. Abraham, and P. Soundararajan, 2009: The risk factors and outcome of fungal peritonitis in continuous ambulatory peritoneal dialysis patients. *Indian J. Med. Microbiol.,* **27,** 59-61.

3. Kumar, K. V., H. M. Mallikarjuna, Gokulnath, and S. Jayanthi, 2014: Fungal peritonitis in continuous ambulatory peritoneal dialysis: The impact of antifungal prophylaxis on patient and technique outcomes. *Indian J. Nephrol.,* **24,** 297-301.

4. Prasad, K. N., N. Prasad, A. Gupta, R. K. Sharma, A. K. Verma, and A. Ayyagiri, 2004: Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis: a single centre Indian Experience. *J. Infect.,* **48,** 96-101.

5. Ram, R., G. Swarnalatha, P. Neela, and K. V. Murty, 2008: Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis: a single-centre experience in India. *Nephron. Clin. Pract.,* **110,** 207-212.

6.Vikrant, S., R. C. Guleria, A. Kanga, B. S. Verma, D. Singh, and S. K. Dheer, 2013: Microbiological aspects of peritonitis in patients on continuous ambulatory peritoneal dialysis. *Indian J. Nephrol.,* **23,** 12-17.

7. Nagappan, R., J. F. Collins, and W. T. Lee, 1992: Fungal peritonitis in continuous ambulatory peritoneal dialysis — the Auckland experience. *Am. J. Kid. Dis.,* **20,** 492–496.

8. Matuszkiewicz–Rowinska, J., 2009: Update on fungal peritonitis and its treatment. *Perit. Dial. Int.,* **29,** 161–165.

9. Chen, C. M., M. W. Ho, W. L. Yu, and J. H. Wang, 2004: Fungal peritonitis in peritoneal dialysis patients: effect of fluconazole treatment and use of the twin-bag disconnect system. *J. Microbiol. Immunol.,* **37,** 115–120.

10. Kalawat, U., A. Verma, V. Chaitanya, B. S. Lakshmi, R. Jayaprada, R. Ram, A. Chaudhury, and V. S. Kumar, 2016: Fungal Peritonitis in CAPD patients a report of five cases. *J. Clin. Sci. Res.,* **5,** 130-135.

11. Goldie, S. J., L. Kiernan-Toidle, C. Torres, N. Gorban-Brennan, D. Dunne, A. S. Kliger, and F. O. Finkelstein, 1996: Fungal peritonitis in a large chronic peritoneal dialysis population: a report of 55 episodes. *Am. J. Kid. Dis.,* **28,** 86—91.

12. Leehey, D. J., V. C. Gandhi, and J. T. Daugirdas, 2001: Peritonits and exit site infection. *Handbook of Dialysis*. Daugirdas, J. T., P. G. Blake, and T. S. Ing, Eds. Philadelphia, LWW, pp 373–398.

13. Zaruba, K., J. Peters, and H. Jungbluth, 1991: Successful prophylaxis for fungal peritonitis in patients on continuous ambulatory peritoneal dialysis: six years' experience. *Am. J. Kid. Dis.,* **17,** 43–46.

14. Robitaille, P., A. Merouani, M. J. Clermont, and E. Hebert, 1995: Successful antifungal prophylaxis in chronic peritoneal dialysis: a pediatric experience. *Perit. Dial. Int.,* **15,** 77–79.

15. Wadhwa, N. K., H. Suh, and T. Cabralda, 1996: Antifungal prophylaxis for secondary fungal peritonitis in peritoneal dialysis patients. *Adv. Perit. Dial.,* **12,** 189–191.

16. Lo, W. K., C. Y. Chan, S. W. Cheng, J. F. Poon, D. T. Chan, and I. K. Cheng, 1996: A prospective randomized control study of oral nystatin prophylaxis for Candida peritonitis complicating continuous ambulatory peritoneal dialysis. *Am. J. Kid. Dis.,* **28,** 549–552.

17. Thodis, E., S. I. Vas, J. M. Bargman, M. Singhal, M. Chu, and D. G. Oreopoulos, 1998: Nystatin prophylaxis: its inability to prevent fungal peritonitis in patients on continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **18,** 583–589.

18. Williams, P. F., N. Moncrieff, and J. Marriott, 2000: No benefit in using nystatin prophylaxis against fungal peritonitis in peritoneal dialysis patients. *Perit. Dial. Int.,* **20,** 352–353.

19. Wong, P. N., K. Y. Lo, G. M. Tong, S. F. Chan, M. W. Lo, S. K. Mak, and A. K. Wong, 2007: Prevention of fungal peritonitis with nystatin prophylaxis in patients receiving CAPD. *Perit. Dial. Int.*, **27,** 531–536.

20. Piraino, B., G. R. Bailie, J. Bernardini, E. Boeschoten, A. Gupta, C. Holmes, E. J. Kuijper, P. K. Li, W. C. Lye, S. Mujais, and D. L. Paterson, 2005: On behalf of the ISPD Ad Hoc Advisory Committee. Peritoneal dialysis-related infections recommendations: 2005 update. *Perit. Dial. Int.,* **25,** 107–131.

21. Mayoor, V., V. P. Sreepada, Subhramanyam, S. Gandhe, S. K. Antony, and K. S. Nayak, 2010: Prophylaxis against fungal peritonitis in CAPD – a single center experience with low-dose fluconazole. *Renal Fail.,* **32,** 802–805.

22. Li, P. K. T., C. C. Szeto, B. Piraino, J. de Arteaga, S. Fan, A. E. Figueiredo, D. N. Fish, E. Goffin, Y. L. Kim, W. Salzer, D. G. Struijk, I. Teitelbaum, and D. W.

Johnson. 2016: ISPD peritonitis recommondations: 2016 update on prevention and treatment. *Perit. Dial. Int.*, **36,** 481–508.

23. Ram, R., G. Swarnalatha, and K. V. Dakshinamurty, 2014: Reinitiation of peritoneal dialysis after catheter removal for refractory peritonitis. *J. Nephrol.*, **27,** 4, 445-449.

Chapter 32

Newer Diagnostic Methods for Peritonitis

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Newer Diagnostic Methods for Peritonitis

Introduction

Peritonitis in patients on peritoneal dialysis (PD) is differentially categorized as PD related peritonitis as the treatment and outcomes of this peritonitis is different from surgical and spontaneous peritonitis. Peritonitis, one of the most common and serious complications, contributes significantly in hospitalisation, morbidity, and death of the patients on PD. Any delay in the diagnosis and treatment of peritonitis may lead to PD termination, catheter loss, transfer to hemodialysis (HD) and permanent peritoneal membrane damage [1]. Overall, peritonitis rate should be no more than 0.5 episodes per year at risk [2].

Presently, the diagnosis of PD related peritonitis is made when at least two of the following three criteria are met [3]:

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1. Signs and symptoms of peritonitis, pain abdomen and tenderness.

2. Cloudy dialysate with white blood cell (WBC) count of >100/µL with more than 50% neutrophils.

3. Demonstration of organisms either by smear examination or by culture of peritoneal dialysate **(Box 1).** The drawback of the present diagnostic criteria is that the patient has to recognize the cloudy effluent, and symptoms of peritonitis which may be missed in early period, particularly in cases of silent peritonitis and culture negative peritonitis. The awareness of the symptoms of peritonitis is a key precondition in the present diagnostic criteria.

The present basis of diagnosis of infection in any body fluid is isolation of the organisms, which is based on the principles of Koch's postulate which was not originally developed for PD related peritonitis. Because of reasons mentioned in BOX 2, the alternative modality is needed to diagnose the infection in multiple scenario, especially for those causative agents that cannot be cultivated in the laboratory; and a causal relationship based on Koch's original postulates cannot be firmly established. An alternative and revised set of Koch's postulates, which depends on isolation of bacterial DNA and sequence-based identification of microbial pathogens, has been proposed by Fredricks and Relman [4]. However, these methods are not widely used in PD practice despite the fact that it can provide rapid diagnosis, especially useful in patients with prior antibiotic exposure and

Box1:

Diagnosis of PD related peritonitis:

The diagnosis of peritonitis is made when at least two of the following three criteria are met [2]

1. Signs and symptoms of peritonitis,
2. Cloudy dialysate with white blood cell (WBC) count of >100/µL (100cells/cmm) with more than 50% neutrophils and
3. Demonstration of organism either by smear examination or by culture of peritoneal dialysate.

Drawbacks of present criteria:

- The fluid does not appear cloudy if cell count is less than 100 cell/cmm. The onset of pain and appearance of cloudy fluid may not occur at the same time. Pain is the presenting symptom with clear dialysate initially and cloudy later on.
- Patient on automated PD frequently miss the cloudy effluent
- Duration of dwell is less than 4-6 hours, total count of less than 50/cmm may be significant
- Lymphocytes may be predominant in fungal and tuberculous peritonitis and eosinophils in allergic peritonitis, drug

culture negative cases.

Unless proved otherwise, patients on PD with cloudy effluent or abdominal pain are considered to be suffering from PD related peritonitis and empirical antibiotics therapy is initiated pending the laboratory results. Rapid and accurate diagnosis is essential for better patient outcome and depends on the identification of the organisms on culture. The present culture techniques are time consuming and yield of the culture is not always up to mark. The International Society of Peritoneal Dialysis (ISPD) recommends that the culture negative episodes should not exceed more than 20% of all episodes of peritonitis [3]. Presently, the incidence of culture negative peritonitis reportedly varied from 2% to 20% and it has been reported up to 36.9% in some studies [5, 6]. Newer and alternative diagnostic methods, particularly molecular diagnostic methods may enable rapid, accurate and specific etiological diagnosis and selective antimicrobials can be administered early for better outcomes.

Box 2:

Possible reasons of culture negative peritonitis:

- Culture technique problem
- Very small volumes of PD effluent was inoculated
- Improper processing of PD effluent for culture
- Uncommon organisms
- Use of antibiotics in previous days

Special culture techniques should be used for the isolation of potential unusual causes of peritonitis, including

- Lipid-dependent yeast,
- Mycobacteria,
- Legionella,
- Slow growing bacteria,
- Campylobacter,
- Fungi,
- Ureaplasma,
- Mycoplasma, and Enteroviruses.

Standard diagnostic methods:

Specimen

First cloudy bag before initiation of antibiotics is the best specimen for identification of pathogens and it should be examined within 2-4 hours of the drainage. Ideally, entire bag containing drained effluent should be sent to the laboratory, large volume approximately 50 ml should be processed by

centrifugation, and sediment culture gives better results. If antibiotics have already been used, *antibiotics removing resins* may be used for better results and it should be clearly mentioned on investigation form.

Culture of biofilms is often present on PD catheters, especially in cases of refractory and relapsing peritonitis. Cultures of scrapings from these biofilms are often positive for growth of organisms.

Catheter tip culture may be used if catheter needs to be removed for resolution of peritonitis. The internal part of Tecnckhoff catheter may be used for culture for the better yield. Pus from exit site infection may be an ideal sample in case of catheter related peritonitis.

Total leukocyte count and differential count

Drain bag containing effluent is inverted several times before taking the sample into EDTA tubes (about 10ml) for cytological analysis. PD fluid usually becomes cloudy, when WBC counts are above 100/µL (cmm). Serially monitoring of effluent cell counts may be of prognostic value. In a study of 565 consecutive episodes of peritonitis, effluent cell count >1090/µl by day-3 was associated with 64% likelihood of treatment failure [7]. Peripheral blood leukocytosis may indicate associated systemic sepsis.

BOX 3:

1. Culturing large amounts of fluid (at least 10ml)
2. Concentration methods: Filtration and Centrifugation
3. Use of blood culture bottles
4. Rapid blood culture bottle kits- BACTEC, etc
5. Lysis centrifugation method # [6, 7]
6. Use of antibiotic removing resins
7. Home based cultures##

- # In lysis centrifugation method, sediment is re-suspended in 100ml of sterile water (hypotonic) to induce lysis of WBC.
- ## In remote locations, patients are advised to keep blood culture bottles at home for use.

Gram stain

In 1884 Hans Christian Gram had developed the traditional Gram stain procedure which relies on the differential cell wall staining properties of Gram-positive and gram-negative bacteria and still it is one of the most widely used laboratory procedure. The reaction is based on the retention of a dye crystal violet complexed with iodine within the cell wall of bacteria. The dye is retained in Gram-positive organisms following an alcohol wash. The Gram-negative bacteria, which lose the dye following the alcohol wash, may subsequently be counterstained with carbolfuchsin or safranin.

It is an insensitive test, identifies bacteria in only about 20-30% of cases. However, it should be performed in all the cases as Gram stain gives rapid yield and can also identify fungi (yeasts). Moreover, the Gram stain should not be used for empiric therapy guidance. Ziehl-Neelsen technique (AFB staining) is useful but not very sensitive for diagnosis of mycobacterium infection.

Conventional culture methods in PD practice

Before proceedings to the newer diagnostic approach, it is important to understand the conventional culture method and its drawbacks. Culture is the gold standard step for diagnosis of peritonitis. It helps in identifying the specific pathogen thus possibly indicate source of infection. Catheter related infection is usually due to Gram positive; and enteric peritonitis is due to Gram negative bacteria. An organism can be isolated in more than 80% of cases by using proper culture techniques. As per ISPD, culture-negative peritonitis should not exceed 20% of episodes in any PD programme [8].

Optimum method of standard culture

Centrifugation of 50-100 ml of effluent at 3000rpm for 15 minutes and inoculation of sediment into standard blood culture media, after re-suspension in 3-5ml of sterile saline, is usually adequate. Use of both aerobic and anaerobic culture systems is recommended. Blood-culture bottles can be directly injected with 5-10 ml of effluent if equipment for centrifuging large amounts of fluid is not available. **BOX 3** summarizes the modifications in standard culture method which gives greater and rapid isolation of organisms on culture of PD fluid. Routine cultures become positive within 24-48 hours, but they should be incubated for 5-7 days as fastidious organisms require longer growth periods. Subculture of previously cultured sample may further improve the yield [2].

Persistently symptomatic patients with culture negative peritonitis should be also evaluated for fungal or mycobacterial peritonitis. Blood cultures are useful if patients have systemic features of sepsis. Culture of purulent discharge from exit site is useful to identify catheter related peritonitis. Among fungi, Candida usually grows quickly in culture, other fungi may require weeks to emerge. Sabouraud-Dextrose agar is more useful for fungal isolation. Routine mycobacterial cultures take 4-6 weeks before a result is obtained. Culturing the sediment, using a combination of solid medium (Lowenstein-Jensen agar) with fluid media (BACTEC, etc.) may improve isolation rates of mycobacteria.

In a study from South India, different culture methods were evaluated and compared for diagnosis of peritonitis [9]. High culture positivity was observed with *water lysis method*, incorporation of *Tween 80* in blood agar and treatment of specimens *with Triton-X*, when compared with automated blood culture systems and direct inoculation of centrifuged deposit of specimen into different culture media. Microorganisms sequestered within WBC preclude their isolation on culture. The high culture positivity of above methods is due to release of intracellular

organisms present in phagocytes by prior treatment of specimens with chemical or physical methods.

Novel diagnostic methods

Newer Gram staining method

Fluorescein-labeled staining: This method is more sensitive than the routine Gram staining [10]. Fluorescein-labeled wheat germ agglutinin; rhodamine 123 a lipophilic cationic dye; a staining technique for unfixed organisms in suspension employing two fluorescent nucleic acid binding dyes hexidium iodide and SYTO 13, have been developed in microbiology practice. However, these methods are more expensive and require expensive instruments such as epifluorescence microscopes or flow cytometers. The yield is better than conventional Gram staining. The data are limited in relation to PD related peritonitis.

Calcofluor white stain and 10% KOH mount: Although Gram stain may identify yeasts; Calcofluor white stain and 10% KOH mount stains are more sensitive, especially for filamentous fungi.

Test based on leukocytes in PD effluents

As a part of host defense barrier, leukocyte and neutrophil recruitment occurs into the peritoneum during acute bacterial peritonitis. It is an important part of the host defense barrier in PD patients. The subsequent phagocytosis of bacteria may also lead to polymorph degranulation and the release of lysosomal enzymes and other contents from neutrophils into PD fluid which can be exploited to use into diagnosis of PD related peritonitis.

First exchange neutrophilia

First exchange effluent neutrophilia (greater than 43%) rather than total WBC count may be an early indicator of infection in patients on chronic intermittent peritoneal dialysis [11].

Box 4: Novel methods of diagnosis of PD peritonitis

Gram staining:

- Fluorescein-labeled staining, a modification in gram staining

Test based on leukocytes in PD effluents:

- First exchange neutrophilia
- Lysozyme (muramidase) content in PD effluent
- Lucigenin and Luminol enhanced chemiluminescence
- Leukocyte esterase reagent strips,
- PeriScreen Test Strip in diagnosing PD related peritonitis
- Biomarker assays (matrix metalloproteinase-8 and -9,
- Intra-peritoneal free elastase level in peritonitis
- Neutrophil gelatinase-associated lipocalin and

Test based on conventional inflammatory markers

- Procalcitonin
- Serum high sensitive C-reactive protein (hs-CRP) level
- Adipokines in acute peritonitis
- Peritoneal fluid amylase and lipase
- Limulus Amebocyte Lysate (LAL) assay for endotoxin
- Serum Cancer Antigen (CA-125) and other collagen peptides in PD effluent

Molecular diagnostic methods

1. Polymerase chain reaction (PCR) for bacterial-derived DNA fragments, 16S rRNA gene sequencing,
2. *In situ* hybridization
3. Peritoneal fluid GeneXpert MTB/RIF assay
4. Pathogen-specific immune fingerprints and cytokine assay
5. NLRP3 inflammasome in PD-Related Peritonitis

Spectroscopic methods

- Surface Enhanced Raman Spectroscopy (SERS):
- Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF), and
- High-resolution ^{1}H and ^{1}H-^{13}C NMR spectroscopy

Radiogarphic and radionuclides methods

Lysozyme (muramidase) content in PD effluent

The lysozyme content of peritoneal fluid samples has been found to be an early indicator of the onset of infection in the course of peritoneal dialysis. A level of 10.0 µg/ml indicates peritoneal infection and one of 7.5 µg/ml is highly suspicious [12].

***Lucigenin and Luminol enhanced chemiluminescence*:**

During phagocytosis, neutrophils undergo striking increase in oxidative metabolism, respiratory burst, and emit light as chemiluminescence which correlates with antimicrobial activity of WBC and helps in early diagnosis of peritonitis [13].

Leukocyte esterase reagent strips test

The values of the urine strip, leukocyte esterase test strip in the early diagnosis of bacterial peritonitis in PD has been studied. At the proposed cut-off point (> 100/mm3 of WBC count), a 3+ reading on the strip had sensitivity (100%) and specificity(100%); and a 2+ reading had sensitivity of 100%, and specificity (71.4%). The good correlation with polymorphs ($r = 0.80$, $P = 0.0001$) has been observed. It is a simple, bedside screening test and helps in rapid diagnosis [14, 15].

PeriScreen Test Strip in diagnosing PD related peritonitis

This reagent strip (Serim Research, Elkhart, IN, USA) for leukocyte esterase was designed to test PD fluid in PD related peritonitis [16]. It has 4 colorimetric grades negative, trace, small, and large. PD fluids in 54 PD patients with 19 episodes of peritonitis were studied. Good sensitivity (100%), specificity (97%), positive predictive value (95%), and a negative predictive value (100%) has been observed.

Matrix metalloproteinase-9 (MMP-9) test

In a study, matrix metalloproteinase (MMP) expression in PD effluent was measured by gelatin zymography, and activities by an enzyme-linked immunosorbent assay (ELISA). An excellent correlation between MMP reactivity and total WBC ($R=0.91$, $P<0.001$); and polymorph count ($r=0.91$, $P<0.001$) was observed. The study concluded that MMP-9 test kit appears to be a simple and reliable method for early diagnosis of peritonitis, and reflects the leukocyte count in peritoneal effluents [17].

Intra-peritoneal free elastase level in peritonitis

Estimation of elastase released from recruited neutrophil after PD peritonitis has been studied in one of the study [18]. The free elastase activity estimated by a casein degradation assay, and level estimated by ELISA revealed strong correlations between the peritoneal leukocyte count and both immunoreactive elastase ($r = 0.816$, $P< 0.001$) and activity ($r=0.687$, $P< 0.01$) respectively. The

study showed significant quantities of uninhibited elastase can be detected in the effluent of patients with acute bacterial peritonitis.

Molecular diagnostic methods

Broad spectrum polymerase chain reaction (PCR) with RNA sequencing

Amongst all the evolving newer techniques for isolation and identification of organisms, polymerase chain reaction (PCR) based techniques are one of the most rapidly adopted technique in practice. Molecular techniques are particularly useful in identifying organisms especially in culture negative peritonitis [19, 20]. We have recently shown that bacterial DNA can be extracted from all culture negative peritonitis samples, using Qiagen DNA extraction kit (Qiagen, Germany) [19]. Subsequently, the isolated DNA was subjected to PCR using universal bacteria specific primers. To avoid amplification of possible bacterial DNA contaminants in the reagents, reaction mixtures were irradiated with UV light for 3 to 3.5 min before the addition of the target DNA. Gel photograph showing PCR products is shown in **Figure 1**. PCR positive samples were further subjected to Gram type specific primers for the differentiation of the etiologic agents into Gram-positive and Gram-negative organism. Bacteria-specific DNA was not detected from any of the normal PD effluents, while all 30 culture-negative peritonitis samples showed bacteria-specific DNAs. The gel images of Gram-positive and Gram-negative bacteria are shown in **Figure 1**. Of the 30 culture-negative samples that were positive by molecular method, 16 (53.33%) samples were positive for Gram-negative bacteria and four (13.33%) for Gram-positive, while the remaining 10 (33.33%) were positive for both Gram-positive and Gram-negative bacteria. The gene sequencing following the isolation of bacterial DNA may help in further identification of individual bacterial species. In our study, we have also observed that many bacteria like Uncultured *Weissella*, Uncultured *Leuconostoc*, Uncultured *Edwardsiella* sp. which are not a usual organisms causing peritonitis in patients on PD, have been isolated from culture negative samples. Usually special culture techniques are required for these unusual organisms.

In another study, Yoo and colleagues have also shown that the PCR assays targeting the 16S rRNA or 23S rRNA genes, as they are universal to all bacteria, but variable enough for species identification, can be used for the detection of infectious organisms in peritonitis, especially in patients with previous or current antibiotic use [21].

Similar observation has been depicted by Jonson and colleagues and they have shown that quantitative bacterial DNA PCR assay by using primer and probes targeted at 16S rDNA can be useful in culture negative cases [22].

In-situ hybridization

In-situ hybridization (Hybrizep), a method for detecting the genes of bacteria ingested in phagocytes, may also help in early diagnosis [23].

Tests based on non-specific inflammatory changes during peritonitis

Procalcitonin and conventional markers of inflammation

Serum procalcitonin was compared with conventional markers of inflammation such as C-reactive protein (CRP), fibrinogen, and erythrocyte sedimentation rate (ESR) in patients on PD with peritonitis [24]. The sensitivity of PCT for peritonitis was lower than the sensitivity of conventional markers; however, the specificity of PCT was higher for procalcitonin.

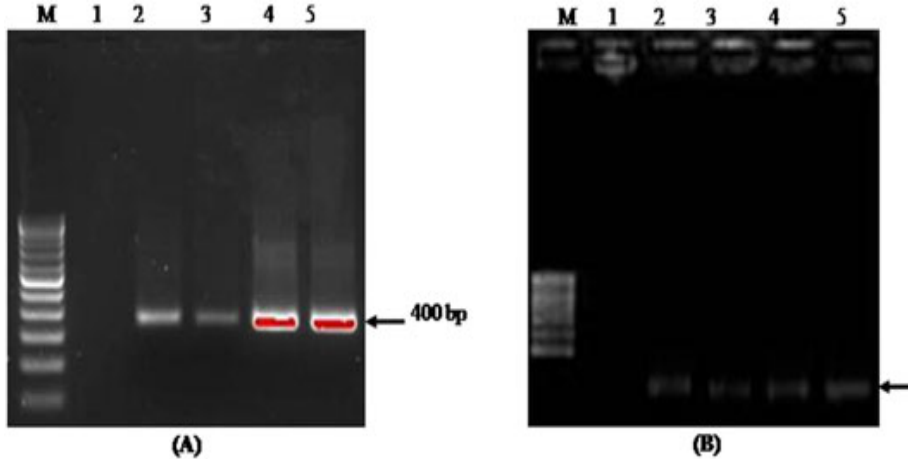

Figure 1: Gel Photograph showing Polymerase Chain Reaction (PCR) Products of Gram-positive (A) and Gram-negative (B) Bacterium in the Peritoneal Dialysis Fluid Samples from a Patient with Peritonitis. Lane M, 100 BP molecular weight marker; lane 1, negative control; lane 2–5 show amplified gene.

Serum high sensitive C-reactive protein (hs-CRP) level

In a study, a progressive increase in hs-CRP level predicted peritonitis risk in CAPD patients and it was also associated with corresponding decline in serum albumin level [25].

Adipokines in acute peritonitis

Peritonitis leads to an increased peritoneal membrane permeability. In a study, authors observed that adipose tissue-derived proteins adiponectin and leptin concentrations were markedly elevated with peritonitis [26]. Receiver operating characteristic analyses revealed that peritoneal effluent adiponectin concentration >180 ng/mL had 100% sensitivity and 100% specificity, while peritoneal effluent

leptin concentration >11.0 ng/mL has 58.3% sensitivity and 95.5% specificity for the diagnosis of acute peritonitis.

2 Peritoneal fluid amylase and lipase

Dialysate amylase level of >100 U/dl indicates either pancreatitis or other intra-abdominal catastrophe, pointing to secondary peritonitis [27]. Icodextrin interferes with amylase assay, giving a falsely low value [28]. Other evidences of secondary peritonitis include presence of feculent material in dialysate and polymicrobial growth on culture.

Limulus Amebocyte Lysate (LAL) assay for endotoxin

This test has been exploited for detection of LPS, endotoxin which is usually present in bacterial cell wall of Gram negative organisms. It is a sensitive test to identify Gram negative infection causing peritonitis [29].

PD effluent NGAL concentration

Neutrophil gelatinase-associated lipocalin (NGAL), a lipocalin which is a key player in innate immunity and rapidly detectable in PD effluent, has been demonstrated to be a useful tool in the early diagnosis of peritonitis [30].

Serum Cancer Antigen (CA-125) and other collagen peptides in PD effluent

CA-125 in PD effluent dialysate has been used as a surrogate biomarker for the health of mesothelium in PD patients [31, 32]. Although it is not specific for the peritoneal epithelium, its serial monitoring and rise in values post peritonitis predict the recovery from peritonitis. The serial monitoring and fall in CA-125 value indicate loss of mesothelium. Several reports described high serum CA-125 in patients with TB peritonitis [33, 34, 35].

The appearance rates of concentrations of CA 125, phospholipids, hyaluronan, and the procollagen peptides procollagen ^{1}C-terminal and procollagen ^{3}N-terminal in dialysate during peritonitis on many consecutive days and after recovery has also been studied [36]. The similarity between the marker concentrations in the effluent after recovery from peritonitis and those in stable CAPD patients implies that complete peritoneal healing is likely to occur after uncomplicated peritonitis.

Diagnostic Immune fingerprints and cytokines in diagnosis of PD related Peritonitis

It has been observed that pathogen specific immune responses identified by multicolor flow cytometry and multiplex ELISA, is helpful in discriminating between Gram positive, Gram negative peritonitis and identifying organisms in culture negative infections [37]. In a study, Lin and colleagues assessed the diagnostic potential of pathogen-specific immune responses in 52 adult patients during episodes of PD related peritonitis and found that immune fingerprints in

Gram-positive infections were markedly different from those in Gram-negative infections and were indicative of a relatively large underlying T cell component with higher numbers of CD4+ and CD8+ T cells and elevated levels of CXCL10, IFN-γ, and IL-22.

The chemokine CXCL10 appeared to be a particularly good predictor of Gram-positive infections. Gram-negative infections were dominated by elevated levels of cytokines such as IL-1β, IL-10, and TNF-α. The differences could be because of differing response of immune cells to bacterial LPS, which is present in the outer cell wall of Gram-negative organisms but absent from Gram-positive organisms. Despite the very low proportion of T cells in acute Gram-negative infections, Vγ9/Vδ2 T cells were selectively enriched among peritoneal T cells in those patients.

Peritoneal phagocytes produce TNF-α, IL-1, initiating an inflammatory cascade which leads to IL-6 and IL-8 secretions. Measuring these cytokines and oxidative metabolism markers, help in early diagnosis [38]. In our own study we observed that the cytokine response differs both locally in PD effluent and systemically in blood during peritonitis episodes. TNF-α was significantly associated with Gram positive and regulatory cytokine IL-10 with Gram negative peritonitis. IL-6 was found to be higher in all cases [20].

NLRP3 inflammasome in PD-Related Peritonitis

The NLRP3 inflammasome, a caspase-1–activating multiprotein complex, is activated during acute bacterial peritonitis in patients on PD, and this activation is associates with the release of IL-1β in the dialysate. Experimental study on mice showed that lipopolysaccharide- or Escherichia coli-induced peritonitis led to IL-1b release in the peritoneal membrane and the genetic deletion of Nalp3, which encodes NLRP3, abrogated defects in solute transport during acute peritonitis and restored ultrafiltration. The administration of the IL-1b receptor antagonist, anakinra, efficiently decreased nitric oxide production and vascular proliferation and restored peritoneal function in mouse models of peritonitis. This basic research provides insight into the future therapeutic use of these biologicals in treatment of peritonitis and preservation of peritoneal membrane after peritonitis [39].

Spectroscopy

Since the evolution of Raman's effect on scattering of light in diagnostic utilities in medical conditions, different spectrometers and techniques have been evolved in evaluation of differing constituents in fluid environment and now in diagnosis of infection as well.

Surface Enhanced Raman Spectroscopy (SERS)

SERS can rapidly identify bacteria using chips coated with nano-sized metal particles40. In this newer method, known bacteria were loaded in the SERS-chips

and illuminated with laser light to establish a reference Raman spectra library. The resulting Raman spectra from dialysate of PD peritonitis patients were compared with library spectra for bacteria identification. Out of 31 bacteria identified in paired-samples by SERS, 29 bacteria were exactly the same as those identified by the reference method. Unfortunately, bacteria not included in the reference library spectra cannot be identified by this method.

Matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS)

In a study, MALDI-TOF MS and conventional standard methods were compared for time to pathogen identification and impact on clinical outcomes in peritoneal dialysis-related peritonitis patients [41]. The MALDI-TOF MS method identified the causative microorganisms earlier average of 64 hr earlier, and as a result patients had a shorter hospital stay.

High-resolution ^{1}H and ^{1}H-^{13}C NMR spectroscopy

In a recent paper from our group, we have shown that high resolution nuclear magnetic resonance (NMR) spectroscopy based characterization of PD effluent metabolites may be useful for detecting/ predicting the complications associated with PD, including peritonitis [42].

We have also shown that the use of 1H NMR spectroscopy based metabolome can diffrentiate bacterial and fungal peritonitis and can predict relapsing peritonitis [43]. Five unused normal PD effluent and 13 normal PD effluents after 6 hours of dwell did not show any peak at NMR spectra between 0.45 to 0.65 ppm while all the 15 cases of bacterial peritonitis showed peak at NMR spectra between 0.45 to 0.65 ppm and these peaks disappeared after treatment with resolution of peritonitis at end of 1 week and 2 weeks of antibacterial therapy except for 3 cases in whom peak was persisting despite absence of clinical and laboratory evidences of peritonitis and all these patients presented with relapsing peritonitis within 2 weeks of stopping antibiotics. The three cases that had culture positive fungal peritonitis also did not show any peak at this region on NMR spectra. (**Figure-2**)

The presence of peak between 0.45 to 0.65 ppm on NMR spectra suggest bacterial peritonitis and the absence of this marker in presence of clinical evidence of peritonitis suggest fungal peritonitis, Such emerging diagnostic tool may be very helpful in quick diagnosis of bacterial peritonitis and differentiating it from fungal peritonitis.

Test for Mycobacterial tuberculosis peritonitis

Peritoneal fluid IFN-gamma level

M. tuberculosis infection initiates an immunologic cascade involving the secretion of various cytokines and recruitment of Th1 lymphocytes. With abundant cell

recruitment at the morbid site, the levels of various cytokines are markedly elevated. Interferon-gamma (IFN-γ) is an important cytokine following infection with *M. tuberculosis*. This may be useful for early diagnosis of TB peritonitis [44, 45].

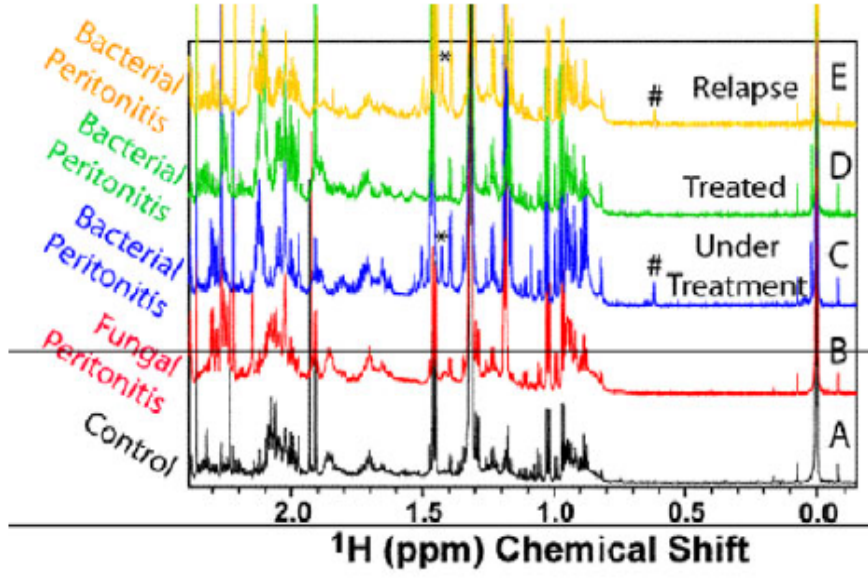

Figure 2: High Resolution NMR spectra were recorded at 298 K on a Bruker Avance III 800 MHz spectrometer (equipped with Cryoprobe). Standard relaxation edited ^{1}D ^{1}H NMR spectra were acquired using the Carr-Purcell-Meiboom-Gill (CPMG) pulse sequence. Each spectrum consisted of the accumulation of 64 scans and lasted for approximately 8 minutes.

To confirm assignment of marker peak, ^{2}D ^{1}H-^{1}H TOCSY and ^{1}H-^{13}C HSQC spectra were acquired for all the samples. The signal between 0.45 and 0.65 ppm might represent cumulative NMR signal from trans methylene protons of cyclopropane ring moiety which indicate peritonitis; the peak disappeared after treatment and reappeared after relapse.

Enzyme linked Immunospot assay (ELISPOT)

The ELISPOT assay, measures IFN-gamma produced T-cell responses to early secreted antigenic targets of M. tuberculosis. Assay on peripheral blood or peritoneal fluid is a useful adjunct in diagnosis of TB peritonitis.

Peritoneal fluid adenosine deaminase level

Adenosine deaminase (ADA) is a purine degrading enzyme, necessary for maturation and differentiation of lymphoid cells. Its level is raised in TB peritonitis. Its high level helps in differentiating from non-tuberculous peritonitis [46].

PCR for tuberculosis

In a study using 16S rRNA and ITS gene sequencing method, authors have shown that it is useful method for rapid diagnosis for mycobacterium tuberculosis peritonitis [47]. PCR assays amplify Mycobacterial 16S rRNA or DNA and used for rapid diagnosis of TB peritonitis [48, 49, 50].

Peritoneal fluid Gene Xpert MTB/RIF assay

The Xpert MTB/RIF assay is a cartridge based nucleic acid amplification test (NAAT), which can identify M. tuberculosis and its resistance to rifampin. A recent case report described feasibility of diagnosing TB peritonitis by this assay [51].

Peritoneal and Omental biopsy

Peritoneal surface studded with tubercles, caseating granulomas on microscopy indicate tuberculous (TB) peritonitis. *Ziehl-Neelsen* (ZN) stain may reveal mycobacteria. Biopsy is also useful in fungal infections. In a recent case report from North India, Zygomycosis was identified on biopsy revealing large areas of necrosis with broad aseptate fungal hyphae [52]. Cultures of peritoneal tissue are more optimal than culture of PD fluid.

Radiographic and radionuclide tests

The role of peritoneal scintigraphy in the detection of PD related complications has been studied [53]. Ultrasound, CT abdomen, CT peritoneography, MRI scan, MR Peritoneography, Gallium scan are useful for detecting an infected fluid collection in a patient with refractory peritonitis or if secondary peritonitis is suspected. Abnormal internal echogenicity, septations, presence of gas, fat stranding, peritoneal or wall enhancement after contrast administration may indicate infected collection. Thickened mesentery or omentum, thickened nodular peritoneum, enlarged necrotic lymphnodes may indicate TB peritonitis [54]. Non-uniform distribution of the dialysate in combination with loculated tracer accumulation suggests the presence of adhesions. The usefulness of fluordeoxyglucose positron emission tomography (PET) in diagnosing EPS was studied in three EPS patients and five asymptomatic long-term PD patients [55].

Peritoneal fluid galactomannan and β-D-glucan for fungal peritonitis

Galactomannan is a component of the Aspergillus cell wall and β-D-glucan is located in cell membranes of most fungal pathogens, exceptions being Mucor and Cryptococcus. They get released into surrounding environment during fungal

growth or tissue invasion. Measuring their levels in PD fluid may help in early diagnosis of fungal infection [56, 57]. The PCR based method can also be used in identification and diagnosis of Fungal Peritonitis in PD patients [58].

Conclusion

New diagnostic methods are useful supplement to standard diagnostic methods of PD related peritonitis particularly in culture negative and antibiotic treated cases prior to standard culture. It helps in rapid diagnosis and early initiation of therapy; however the cost, availability of instruments, expertise in the techniques for diagnosis limits its use in day to day practice. Molecular techniques identify bacteria causing peritonitis and may provide idea of resistant genes of bugs, but do not provide sensitivity to antibiotics used for the treatment.

References

1. Schreiber, M., J. M. Burkart, and T. Tabor, 1996: Peritonitis remains the leading cause of transfer from PD to HD (abstract). *Perit. Dial. Int.,* 16, 66.
2. Li, P. K., C. C. Szeto, B. Piraino, J. de Arteaga, S. Fan, A. E. Figueiredo, D. N. Fish, E. Goffin, Y. L. Kim, W. Salzer, and D. G. Struijk, 2016: ISPD peritonitis recommendations: 2016 Update on Prevention and Treatment. *Perit. Dial. Int.,* 36, 481-508.
3. Piraino, B., G. R. Bailie, J. Bernardini, E. Boeschoten, A. Gupta, C. Holmes, E. J. Kuijper, P. K. Li, W. C. Lye, S. Mujais, and D. L. Paterson, 2005: Peritoneal dialysis-related infections recommendations: 2005 update. *Perit. Dial. Int.,* 25, 107-131.
4. Fredericks, D. N., and D. A. Relman, 1996: Sequence-based identification of microbial pathogens: a reconsideration of Koch's postulates. *Clin. Microbiol. Rev.,* 9, 18–33.
5. Lye, W. C., P. L. Wong, S. O. Leong, and E. J. Lee, 1994: Isolation of organisms in CAPD peritonitis: a comparison of two techniques. *Adv. Perit. Dial.,* 10, 166–168.
6. Prasad, N., A. Gupta, R. K. Sharma, K. N. Prasad, S. Gulati, and A. P. Sharma, 2003: Outcome of gram-positive and gram-negative peritonitis in patients on continuous ambulatory peritoneal dialysis: a single center experience. *Perit. Dial. Int.,* 23, 144–147.
7. Chow, K. M., C. C. Szeto, K. K. Cheung, C. B. Leung, S. S. Wong, M. C. Law, Y. W. Ho, and P. K. Li, 2006: Predictive value of dialysate cell counts in peritonitis complicating peritoneal dialysis. *Clin. J. Am. Soc. Nephrol.,* 1, 768-773.
8. Li, P. K., C. C. Szeto, B. Piraino, J. Bernardini, A. E. Figueiredo, A. Gupta, D. W. Johnson, E. J. Kuijper, W. C. Lye, W. Salzer, and F. Schaefer, 2010: Peritoneal dialysis-related infections recommendations: 2010 update. *Perit. Dial. Int.,* 30: 393-423.

9. Iyer, R. N., A. K. Reddy, S. Gande, and A. Aiyangar, 2014: Evaluation of different culture methods for the diagnosis of peritonitis in patients on continuous ambulatory peritoneal dialysis. *Clin. Microbiol. Infect.,* 20, 294-296.

10. Pital, A., S. L. Janowitz, C. E. Hudak, and E. E. Lewis, 1967: Fluorescein-labeled β-Glucosidase as a Bacterial Stain. *Applied Microbiol.,* 15, 1165-1171.
11. Riera, G., D. Bushinsky, and D. S. Emmanouel, 1985: First exchange neutrophilia: An index of peritonitis during chronic intermittent peritoneal dialysis. *Clin. Nephrol.,* 24, 5-8.
12. Wardle, E. N., 1973: Simple method for detection of infection of peritoneum during dialysis. *Br. Med. J.,* 2, 518-520.

13. Dalaman, G., G. Haklar, A. Sipahiu, C. Ozener, E. Akoĝlu, and A. S. Yalçin, 1998: Early detection of peritonitis in continuous ambulatory peritoneal dialysis patients by use of chemiluminescence: evaluation of diagnostic accuracy by receiver-operating characteristic curve analysis. *Clin. Chem.,* 44, 1680-1684.

14. Park, S. J., J. Y. Lee, W. T. Tak, and J. H. Lee, 2005: Using reagent strips for rapid diagnosis of peritonitis in peritoneal dialysis patients. *Adv. Perit. Dial.,* 21, 69–71.
15. Akman, S., V. Uygun, and A. G. Guven, 2005: Value of the urine strip test in the early diagnosis of bacterial peritonitis. *Pediat. Int.,* 47, 523–527.
16. Park, S. J., J. Y. Lee, W. T. Tak, and J. H. Lee, 2005: Using reagent strips for rapid diagnosis of peritonitis in peritoneal dialysis patients. *Adv. Perit. Dial.,* 21, 69-71.
17. Ro, Y., C. Hamada, H. Io, K. Hayashi, I. Hirahara, and Y. Tomino, 2004: Rapid, simple, and reliable method for the diagnosis of CAPD peritonitis using the new MMP-9 test kit. *J. Clin. Lab. Anal.,* 18, 224-230.
18. Donovan, K. L., S. Pacholok, J. L. Humes, G. A. Coles, and J. D. Williams, 1993: Intra-peritoneal free elastase in CAPD peritonitis. *Kid. Int.,* 44, 87-90.
19. Ahmadi, S. H., V. Neela, R. A. Hamat, B. L. Goh, and A. N. Syafinaz, 2013: Rapid detection and identification of pathogens in patients with continuous ambulatory peritoneal dialysis (CAPD) associated peritonitis by 16s rRNA gene sequencing. *Trop. Biomed.,* 30, 602–607.
20. Prasad, N., K. Singh, A. Gupta, and K. N. Prasad, 2016: Isolation of bacterial DNA followed by sequencing and differing cytokine response in peritoneal dialysis effluent help in identifying bacteria in culture negative peritonitis. *Nephrol.,* doi: 10.1111/nep.12969.
21. Yoo, T. H., K. H. Chang, D. R. Ryu, J. S. Kim, H. Y. Choi, H. C. Park, S. W. Kang, K. H. Choi, J. M. Kim, S. K. Ha, and D. S. Han, 2006: Usefulness of 23S rRNA amplification by PCR in the detection of bacteria in CAPD peritonitis. *Am. J. Nephrol.,* 26, 115-120.
22. Johnson, G., M. Wilks, S. Warwick, M. R. Millar, and S. L. Fan, 2006: Comparative study of diagnosis of PD peritonitis by quantitative polymerase chain reaction for bacterial DNA vs culture methods. *J. Nephrol.,* 19, 45-49.
23. Ota, K., H. Maruyama, N. Iino, G. Nakamura, M. Shimotori, Y. Tanabe, H. Tsukada, and F. Gejyo, 2007: Rapid detection of causative pathogen of peritonitis using in-situ hybridization in a patient with continuous ambulatory peritoneal dialysis. *J. Infect. Chemother.,* 13, 273-275.
24. Guz, G., B. Colak, K. Hizel, K. A. Reis, Y. Erten, M. Bali, and S. Sindel, 2006: Procalcitonin and conventional markers of inflammation in peritoneal dialysis patients and peritonitis. *Perit. Dial. Int.,* 26, 240-248.
25. Su, Y. J., S. C. Liao, B. C. Cheng, J. C. Hwang, and J. B. Chen, 2013: Increasing high-sensitive C-reactive protein level predicts peritonitis risk in chronic peritoneal dialysis patients. *BMC Nephrol.,* 14, 185-193.
26. Kolonko, A., J. Chudek, and A. Wiecek, 2008: Concentration of adipokines in peritoneal effluent: a new marker of acute peritonitis in peritoneal dialysis patients? *Perit. Dial. Int.,* 28, 527-532.
27. Robert, J. H., P. Meyer, and A. Rohner, 1986: Can serum and peritoneal amylase and lipase determinations help in the early prognosis of acute pancreatitis? *Ann. Surg.,* 203, 163-168.

28. Hamrahian, M., T. Fülöp, M. Mollaee, A. Lopez-Ruiz, and L. A. Juncos, 2012: Recurrent Acute Pancreatitis in a Patient on Peritoneal Dialysis Using 7.5% Icodextrin. *Perit. Dial. Int.,* 32, 568-570.
29. Peer, G., I. Serban, M. Blum, S. Cabili, and A. Iaina, 1992: Early diagnosis of gram-negative peritonitis in continuous ambulatory peritoneal dialysis patients with the Lymulus amebocyte lysate assay. *Am. J. Nephrol.,* 12, 19-21.
30. Martino, F., E. Scalzotto, D. Giavarina, M. P. Rodighiero, C. Crepaldi, S. Day, and C. Ronco, 2015: The role of NGAL in peritoneal dialysis effluent in early diagnosis of peritonitis: Case-control study in peritoneal dialysis patients. *Perit. Dial. Int.,* 35, 559-565.

31. Koomen, G. C. M., M. G. H. Betjes, D. Zemel, R. T. Krediet, and F. J. Hoek, 1994: Dialysate cancer antigen (CA) 125 is a reflection of the peritoneal mesothelial mass in CAPD patients. *Perit. Dial. Int.,* 14, 132-136.

32. Visser, C. E., J. J. Brouwer-Steenbergen, M. G. Betjes, G. C. Koomen, R. H. Beeleen, and R. T. Krediet, 1995: Cancer antigen 125: a bulk marker for the mesothelial mass in stable peritoneal dialysis patients. *Nephrol. Dial. Transplant.,* 10, 64-69.

33. Candocia, S. A., and G. Y. Locker, 1993: Elevated serum CA 125 secondary to tuberculous peritonitis. *Cancer,* 72, 2016-2018.
34. Mas, M. R., B. Comert, U. Saglamkaya, L. Yamanel, O. Kuzhan, U. Ateşkan, and F. Kocabalkan, 2000: CA-125: a new marker for diagnosis and follow-up of patients with tuberculous peritonitis. *Dig. Liver Dis.,* 32, 595-597.
35. Younossian, A. B., T. Rochat, L. Favre, and J. P. Janssens, 2006: Ascites and highly elevated CA-125 levels in a case of peritoneal tuberculosis. *Scand. J. Infect. Dis.,* 38, 216-218.

36. Pannekeet, M. M., D. Zemel, G. C. Koomen, D. G. Struijk, and R. T. Krediet, 1995: Dialysate markers of peritoneal tissue during peritonitis and in stable CAPD. *Perit. Dial. Int.,* 15, 217-225.

37. Lin, C. Y., G. W. Roberts, A. Kift-Morgan, K. L. Donovan, N. Topley, and M. Eberl, 2013: Pathogen-specific local immune fingerprints diagnose bacterial infection in peritoneal dialysis patients. *J. Am. Soc. Nephrol.,* 24, 2002–2009.

38. Oymak, Y., A. Velioğlu, G. Haklar, C. Ozener, and A. S. Yalçin, 2003: Early detection of peritonitis in continuous ambulatory peritoneal dialysis patients by cytokine measurements. *Clin. Chem. Lab. Med.,* 41, 640-645.

39. Hautem, N., J. Morelle, A. Sow, C. Corbet, O. Feron, E. Goffin, F. Huaux, and O. Devuyst, 2017: The NLRP3 Inflammasome Has a Critical Role in Peritoneal Dialysis-Related Peritonitis. *J. Am. Soc. Nephrol.,* ASN.2016070729.
40. Tien, N., H. C. Chen, S. L. Gau, T. H. Lin, H. S. Lin, B. J. You, P. C. Tsai, I. R. Chen, M. F. Tsai, I. K. Wang, and C. J. Chen, 2016: Diagnosis of bacterial

pathogens in the dialysate of peritoneal dialysis patients with peritonitis using surface-enhanced Raman spectroscopy. *Clin. Chim. Acta.,* 461, 69-75.
41. Lin, W. H., J. C. Hwang, C. C. Tseng, Y. T. Chang, A. B. Wu, J. J. Yan, J. J. Wu, and M. C. Wang, 2016: Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry accelerates pathogen identification and may confer benefit in the outcome of peritoneal dialysis-related peritonitis. *J. Clin. Microbiol.,* 54, 1381-1383.
42. Guleria, A., N. K. Bajpai, A. Rawat, C. L. Khetrapal, N. Prasad, and D. Kumar, 2014: Metabolite characterization in peritoneal dialysis effluent using high-resolution ^{1}H and ^{1}H-^{13}C NMR spectroscopy. *Magn. Reson. Chem.,* 52, 475-479.
43. Prasad, N., A. Guleria, N. Bajpai, C. L. Khetrapal, A. Rawat, D. Kumar, and A. Gupta, 2015: 1H NMR based metabolome differentiate bacterial and fungal peritonitis and can predict relapsing peritonitis. *Nephrol. Dial. Transplant.,* 30, 28–29.
44. Lewinsohn, D. M., M. K. Leonard, P. A. LoBue, D. L. Cohn, C. L. Daley, E. Desmond, J. Keane, D. A. Lewinsohn, A. M. Loeffler, G. H. Mazurek, and R. J. O'Brien, 2017: Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin. Infect. Dis.,* 64, 1-33.
45. Su, S. B., S. Y. Qin, X. Y. Guo, W. Luo, and H. X. Jiang, 2013: Assessment by meta-analysis of interferon-gamma for the diagnosis of tuberculous peritonitis. *World J. Gastroenterol.,* 19, 1645-1651.

46. Vaid, U., and G. C. Kane, 2017: Tuberculous Peritonitis. *Microbiol. Spectr.,* 5, doi: 10.1128/microbiolspec.

47. Ahmadi, S. H., V. Neela, R. A. Hamat, B. L. Goh, and A. N. Syafinaz, 2013: Rapid detection and identification of pathogens in patients with continuous ambulatory peritoneal dialysis (CAPD) associated peritonitis by 16s rRNA gene sequencing. *Trop. Biomed.,* 30, 602–607.

48. Abraham, G., M. Mathews, L. Sekar, A. Srikanth, U. Sekar, and P. Soundarajan, 2001: Tuberculous peritonitis in a cohort of continuous ambulatory peritoneal dialysis patients. *Perit. Dial. Int.,* 21, 202-204.

49. Dervisoglu, E., M. Sayan, E. Sengul, and A. Yilmaz, 2006: Rapid diagnosis of Mycobacterium tuberculous peritonitis with real-time PCR in a peritoneal dialysis patient. *APMIS,* 114, 656-658.

50. Waness, A., and S. Al Shohaib, 2012: Tuberculous peritonitis associated with peritoneal dialysis. *Saudi J. Kid. Dis. Transpl.,* 23, 44-47.

51. Edwards, S., P. Glynn, M. D. David, and L. Kamesh, 2016: Diagnosing tuberculous peritonitis early in patients on peritoneal dialysis: Use of Xpert MTB/RIF assay. *Perit. Dial. Int.,* 36, 461-463.

52. Rathi, M., U. Sengupta, T. D. Yadav, and S. Kumar, 2014: Zygomycetes peritonitis in ambulatory peritoneal dialysis: Case report and review of literature. *Indian J. Nephrol.,* 24, 252-254.

53. Tokmak, H., A. Mudun, C. Türkmen, Y. Sanli, S. Cantez, and S. Bozfakioğlu, 2006: The role of peritoneal scintigraphy in the detection of continuous ambulatory peritoneal dialysis complications. *Ren. Fail.,* 28, 709-713.

54. Debi, U., V. Ravisankar, K. K. Prasad, S. K. Sinha, and A. K. Sharma, 2014: Abdominal tuberculosis of the gastrointestinal tract: Revisited. *World J. Gastroenterol.,* 20, 31-40.

55. Tarzi, R. M., J. W. Frank, S. Ahmad, J. B. Levy, and E. A. Brown, 2006: Fluorodeoxyglucose positron emission tomography detects the inflammatory phase of sclerosing peritonitis. *Perit. Dial. Int.,* 26, 224–230.

56. Hsu, J. L., S. J. Ruoss, N. D. Bower, M. Lin, M. Holodniy, and D. A. Stevens, 2011: Diagnosing invasive fungal disease in critically ill patients. *Crit. Rev. Microbiol.,* 37, 277-312.

57. Preuner, S., and T. Lion, 2009: Towards molecular diagnostics of invasive fungal infections. *Expert Rev. Mol. Diagn.,* 9, 397-401.

58. Scotter, J. M., J. M. Stevens, S. T. Chambers, K. L. Lynn, and W. N. Patton, 2004: Diagnosis of Aspergillus Peritonitis in a Renal Dialysis Patient by PCR and Galactomannan Detection. *J. Clin. Pathol.,* 57, 662–664.

Chapter 33

Exit Site and Tunnel Infection

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Exit Site and Tunnel Infection

Peritoneal dialysis (PD) is an important home based modality of renal replacement therapy (RRT) that is gaining importance worldwide including the developing countries. PD is associated with various infectious and non-infectious complications. Infective complications include exit site infection (ESI), tunnel infection and peritonitis. PD peritonitis, when fulminant is associated with adverse outcomes such as catheter loss, ultrafiltration failure and patient mortality [1, 2, 3]. ESI is one of the significant risk factors for PD related peritonitis. So, prevention of ESI can decrease the risk of peritonitis and thus improve overall patient outcomes [1, 2, 3, 4].

Exit site infections constitute about 20% of peritoneal infections. These are responsible for 20% of catheter removals [5]. In about 15-20% of patients, it is implicated in the transfer to haemodialysis (HD) [6].

Many centres report exit site infection rates of 0.5 – 0.6 per patient – year at risk [7, 8]. The rate of clinically obvious tunnel infection is 0.19 per year [8].

Pathogenesis and Microbiology of ESI in PD patients

In most PD patients, colonization of catheter and exit site with microorganisms occurs shortly after PD catheter implantation. Colonization does not equate clinical infection, but predisposes patients on PD to ESI, especially following trauma to the exit site. Colonization may lead to biofilm formation, which prevents exposure of microorganisms to antibiotics and thus may promote further bacterial growth. The organisms which cause ESI are same as those which colonize the exit site [7]. *Staphylococcus aureus*, Coagulase negative *Staphylococcus aureus* (CNS), *Pseudomonas aeruginosa*, and other Gram negative bacilli are the common pathogens causing ESI in patients on PD [1]. There is shift in causative agents for ESI following widespread application of exit site prophylaxis. In some studies, use of mupirocin and gentamycin ointment predisposed patients to fungal exit site infections [9, 10]. In other studies, there was an emergence of exotic organisms such as non tuberculous mycobacteria, Corynebacteria and Burkholderia species to cause ESI [1, 11-13].

Staphylococcus aureus:

It is one of the commonest causative agents for ESI, constituting about 50% of ESI's [7].The risk factors for methicillin resistant *Staphylococcus aureus* (MRSA) infections are advanced age, diabetes mellitus, immune compromised state and prolonged hospital stay [14].

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Coagulase negative *Staphylococcus aureus* (CNS):

The common CNS include *Staphylococcus epidermidis* and *Staphylococcus saprophyticus*. *Staphylococcus epidermidis* constitute about 20% of all ESI's [7]. Other CNS that cause ESI are *Staphylococcus lugdunensis* and *Staphylococcus warneri* [15].

Other Gram positive organisms:

Corynebacterium species (*i.e.*, diphtheroids) are common skin commensals that cause ESI. Other Gram positive organisms implicated in causing ESI are Streptococcal species (*Streptococcus sanguinis*) and Enterococcus species [1, 15].

Pseudomonas aeruginosa

It constitutes about 8% of all the ESI's [7]. *Pseudomonas aeruginosa* has intrinsic resistance to common antimicrobial agents and it is associated with persistent infection because of biofilm formation. Because of these properties, *Pseudomonas aeruginosa* often causes refractory ESI, requiring prolonged antibiotics and is associated with high risk of catheter loss [16, 17]. *Pseudomonas aeruginosa* associated peritonitis is reported in about 20% of patients following several months after the resolution of ESI [16].

Other Gram negative organisms and anaerobes

Escherichia coli accounts for about 4% of all ESI's [7]. *Klebsiella pneumonia*e, Enterobacter species, and *Proteus mirabilis* are other Gram negative organisms that can cause ESI [15]. *Burkholderia cepacia* is other Gram negative organism with a high rate of recurrence after successful antibiotic therapy. There are few case reports with anaerobes (e.g. Micrococcus) causing ESI in PD patients [15].

Mycobacterium

Non tuberculous mycobacteria (Atypical mycobacteria) are more common causative agents for ESI than *Mycobacterium tuberculosis*. *M. chelonae*, *M. abscessus* and *M. fortuitum* are the common atypical mycobacteria that cause ESI [11, 18]. Non tuberculous mycobacteria associated ESI need protracted course of antimicrobial therapy and is associated with high rates of catheter loss [18]. ESI due to *Mycobacterium tuberculosis* occurs as a part of disseminated tuberculosis.

Fungi

ESI due to fungal infection is rare. In various case reports, Candida species are the commonest organisms isolated. In some studies, increased risk of fungal ESI is seen with prophylaxis with mupirocin and gentamycin ointment [9, 10].

Classifying Exit Sites and Diagnosing Exit Site Infections

Catheter exit sites are classified based on clinical criteria. Gentle manipulation of the catheter allows expression of drainage and inspection of the catheter sinus [19]. Certain manifestations such as erythema, pericatheter in duration, and serosanguineous drainage from the exit site are signs of either exit-site infection or trauma, which predisposes patients to infection [20].

Purulent discharge from the exit site is considered a clear sign of infection and is a risk factor for catheter loss [21, 22]. Occasionally, exit-site infection presents as hypertrophic, friable tissue with purple discoloration, the so-called proud flesh.

When assessing the exit site, there are a few characteristics that should be examined. It is important to determine whether inflammation is present; the degree of redness of the skin and the size or diameter of the inflamed area should be carefully assessed. It is also important to note the duration of the inflammation, whether it has been present for more than or less than 4 weeks. Also, we should examine for the presence of crust, external exudate and drainage, as well as external or internal granulation. The appearance of the internal catheter zone and whether internal secretion is present or absent are also important to note. It is important to bear in mind that visual attributes of the exit and sinus are essential but not sufficient for diagnosis. History, culture, and comparison with previous exit appearance are also necessary elements for a complete diagnosis. Assessment by palpation provides additional diagnostic information not attained from visualization alone. An exit-site infection can be limited to the exit site or may extend into the subcutaneous tunnel causing a tunnel infection. Exit sites can be classified according to guidelines outlined by Teixidó or Twardowski [23-26].

These criteria are summarized below:

Grade 0: Perfect

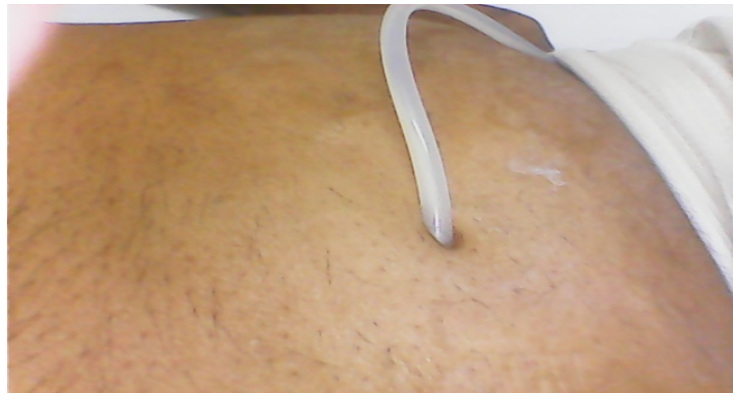

Figure 1: Perfect Exit Site

Photo courtesy of Miss Deepa, Latha and Hema

A perfect exit-site is usually reached 6 months after catheter implant. However, Teixidó suggests that "perfect" sites can occur as early as 3 months after placement. With a perfect exit site, there is normal skin with natural skin color. There should be a mature and dry epithelium in the sinus where crust formation occurs no more than once every 7 days. There should be no pain, swelling, pink or red skin, granulation tissue, external exudation, or internal secretion.

Grade 1: Good

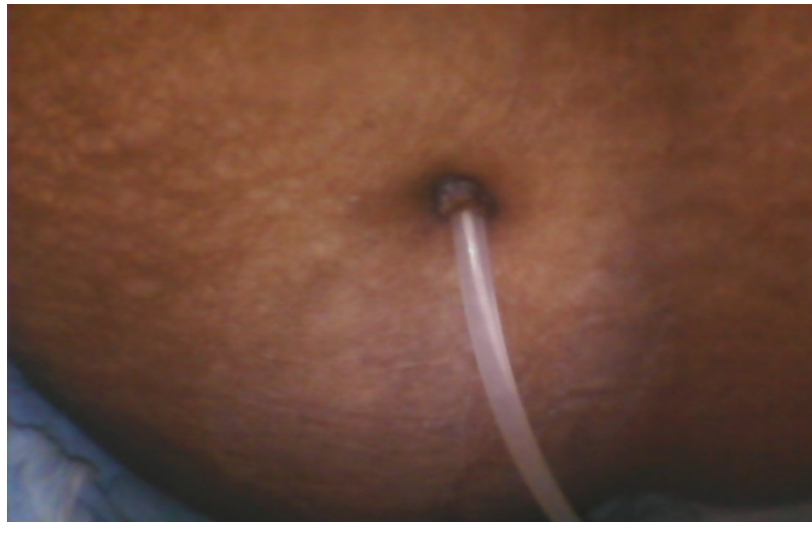

Figure 2: Good Exit Site.

Photo courtesy of Miss Deepa, Latha and Hema

A good exit site usually takes more than 6 weeks of healing time to occur. The skin is natural in color and redness should not extend from the catheter more than 1-2 mm according to Teixidó's guidelines. Twardowski suggests measuring the redness diameter from border to border, including the width of the catheter. Following the Twardowski guidelines, 13 millimeters is the maximum diameter for redness measurement for an exit to be classified as "good." There should be no pain, swelling, bright pink or red color, exuberant granulation tissue, external exudation, or abundant internal secretion.

Grade 2: Equivocal

An equivocal exit-site can be thought of as neither a good exit-site nor an obvious infection. In equivocal exit sites, purulent or bloody drainage is only present in the sinus and cannot be expressed outside and is accompanied by regression of the epithelium and slight exuberant granulation tissue in the sinus.

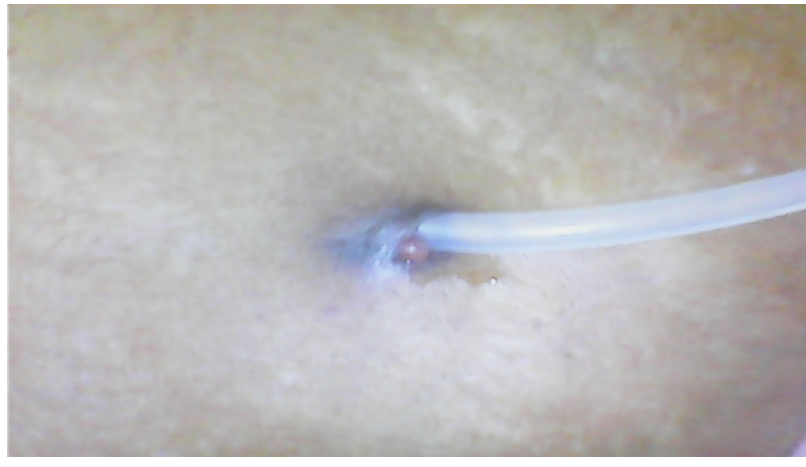

Figure 3: Equivocal Exit Site.

Photo courtesy of Miss Deepa, Latha and Hema

There might be some mild redness extending two to three millimeters (less than 13 mm) from the sinus edge to the border edge (according to Teixidó), but there is no pain, swelling or external drainage. Crust usually develops every one to two days. This crust may occur in the form of a cuff that is large or difficult to detach. Equivocal sites often suggest low-grade infections that may improve spontaneously or progress if left untreated.

Acute exit-site infection

An acute infection is characterized by redness, swelling and tenderness. The measurement from the sinus edge to the border edge is greater than three to four millimeters. The outside diameter of the catheter is approximately five millimeters. Twardowski's measurement suggests that the area of redness is greater than 13 mm in diameter. The erythema is more than twice the diameter of the catheter, and there is regression of the epithelium in the sinus. An acute infection is often painful and a scab might be present and/or daily crust. Scabs are composed of hardened serum and blood and can form as a result of capillary bleeding in the granulation tissue. Crusting alone does not mean infection. External drainage is purulent or bloody. This drainage may be spontaneous or may be expressed after pressing on the sinus.

Purulent drainage may be present in the form of a white, yellow, or green liquid. In addition to these obvious characteristics, a large amount of serous drainage may also signal an infection. Purulent drainage should always be cultured. Although, positive cultures of normal-appearing exit sites indicate colonization but not infection.

Acute catheter inflammation lasts less than 4 weeks. The common pathogens are *S. aureus* and *P. aeruginosa*. Other organisms causing exit-site infection are coagulase-negative Staphylococcus, diphtheroids, anaerobes, streptococci, legionella, and fungi. Exit-site culture may be negative in patients receiving antibiotics.

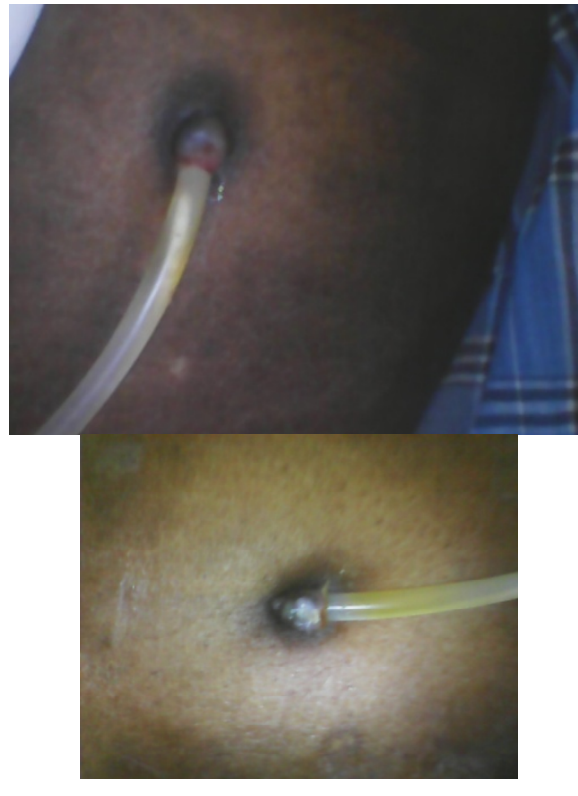

Figure 4: Acute Infection Exit Site.

Photo courtesy of Miss Deepa, Latha and Hema

Chronic exit-site infection

Granulation tissue is typically present both externally and in the sinus of the exit site in chronic infections. The exit is sometimes covered by a large, persistent crust or scab. There is usually no pain, redness or swelling, and the skin is often hyper-

pigmented. Drainage from a chronically infected or Grade 4 exit site is the same as for the acutely infected or grade 3 exit site. It is important to note that the key distinction between the acute or Grade 3 and chronic or grade 4 infected sites is the duration of the infection. Chronic infection persists for more than 4 weeks and crust or scab is frequently present. Swelling, erythema, and/or pain indicate exacerbation.

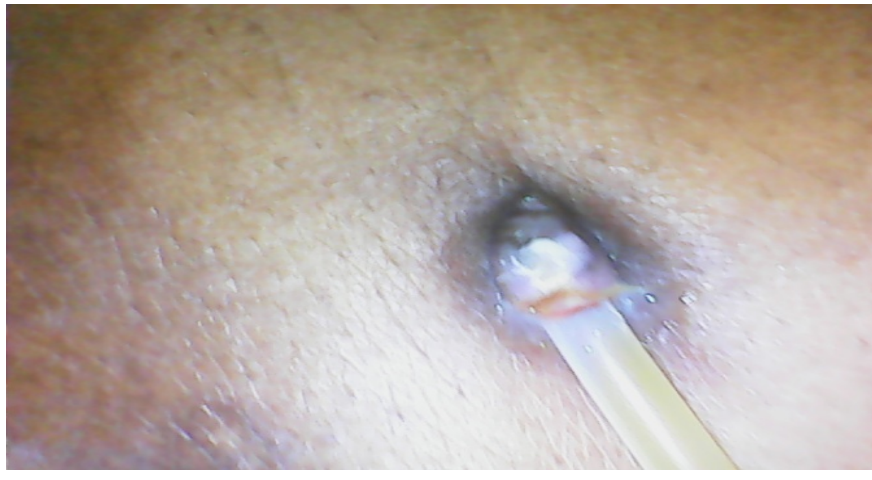

Figure 5: Chronic Infection Exit Site.

Photo courtesy of Miss Deepa, Latha and Meena

Traumatized exit

A traumatized exit-site is not an infection but may involve pain, bleeding, scab development, and deterioration of the exit. Extravasated blood is a good medium for bacterial growth. Bacteria that have colonized exit site multiply rapidly in the presence of decomposing blood and infect the disrupted tissue. Infection occurs as early as 24-48 hours after trauma.

Tunnel infections

Tunnel infections are associated with redness, swelling and tenderness over the tunnel and may be accompanied by intermittent or chronic, purulent or bloody drainage that discharges spontaneously or after pressure on the cuff. These infections are often occult and are usually located between the internal and external cuffs. Ultrasonic evaluation of the tunnel is useful in confirming and assessing the extent of the peri-catheter abscess [27, 28].

Most, but not all, tunnel infections occur in conjunction with exit site infections. The presence of a tunnel infection increases the risk for peritonitis. *S. aureus* and

Pseudomonas aeruginosa exit site infections are often associated with concomitant tunnel infections and are the organisms that most often result in catheter infection-related peritonitis. Korzets *et al.* examined the usefulness of ultrasound examination of the catheter tract in delineating catheter-related (exit site and tunnel) infections, and their relationship to each other and to peritonitis [29]. They regarded the findings as positive if an area of hypoechogenicity (indicative of fluid collection) > 2 mm in width along any portion of the catheter tract. They performed a total of 56 ultrasound examinations (26 episodes of peritonitis, four TI, 13 ESI and 13 controls) and reported that majority of the collections (13/16 in episodes of peritonitis and 5/8 ESI were localized to the internal cuff region [29].

Other imaging techniques like positron emission tomography scanning and scintigraphy, may be useful for diagnosing and managing PD catheter infections [30]. Continued treatment failure, especially with *S. aureus*, may be the result of a concomitant catheter tunnel infection and should result in catheter removal [31]. In relapsing peritonitis caused by *S. aureus*, an occult (e.g., subclinical) tunnel infection or intraabdominal abscess should be sought [32].

A traumatized exit-siteis not an infection but may involve pain, bleeding, scab development, and deterioration of the exit.

Trauma may result in pain, bleeding, scab, and deterioration of exit appearance. Exit appearance depends on intensity of trauma and time of evaluation. A scoring system developed by pediatricians, while not examined critically in adults, may be a useful method of monitoring exit sites. (**Table 2**)

Infection should be assumed with exit-site score of 4 or greater. Purulent drainage, even if alone, is sufficient to indicate infection. A score of less than 4 may or may not represent infection [33].

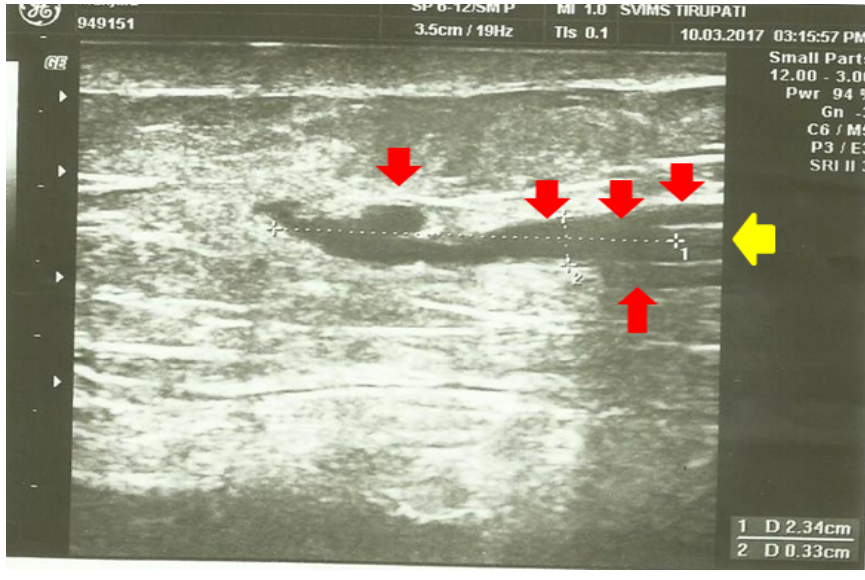

Figure 6: Ultrasound of Tunnel.

Red arrows: collection around the catheter, yellow arrow: catheter.

Bacteriologic studies of the exit site can be difficult to interpret. Dry swabs of the exit site or cultures of serosanguineous exudate will usually reveal skin flora unrelated to the cause of infection. Even recovery of *Staphylococcus aureus* in culture should be interpreted in the context of the clinical picture, because chronic dialysis patients are frequently staphylococcal carriers. Infection may develop several months after colonization of the exit site with the same bacterial species.

However, recovery of a single species of bacteria from a purulent exudate is a fairly reliable indicator of the cause of exit site infection, generally as *Staphylococcus aureus, Staphyloccus epidermidis* or Pseudomonas species [34].

Table 1: Characteristics of each category of exit-site appearance

	Perfect	**Good**	**Equivocal**	**Acute infection <4 weeks**	**Chronic infection >4 weeks**	**Cuff infection without exit infection**
Pain/ tenderness	None	None	None	May be present	Only if exacerbation	May be present over cuff
Colour	Natural, pale pink or dark	Natural, pale pink, purplish or dark, bright pink	Bright pink or red < 13 mm	Bright pink or red > 13 mm	Bright pink or red >13 mm only if exacerbation	Natural, pale pink, purplish or dark, bright pink <13 mm
Crust	None or small, easily detached or specks of crust on	None or small, easily detached or specks of crust on	Present, may be large and difficult to detach	Present	Present, may be difficult to detach	Typically absent
Scab	None	None	None	May be present	May be present	Absent
Drainage	None	None	None even with pressure on sinus; dried exudate on dressing	Purulent or bloody, spontaneous or after pressure on sinus; wet exudate on dressing	Purulent or bloody, wet exudate on dressing	Chronic or intermittent; purulent, bloody, tenacious or "gluey"
Swelling	None	None	None	May be present	Occurs only if exacerbation	Cuff induration may be felt on palpation; negative ultrasound does not rule out the
Granulation tissue	None	None	Plain or slightly exuberant	Slightly exuberant or "proud flesh" may be present	"Proud flesh" or slightly exuberant typically visible	None
Epithelium	Strong, mature; covers visible	Strong, mature at rim; fragile or mucosal	Absent or covers part of sinus	Absent or covers part of sinus	Absent or covers only part of sinus	Covers most oral!of sinus; may be macerated

Granulation tissue	None	Plain beyond epithelium	Slightly exuberant	Slightly exuberant or "proud flesh"	"Proud flesh" or slightly exuberant	None or exuberant deep in sinus
Drainage	None or barely visible; clear or thick	None or barely visible clear or thick	Purulent or bloody, sometimes clear	Purulent or bloody	Purulent or bloody	Purulent, bloody, gluey; may be seen only after pressure on cuff; clot or dried

Table 2: Exit-Site Scoring System [33]

	0 points	**1 point**	**2 points**
Swelling	No	Exit only;< 0.5 cm	>0.5 and/or tunnel
Crust	No	< 0.5 cm	>0.5 cm
Redness	No	< 0.5 cm	>0.5 cm
Pain	No	Slight	Severe
Drainage	No	Serious	Purulent

Empiric therapy

1. Empiric therapy should always cover *S. aureus.* Empiric therapy should cover *Pseudominas aeruginosa* if patient had history of exit-site infections due to it. (ISPD guidelines 2005) [35].

Oral first-generation cephalosporins (cephradine, cephalexin) or penicillinase-resistant semisynthetic pencillins (dicloxacillin) can be used against staphylococci [36]. Sulfamethoxazole-trimethoprim may also be used [37]. For Gram positive infections, sulfamethoxazole-trimethoprim is as effective as vancomycin with rifampin and more effective than vancomycin alone [37]. Quinolones are commonly used against both Gram-positive and Gram negative organisms. The absorption of quinolones may be reduced with concurrent ingestion of calcium salts, iron salts, zinc preparations, sucralfate, magnesium/aluminum antacids, and milk. Hence, a period of 2 hours between the ingestion of ciprofloxacin, which should be taken first, and the other preparations is recommended [38]. Pseudomonas exit-site infections may also be treated with aminoglycosides. If used the levels should be monitored.

2. In some cases, intensifiedlocal care or a local antibiotic cream may be felt tobe sufficient in the absence of purulence, tenderness and oedema (ISPD guidelines 2005) [35].
3. Topical antibiotics in acute or chronic infection are of little value because they cannot achieve sufficient local concentrations before being washed away with large drainage. Antibiotics administered systemically can provide therapeutic concentrations locally by being excreted into the drainage. Local antibiotics can achieve high concentrations in the sinus in equivocal, good, or perfect exit sites but are most useful for equivocal exit sites.
4. Especially severe exit-site infections may be treated by hypertonic saline dressings twice daily, as well as oral antibiotic therapy. This procedure involves adding 1 tablespoon of salt to 1 pint (500 mL) of sterile water; this solution is then applied to gauze and wrapped around the catheter exit site for 15 minutes, once or twice daily (ISPD guidelines 2005) [35].

Specific Treatment

Antibiotic sensitivities should guide the choice of agents in specific treatment.
Gram-positive organisms are treated with oral penicillinase-resistant penicillin or a first-generation cephalosporin such as cephalexin. Vancomycin should be avoided in the routine treatment of gram-positive exit-site and tunnel infections for it causes emergence of resistant organisms; but will be required for MRSA infections. In slowly resolving or particularly severe-appearing *S. aureus* exit-site infections, rifampin 600 mg daily may be added. Rifampin should never be given as monotherapy. However in tuberculosis endemic areas, this drug should be held in reserve (ISPD guidelines 2005) [35]. (**Table 3**)
Pseudomonas aeruginosa exit-site infections are particularly difficult to treat and often require prolonged therapy with two antibiotics. Oral quinolones are recommended as the first choice. If resolution of the infection is slow orif there is recurrence, a second anti-pseudomonal drug, such as IP/IV ceftazidime, should be added (ISPD guidelines 2005) [35].
Antibiotic therapy must be continued until the exit site appears entirely normal. Two weeks is the minimum length of treatment time, and longer may be necessary (ISPD guidelines 2005) [35].
The consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis, 2012 update suggested different guidelines, treatment should continue for a minimum of 2 weeks and for at least 7 days after complete clinical resolution of the infection—that is, until the exit-site appears entirely normal.

Table 3: Oral Antibiotics Used in Exit-Site and Tunnel Infections

Antibiotic	Dose
Amoxicillin	250–500 mg b.i.d.
Cephalexin	500 mg b.i.d.
Ciprofloxacin	250–500 mg b.i.d.
Clarithromycin	250–500 mg b.i.d.
Dicloxacillin	250–500 mg b.i.d.
Fluconazole	200 mg q.d.
Flucloxacillin	500 mg b.i.d.
Flucytosine	2 g load, then 1 g p.o., q.d.
Isoniazid	300 mg q.d.
Linezolid	600 mg b.i.d.
Metronidazole	400 mg b.i.d. for <50 kg; 400–500 t.i.d. for >50 kg
Ofloxacin	400 mg first day, then 200 mg q.d.
Pyrazinamide	35 mg/kg q.d. (given as b.i.d. or once daily)
Rifampin	450 mg q.d. for <50 kg600 mg q.d. for >50 kg
Trimethoprim/sulfamethoxazole	80/400 mg q.d.

Treatment for at least 3 weeks is recommended for ESIs caused by *S. aureus* or *P. aeruginosa* [39]. Data from a survey conducted by the Japanese Study Group of Pediatric Peritoneal Dialysis among 130 patients less than 15 years of age showed a relapse rate of 15%; the relapse rate was 40% among infection episodes caused by MRSA [40]. Close follow-up of the exit-site and tunnel conditions is therefore necessary after completion of therapy.

1. Coagulase negative staphylococcus are more likely to resolve (>90 percent) than infections with S. aureus and Pseudomonas (40 to 50 percent). A tunnel infection should be suspected for an unresolving exit site infection if the organism is *S. aureus* or Pseudomonas.
2. If deep cuff involvement is not present, externalization and curettage of the external cuff ("cuff shaving") and revision of the tunnel may help to resolve the infection [41, 42].Ultrasonography of the tunnel is a valuable tool in the diagnosis of cuff infection. It may be used to evaluate the extent of infection along the tunnel and the response to therapy, and may be used to decide on tunnel revision, replacement of the catheter, or continued antibiotic therapy (ISPD guidelines 2005) [35, 43]. Although positive findings with ultrasound help to establish a diagnosis of tunnel infection, a negative examination does not rule out cuff infection. Antibiotics must be continued during and after cuff shaving (ISPD guidelines 2005) [35].
3. When the external cuff is almost completely exposed, the cuff may move in and out of the exit like a piston, causing local trauma, disrupting healthy granulation tissue, and causing an infection. If so, the exposed cuff should be shaved.
4. If only partially exposed or if the cuff is involved, the external cuff shaving is performed as an out-patient ambulatory procedure in the under local anaesthesia (lidocaine 1%). A small incision is made at the external exit site towards the external subcutaneous cuff, which is usually easily palpated. When the external cuff is exteriorised, it is then removed, literally by shaving, with a bistoury knife or a shaving blade. Alternatively, sand paper and a toothed forceps to pick the cuff may also be used. Skill is necessary to avoid injuring the silicone catheter. In our experience it takes 45 minutes to polish off the external cuff. Our experience also helps us to understand that the cuff shaving prolongs the catheter life for 6 months to one year. It may help in a patient who is planned for a transplant surgery.
5. Some dissect the entire area of granulation tissue and cellulitis resulting in an open wound which is then packed until healing occurs [44, 45].
6. External cuff extrusion without infection does not require removal of the cuff [46]. The reimplantation of the extraperitoneal portion of the catheter with creation of a new subcutaneous tunnel on the opposite side may also be performed [47].
7. An alternative approach is to replace the external catheter segment, including the superficial cuff, by splicing a new portion to the preexisting catheter and forming a new exit site [48].

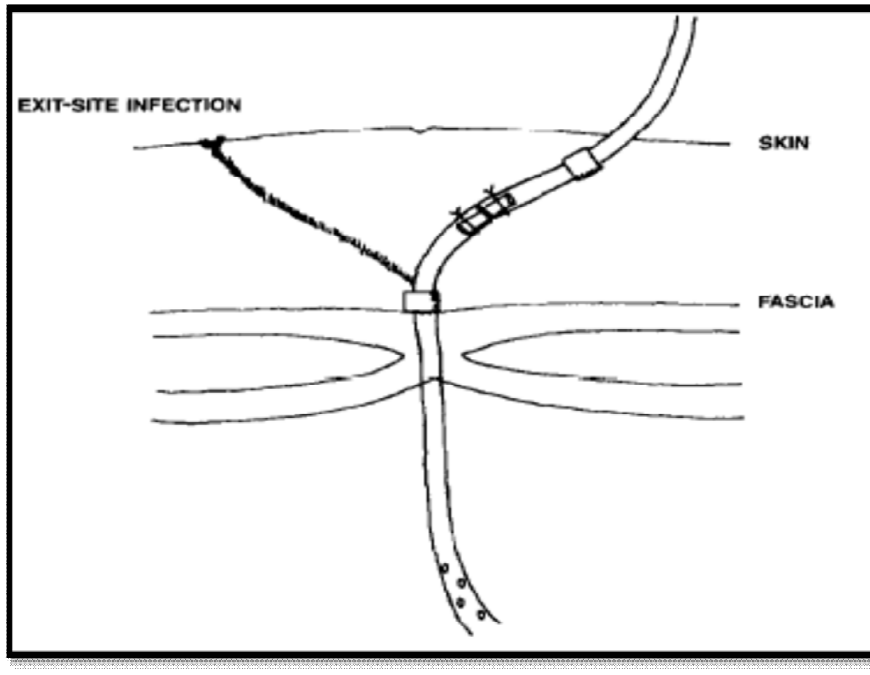

Figure 7: Catheter is Divided between the Cuffs.

A Teflon connector is inserted, followed by a new external half of the catheter. Both catheter ends were tied with 5.0 prolene stitches. The new catheter is tunneled through the opposite abdominal subcutaneous tissue. The old and infected catheter is removed.

8. Cuff shaving and tunnel revision are never effective if catheter related peritonitis is present [49].
9. If exit site infection persists despite these measures and the catheter should be replaced [50, 51]. It is done under antibiotic coverage (ISPD guidelines 2005) [35]. The peritonitis is best avoided with this step [51].
10. If the infectious exudate reaches on the deep cuff, the peritoneal catheter should be removed and antibiotics continued for at least 7 to 10 days before implantation of a new catheter through a different route [52]. The minimal waiting period before new catheter placement is extended to 3 to 4 weeks if peritonitis coexists [21].
11. The usual procedure, especially for infections by *S. aureus,* is tunnel exploration and removal or shaving of the external catheter cuff [21]. Overall, *S. aureus* exit site infections resolve approximately one half of the time with antibiotic therapy with most failures being due to relapses [53-55].

Removal of the external cuff with excision of granulation tissue and the surrounding cellulitis cures another 23% of *S. aureus* catheter infections but most of

the remainder develop peritonitis [55]. When *S. aureus* peritonitis appears to have resolved with therapy but effluent cultures remain positive, a catheter infection is generally present; delay of catheter removal may result in the patient's death [56].

12. Pseudomonas tunnel infections, shaving of the external cuff and draining of the tunnel abscess are unlikely to affect a cure. The persistence of Pseudomonas exit site infection beyond 3 weeks of appropriate antibiotic therapy automatically mandates catheter removal [57].
13. A patient with an exit-site infection that progresses to peritonitis, or who presents with an exit-site infection in conjunction with peritonitis with the same organism, will require catheter removal. Catheter removal should be done promptly (ISPD guidelines 2005). The exception is peritonitis due to coagulase-negative staphylococcus, which is generally readily treated (ISPD guidelines 2005) [35].

Prevention

Risk factors for exit site infection: *S. aureus* nasal carriage is strongly associated with *S. aureus* exit site colonization, exit site infection and peritonitis [58-61]. The same subtype is found in the nares, colonizing the exit site and in the dialysate when peritonitis is present [62, 63].

S. aureus nasal carriage can lead to *S. aureus* peritonitis by two routes: via exit site/tunnel infection and via touch contamination at the time of an exchange. Forty five percent of patients starting CAPD will have *S. aureus* in their nares [59].

With time on CAPD 30% of patients who were not initially *S. aureus* carriers will have one or more positive nose cultures [64]. If carriage is defined as 2 of 3 positive nose cultures, 44% of peritoneal dialysis patients are carriers compared to 17% of the patients' partners [65].

Approximately one third of peritoneal dialysis patients are chronic carriers with *S. aureus* in the nares or exit site in > 75% of cultures, one third are intermittent carriers, and one third have zero or one positive nose cultures [62, 63]. Age, sex, diabetes mellitus, and the use of subcutaneous erythropoietin are not known risk factors for *S. aureus* carriage [60, 64].

Few risk factors for catheter infections other than *S. aureus* nasal carriage have been identified. Insulin dependent diabetes does not appear to be associated with an increased risk of catheter infection, although tunnel infection rates are higher in diabetic women than non-diabetic men [66, 67]. Black patients may have slightly higher catheter infection rates, but fewer *S. aureus* catheter infections than white patients [68].

Obesity does not increase exit site infection rate but infections in such patients are more difficult to treat, increasing the probability of catheter loss [69].

Pre-operative and early exit site care

1. Ideally, the patient should see the surgeon and/or training nurse prior to catheter placement, and the ideal location for the exit site determined. The data from registries show that the double-cuff catheter had superior survival compared to the single-cuff catheter was less likely to result in catheter removal for exit-site infection [70]. This benefit was not confirmed in a single-center randomized trial with much smaller numbers [71]. The role of the external cuff is to prevent infection by primarily anchoring the catheter. The external cuff should be 2 – 3 cm from the exit site.
2. A downward directed tunnel may decrease the risk of catheter-related peritonitis [72]. However, randomized trials have not confirmed the benefit of the swan neck configuration on reducing PD-related infections [73, 74, 75].
3. Nor has burying the catheter proved effective in reducing the risk of infection [76]. Every effort should be made to avoid trauma and hematoma during catheter placement. The exit site should be round and the tissue should fit snugly around the catheter. Sutures increase the risk of infection and are contraindicated.
4. Peritoneal catheters are implanted surgically in the operating room, blindly at the bedside, or peritoneoscopically. Good results have been claimed for all techniques. Meticulous aseptic technique during implantation; proper positioning of the cuffs; and avoidance of excessively long incisions, open spaces for fluid collection in the tunnel, and tissue damage are far more important than the insertion technique chosen. The operator's experience is much more important than the implantation technique in ensuring both good catheter function and lower infection rates.
5. The goal of early care is to delay bacterial colonization and to minimize trauma to the exit site. After implantation, the exit site should be covered with sterile gauze and occlusive dressings must be avoided. Gauze dressings can wick away drainage from the exit and keep the exit site dry. It is generally agreed that postoperative dressing changes should be restricted to specially trained staff. Dressings should not be changed frequently unless there is evidence of bleeding or significant drainage. Our usual practice is to untouch the dressing for one week for healing, unless excessive bleeding is noticed. We change dressings every week for the first 2 weeks. Once the exit is colonized, by week 3 in the majority of cases, more frequent dressing changes are indicated, because the major rationale for infrequent dressing changes, avoidance of exit colonization, no longer exists. Moreover, more frequent cleansing of the exit will decrease the number of bacteria at the exit.
6. Once the exit site is well healed, the patient should be taught how to do routine exit-site care.
7. Nonionic surfactant such as 20% poloxamer 188 (Shur-Clens1) is used to help gauze removal if it is attached to the scab. If the scab is forcibly removed, the epidermal layer is broken, a new scab has to be made, and the epidermization is prolonged.
8. Antibacterial soap and water are recommended for cleaning of exit sites. Use of an antiseptic to clean the exit site is preferred by some. Povidone iodine or chlorhexidine for cleansing are reasonable options [77]. Hydrogen peroxide is drying and should be avoided for routine care (ISPD guidelines 2005) [35].

9. After cleansing, the exit site should be patted dry with sterile gauze, covered with several layers of gauze dressings, and secured with air-permeable tape.
10. If healing does not progress, if there are signs of deterioration or infection at the end of 6 weeks, the exit is probably already colonized. A clinical culture of the exudate should be taken, and an appropriate systemic antibiotic should be given.
11. The catheter should always be kept immobile to prevent pulling and trauma to the exit site, which may lead to infection.
12. Patients should not take shower or take tub baths post-catheter implantation, to avoid colonization with waterborne organisms, and to prevent skin maceration. Once more frequent dressing changes are started (after approximately 2 weeks), the patient may take a shower, but only before the dressing change, otherwise he/she must take sponge baths and avoid exit wetting.

Chronic exit site care

Local Care

1. Daily, exit site care is desired. Cleansing of the exit site is essential to reduce resident bacteria.
2. The exit site is first washed with antibacterial soap and water or with anonionic surfactant such as 20% poloxamer 188 (Shur-Clens1). Povidone-iodine, chlorhexidine, and Amuchina may be used as disinfectants in routine exit-site care. These agents should not be allowed into the exit-site sinus. After cleansing, the exit has to be patted dry with sterile gauze.
3. However, the study results are different. In a randomized trial comparing povidone iodine and a non-occlusive dressing to soap and water, there were more exit site infections in the soap and water group [77]. *S. aureus* exit site infection rates were 0.22 /y using povidone iodine and 0.47/y using soap and water. Jindal and Hirsch also reported very low exit site infections with an exit site care protocol that included occlusive dressings and cleaning of the exit site with povidone iodine every 5 days [78].
4. Cleaning with soap and water is the least expensive and tends to prevent infections better than povidone-iodine painting and hydrogen peroxide cleaning Amuchina is an electrolytic chloroxidizing solution containing sodium hypochlorite [79]. Amuchina exerts bactericidal, viricidal, and fungicidal effects on a variety of pathogens through generation of hypochlorous acid. Amuchina 3% is the most cost effective option compared to Amuchina 50%, povidone iodine 10% or chlorhexidine 4% [80].However, in some patients Amuchina may cause scab formation and exit-site irritation [81].
5. A dressing cover for 6–12 months after implantation is recommended. We prefer for life time. Continued use of dressings is indicated for infected exit sites or likely to be contaminated.
6. Swimming and bath tubs: Submersion in a Jacuzzi, hot tub, or public pool should be avoided, unless watertight exit protection can be implemented. The surrounding skin is coated with a skin protector and secured with Tegaderm1. Prolonged submersion in water containing high concentrations of bacteria frequently leads to

severe infection with consequent loss of catheter. Swimming in the ocean, and well-sterilized private pools, is less dangerous. An advisory is against swimming in creeks and ponds. Prolonged submersion of the exit site in water can lead to infection, particularly with *P. aeruginosa* [82, 83]. Exit care must be performed immediately after a shower or water submersion, with particular attention to obtaining a well-dried exit.

7. The swan neck presternal catheter composed of two flexible (silicon rubber) tubes joined by a titanium connector at the time of implantation. The exit site is located in the presternal or parasternal area. In high risk patients like obesity, patients with ostomies and suprapubic catheters and patients who desire to use a bathtub and wear sweatpants with an elastic waist, the exit site and tunnel infection rates were better with swan neck presternal catheters than with swan neck abdominal catheters. No specific contraindications to the presternal catheter implantation have been identified. Patients with the swan-neck presternal catheter may take a hot tub bath without exit-site submersion [84]. Because of this feature this catheter was dubbed the ''bath-tub'' catheter [85]. Presternal catheters have three cuffs. Cuff shaving of the subcutaneous cuff have better results as the remaining two cuffs acts a double barrier against periluminal bacterial penetration.

Antibiotic Prophylaxis

1. There is no evidence to support the use of prophylactic antibiotics to reduce the incidence or frequency of infections in healed exit sites and tunnels. Healthy exit sites usually do not become infected unless traumatized. Therefore, a prophylactic antibiotic is not recommended for good or perfect exit sites in the absence of trauma. A prophylactic antibiotic is indicated for the management of accidentally traumatized exits. In most cases of trauma, this may be considered a treatment and not a prophylaxis because in most reported trauma cases the exit site deteriorates to equivocal—which is a subclinical form of exit-site infection. The other indication for prophylaxis is the chronic infection in which discontinuation of systemic antibiotics results in reappearance of the infection. In such a case, long-term prophylaxis with a suppressive dose of an antibiotic is useful.
2. Exit-site infections are commonly caused by *S. aureus* and *P. aeruginosa* [86-89].Data supports the use of mupirocinat the exit site to decrease exit-site infections and peritonitis by *S. aureus* [90]. The usual recommendation is to apply mupirocin daily after cleansing. Once-weekly application of mupirocin to the exit site has also been shown to be effective in decreasing exit-site infections and peritonitis episodes comparable to those obtained with daily application [91]. Alternative to mupirocin, gentamicin cream and ciprofloxacin otologic solution are effective in reducing the incidence of *S. aureus* as well as Gram-negative exit-site infections [92, 93].
3. With the reduction in *S. aureus* infections using mupirocin, *Pseudomonas aeruginosa* becomes the most troublesome organism at the exit site [94].
4. There are no published RCTs that have looked at the effectiveness of applying mupirocin to the catheter exit site as routine practice [95].
5. Exit site prophylaxis: mupirocin versus gentamicin cream: Bernardini *et al*, randomized 133 individuals to exit-site mupirocin or gentamicin cream [96].

Catheter infection rates were 0.23/year with gentamicin cream versus 0.54/year with mupirocin (p = 0.005). *S. aureus* exit-site infections were infrequent in both groups (0.06 and 0.08/year; p = 0.44). While there were no pseudomonal exit-site infections in the gentamicin group, there were 0.11 episodes per patient year in the mupirocin arm. Peritonitis rates were 35% lower in the gentamicin arm, with a striking decrease in Gram-negative peritonitis.

6. Exit site prophylaxis: Ciprofloxacin solution: Montenegro *et al,* randomized 164 individuals to exit-site care with soap and water only versus exit-site care with soap and water plus application of 1 mg ciprofloxacin (0.5 mL otologic solution) [93]. Ciprofloxacin reduced exit-site infections to 0.06 episodes per patient-year of exposure in contrast to 0.41 episodes in the control group (p = 0.001). *S. aureus* infections were significantly reduced and none of the treated patients developed pseudomonal exit-site infections.

7. A potential alternative agent is medical-grade honey. Honey has long been known to possess antimicrobial properties and is thought to potentially be less likely to lead to the development of drug-resistant microorganisms compared with antibiotics. Medical-grade honey has been shown to be as efficacious as topical mupirocin in the prevention of catheter associated sepsis in haemodialysis patients but without the problem of antibiotic resistance [97]. An RCT of its use in adult and paediatric PD patients in Australia and New Zealand has been completed, but the findings do not support a role for antibacterial honey in the prevention of PD-associated infections [98]. The intervention involved daily application of honey to the PD catheter exit site in one group and standard prophylactic care in the other group (application of mupirocin intranasally for 5 days each month for the duration of the study in *S. aureus* carriers only).

8. A multicentre randomized controlled trial of mupirocin versus Polysporin Triple (P3) antibiotic ointment (containing bacitracin, gramicidin and polymyxin B) randomized to adult peritoneal dialysis patients to apply one or other of the ointments to the exit site with each dressing change [99]. The study found no difference between the two groups in the composite endpoint of exit site infections, tunnel infection or peritonitis. However, a higher rate of fungal exit site infections was seen in patients using P3 and there was a corresponding increase in fungal peritonitis. Consequently, the use of P3 over mupirocin as a prophylactic agent cannot be advocated.

9. A single-centre randomized controlled trial compared the antibiotic polyhexanide (solution) versus standard care at the exit site (saline solution and povidone-iodine) [100]. The study found a significant difference between the exit site infections rate for the polyhexanide group compared with the standard care group. The authors suggest polyhexanide is efficient in the prevention of ESI and should be considered a prophylactic agent that can be routinely used at the exit site.

10. The nasal carriage of *S. aureus* is also a risk factor in peritoneal dialysis–related infections [59, 101-103]. The treatment of *S.aureus* nasal carriage with intranasal mupirocin twice a day for 5–7 days has been shown to decrease the incidence of *S. aureus* exit-site infections, and in some studies peritonitis and catheter loss [65, 102, 103]. However, meta-analysis revealed intranasal mupirocin has no benefit on

decreasing peritonitis rates and catheter loss [104]. Periodic retreatment is frequently necessary because of a high recolonization rate [65, 102, 103]. This may be done routinely at monthly intervals or based on periodic screening.

11. Since the strains of Staphylococcus colonizing the exit site may be different from the nose, exit-site prophylaxis may be the preferred option and is more convenient [105].

12. An alternative to intranasal mupirocin is the use of oral rifampin in a dose of 600 mg/day for 5 days every 3 months to reduce *S. aureus* exit-site infections [90, 105]. In a randomized study, mupirocin and rifampin were equally effective in reducing *S. aureus* peritonitis and catheter loss, however, rifampin was often poorly tolerated, has drug interactions and developed resistance [90].

13. The overall benefit of mupirocin prophylaxis (nasal and exit-site) were evaluated in another meta-analysis; there was a highly significant relative risk reduction of 37% for all *S. aureus* infections, 34% for peritonitis, and 38% for exit-site infections [106]. There are few side-effects associated with the mupirocin, mainly nasal irritation and discharge for the nasal route [102].

14. A systematic review published in 2010 investigated whether the application of mupirocin (at the exit site or intranasally) was effective in the prevention of exit site infection and peritonitis in PD patients [107]. A total of 14 studies with 1233 enrolled patients and 1217 controls were included in the review. Mupirocin was associated with a significantly lower risk of ESI (0.57, 95% CI: 0.46–0.66, $P<0.0001$) and peritonitis (0.41, 95% CI: 0.24–0.54, $P<0.0001$) due to all organisms. When only ESI and peritonitis due to *S. aureus* were considered, a bigger reduction in risk was seen for both outcomes (0.72, 95% CI: 0.60–0.81, $P<0.0001$; 0.70, 95% CI: 0.52–0.81, $P<0.00001$).

15. Exit-site mupirocin ointment can structurally damage polyurethane and should be avoided with these catheters [108]. However mupirocin cream as opposed to ointment is preferred in polyurethane catheters since the ointment may damage the integrity of the catheter due to the alcoholic polyethylene glycol bas (though cream has a small amount of alcohol). Silicone catheters are unaffected by the ointment.

16. Mupirocin resistance: An increasing prevalence of mupirocin resistance is being reported [65, 109].Resistance to mupirocin can be classified as low if the minimal inhibitory concentration (MIC) is greater than or equal to 8 μg/mL, or high if the MIC is greater than or equal to 512 μg/mL. Prolonged usage and multiple intermittent courses of mupirocin appear to be the factors most frequently associated with the development of mupirocin resistance [110]. Resistance to mupirocin does not yet appear to have eliminated its efficacy, but this may occur eventually

17. The International Society of Peritoneal Dialysis 2005 recommendations on antibiotic protocols for preventing exit-site infections are reproduced in the following sections [35].

Antibiotic Protocol Options for Preventing Exit-Site Infections

1. Exit site mupirocin

i Daily after cleansing in all patients

ii. Daily after cleansing in carriers only

iii. In response to a positive exit-site culture for Staphylococcus aureus denoting carriage

2. Intranasal mupirocin twice per day for 5–7 days

i.Every month, once patient identified as a nasal carrier

ii.Only in response to positive nose culture

iii.Exit-site gentamicin cream daily in all patients after cleansing

18. Randomized trials in exit site prophylaxis are limited. It is difficult to recommend a specific protocol. Each programme should evaluate the organisms causing exit-site infections and institute a protocol to diminish such risk as seems appropriate for the programme.

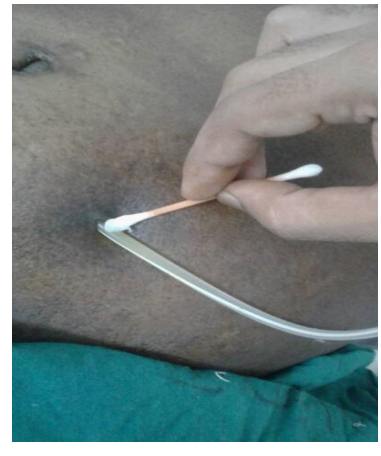

Figure 8: Application of Antibiotic Ointment over the Exit Site

Care of exit site involves

Immediate care after catheter placement (first week)

Surgical gauze dressing

Sterile dressing changes by nurse until healed

No water exposure until healed

Chronic care

Clean daily with antibacterial soap and water

Keep exit site clean and dry

Untreated well water should be avoided

Catheter should be anchored to avoid trauma

No swimming in lakes or rivers

Strict avoidance of hot tubs

Exit-site antibiotic cream/ointment

Experience at SVIMS

We conducted a cross-sectional study on 71 patients of End stage renal disease (ESRD) on chronic peritoneal dialysis (CPD) during a period of 6 months (2016) to evaluate the utility of ISPD exit site scoring system in diagnosing exit site infections and compared its scores to the well-established exit site categories outlined by Twardowski and Prowant.

The mean age was 48 years (Range: 18 – 80 years). Males were 60. Diabetics were 38; the remaining 33 patients were non diabetics ESRD patients. With regard to the performance of exchanges in CPD, 28 patients were self-care group and 48 patients were supported with care givers. Our assessment of exit site appearance based on Twardowski method is given in **Table 5**.

In ISPD exit site score, it was < 4 points in 88.7% and ≥ 4 points in 12%. The distribution of exit site scores (ISPD) and exit site categories (Twardowski) among the study population was tabulated for comparative analysis (**Table 6).**

Table 4: Exit Site Treatment and Care for Each Category of Exit Site Appearance

Equivocal infection	Acute infection	Chronic infection	Cuff infection
Evaluation	Culture and sensitivities on peri-exit smear; Gram stain	Culture and sensitivities on exudate; Gram stain	Palpation of cuff and tunnel; culture and sensitivities and Gram stain of exudate (spontaneous or after pressure on cuff); ultrasound of cuff/tunnel.
Initial therapy	Cauterize slightly exuberant granulation tissue. Topical mupirocin. Exit care daily; clean with mild disinfectant soap; do not use strong oxidants on granulation tissue; use a sterile absorbent dressing.	Cauterize slightly exuberant and exuberant granulation tissue. First-generation cephalosporin for Gram-positive organisms; quinolone for Gram-negative organisms; vancomycin for methicillin-resistant *S. aureus*. Exit care daily or b.i.d.; clean with mild disinfectant liquid soap or nonionic surfactant agent; do not use strong oxidants on granulation tissue; use a sterile, absorbent dressing.	Cauterize proud flesh. Initial antibiotic therapy based on Gram stain results.

48 h	Change to Neosporin, gentamicin, or chloramphenicol ointment if Gram-negative organisms on culture.	Adjust therapy according to culture and sensitivities.	Adjust antibiotic according to culture and sensitivities.
Follow-up	If no improvement in 2 weeks, change to systemic antibiotic based on initial culture and sensitivities. Continue therapy 7 days past achieving a good appearance.	Evaluate weekly; reculture if no improvement. Continue to treat for 7 days after achieving a good appearance.	Re-evaluate every 2 weeks; reculture monthly. If no remission: (a) consider cuff shaving; (b) consider catheter replacement. If accompanying peritonitis, remove catheter.

Table 5: Exit Site Appearance Based on Twardowski Method

Exit site appearance	Number of patients (%)
Perfect	26 (36.6%)
Good	24 (33.8%)
Equivocal	15 (21.3%)
Infection	6 (8.3%)

Table 6: Distribution of exit site scores (ISPD) and exit site categories (Twardowski)

Exit site	Perfect	Good	Equivocal	Infection	Total
0	26	-	-	-	26
1	-	18	-	-	18
2	-	06	02	-	08
3	-	-	11	-	11
≥ 4	-	-	02	06	08
Total	26	24	15	06	71

We observed 11 exit sites encountered as equivocal under Twardowski system and were recorded by ISPD exit site score system with 3 points.

Of the 15 patients who were in equivocal category, 38.4% developed peritonitis subsequently and there was catheter loss in 27.3%. Under ISPD categorization, patients with score 3, 27.2% developed peritonitis and 27.7% had catheter loss.

In addition, we observed 100% sensitivity and 100% specificity with Twardowski system and the specificity of 100%, sensitivity of 75% with ISPD system.

References

1. Li, P. K., C. C. Szeto, B. Piraino, T. Grenader, and I. Slotki, 2010: Peritoneal dialysis-related infections recommendations: 2010 update. *Perit. Dial. Int.,* **30,** 393–423.

2. Piraino, B., J. Bernardini, and M. Sorkin, 1986: The influence of peritoneal catheter exit-site infections on peritonitis, tunnel infections, and catheter loss in patients on continuous ambulatory peritoneal dialysis. *Am. J. Kid. Dis.,* **8,** 436–440.

3. Piraino, B., J. Bernardini, and M. Sorkin, 1989: Catheter infections as a factor in the transfer of continuous ambulatory peritoneal dialysis patients to hemodialysis. *Am. J. Kid. Dis.,* **13,** 365–369.

4. Gupta, B., J. Bernardini, and B. Piraino, 1996: Peritonitis associated with exit site and tunnel infections. *Am. J. Kid. Dis.,* **28,** 415–419.

5. Montenegro, J., 1999: Prevention and treatment of peritoneal catheter exit-site infection. *Nefrología,* **19,** 502–507.

6. Castro Notario, M. J., 2005: Chapter 34. In: Manual práctico de diálisis peritoneal. Badalona, Spain: SEN-SEDEN, 293–297.

7. Scalamogna, A., C. Castelnovo, A. De Vecchi, and C. Ponticelli, 1991: Exit-site and tunnel infections in continuous ambulatory peritoneal dialysis patients. *Am. J. Kid. Dis.,* **18,** 674–677.

8. Pollock, C. A., L. S. Ibels, R. J. Caterson, J. F. Mahony, D. A. Waugh, and B. Cocksedge, 1989: Continuous ambulatory PD. Eight years of experience at a single center. *Medicine*, 68, 293-308.

9. Bernardini, J., F. Bender, T. Florio, J. Sloand, L. PalmMontalbano, L. Fried, and B. Pirano, 2005: Randomized, double-blind trial of antibiotic exit site cream for prevention of exit site infection in peritoneal dialysis patients. *J. Am. Soc. Nephrol.,* **16,** 539–545.

10. McQuillan, R. F., E. Chiu, S. Nessim, C. E. Lok, J. M. Roscoe, P. Tam, and S. V. Jassal, 2012: A randomized controlled trial comparing mupirocin and polysporin triple ointments in peritoneal dialysis patients: the MP3 Study. *Clin. J. Am. Soc. Nephrol.,* **7,** 297–303.

11. Tse, K. C., S. L. Lui, V. C. Cheng, T. P. Yip, and W. K. Lo, 2007: A cluster of rapidly growing mycobacterial peritoneal dialysis catheter exit-site infections. *Am. J. Kid. Dis.,* **50,** 1–5.

12. Yap, D. Y., C. B. Choy, M. M. Mok, T. K. Wong, and T. M. Chan, 2014: Burkholderia cepacia-an uncommon cause of exit-site infection in a peritoneal dialysis patient. *Perit. Dial. Int.,* **34,** 471–472.

13. Yap, D. Y., J. F. Chan, T. Yip, M. M. Y. Mok, L. P. Y. Kwan, W. K. Lo, and T. M. Chan, 2015: Burkholderia cepacia exit-site infection in peritoneal dialysis patients-clinical characteristics and treatment outcomes. *Perit. Dial. Int.,* **36,** 390-394.

14. Vandecasteele, S. J., J. R. Boelaert, and A. S. De Vriese, 2009: Staphylococcus aureus infections in hemodialysis: what a nephrologist should know. *Clin. J. Am. Soc. Nephrol.,* **4,** 1388–1400.

15. Pihl, M., J. R. Davies, A. C. Johansson, and G. Svensater, 2013: Bacteria on catheters in patients undergoing peritoneal dialysis. *Perit. Dial. Int.,* **33,** 51–59.

16. Kazmi, H. R., F. D. Raffone, A. S. Kliger, and F. O. Finkelstein, 1992: Pseudomonas exit site infections in continuous ambulatory peritoneal dialysis patients. *J. Am. Soc. Nephrol.,* **2,** 1498–1501.

17. Szabo, T., Z. Siccion, S. Izatt, S. I. Vas, J. Bargman, and D. G. Oreopoulos, 1999: Outcome of Pseudomonas aeruginosa exit-site and tunnel infections: a single center's experience. *Adv. Perit. Dial.,* **15,** 209–212.

18. Lo, M. W., S. K. Mak, Y. Y. Wong, K. Lo, S. F. Chan, G. M. W. Tong, K. Y. Lo, C. W. S. Tse, K. Kam, and A. K. M. Wong, 2012: Atypical Mycobacterial exit-site infection and peritonitis in peritoneal dialysis patients on prophylactic exit-site gentamicin cream. *Perit. Dial. Int.,* **33,** 267-272.

19. Gonthier, D., J. Bernardini, J. L. Holley, and B. Piraino, 1992: Erythema: does it indicate infection in a peritoneal catheter exit site? *Adv. Perit. Dial.,* **8,** 230-233.

20. Ferguson, B. J., and A. H. Tzamaloukas, 1988: Exit site infections in CAPD wearing tight clothes. *ANNA J.,* **15,** 180-181.

21. Oreopoulos, D. G., G. Baird, R. Khanna, G. M. Lum, R. Mathews, K. Paulsen, Z. J. Twardowski, and S. I. Vas, 1987: Peritoneal catheter and exit-site practices: current recommendations. *Perit. Dial. Bull.,* **7,** 130-138.

22. Nolph, K. D., Z. J. Twardowski, B. F. Prowant, and R. Khanna, 1996: How to monitor and report exit/tunnel infections. *Perit. Dial. Int.,* **3,** 115-117.23. Prowant, B. F., and Z. J. Twardowski, 1996: Recommendations for exit care. *Perit. Dial. Int.,* **3,** 94-99.

24. Twardowski, Z. J., and B. F. Prowant, 1996: Classification of normal and diseased exit sites. *Perit. Dial. Int.,* **3,** 32-50.

25. Teixidó, J., N. Arias, L. Tarrats, and R. Romero, 2007: The microbial pattern of the catheter exit-site infection in peritoneal dialysis: A non-diphtheria Corynebacteria emergence? *Nefrol. Publicación Of la Soc. Española Nefrol.,* **27,** 350-358.

26. Tiexidó, J., and N. Arias, 1998: Catheter exit-site: photographic diagnostic table based on graded attributes (criteria). *Perit. Dial. Int. J. Int. Soc. Perit. Dial.,* **18,** 1-40.

27. Buxo, J. A. D., E. B. Black, and J. Tyroler, 1988: Ultrasonography in the diagnosis of peritoneal dialysis catheter tunnel abscess. *Perit. Dial. Int.,* **8,** 21828. Plum, J., S. Sudkamp, and B. Grabensee, 1994: Results of ultrasound assisted diagnosis of tunnel infections in continuous ambulatory peritoneal dialysis. *Am. J. Kid. Dis.,* **23,** 99-104.

29. Korzets, Z., A. Erdberg, E. Golan, S. Ben-Chitrit, M. Verner, V. Rathaus, and J. Bernheim, 1996: Frequent involvement of the internal cuff segment in CAPD peritonitis and exit-site infection – an ultrasound study. *Nephrol. Dial. Transplant.,* **11,** 336-339.

30. Singh, P., B. Wiggins, Y. Sun, K. S. Servilla, R. E. Last, M. F. Hartshorne, and A. H. Tzamaloukas, 2010: Imaging of peritoneal catheter tunnel infection using positron-emission tomography. *Adv. Perit. Dial.,* **26,** 96-100.

31. Gokal, R., S. Alexander, S. Ash, T. W. Chen, A. Danielson, C. Holmes, P. Joffe, J. Moncrief, K. Nichols, B. Piranio, B. Prowant, A. Slingeneyer, B. Stegmayr, Z. Twardowski, and S. Vas, 1998: Peritoneal catheters and exit-site practices toward optimum peritoneal access: 1998 update (official report from the International Society for Peritoneal Dialysis). *Perit. Dial. Int.,* **18,** 11–33.

32. Warady, B. A., F. Schaefer, M. Holloway, S. Alexander, M. Kandert, B. Piraino, I. Salusky, A. Tranaeus, J. Divino, M. Honda, S. Mujais, and E. Verrina, 2000: International Society forPeritoneal Dialysis (ISPD) Advisory Committee onPeritonitisManagement inPediatricPatients. Consensusguidelinesfor the treatment of peritonitis in pediatric patients receiving peritoneal dialysis. *Perit. Dial. Int.,* **20,** 610-624.

33. Schaefer, F., G. Klaus, D. E. Muller-Wiefel, and O. Mehls, 1999: Intermittent versus continuous intraperitoneal glycopeptide/ceftazidime treatment in children with peritoneal dialysis-associated peritonitis. The Mid-European Pediatric Peritoneal Dialysis Study Group (MEPPS). *J. Am. Soc. Nephrol.,* **10,** 136–145.

34. Piraino, B., 1996: Management of catheter related infections. *Am. J. Kid.,* **27,** 714-718.35. Piraino, B., G. R. Bailie, J. Bernardini, E. Boeschoten, A Gupta, C. Holmes, E. J. Kuijper, P. K. Li, W. C. Lye, S. Mujais, D. L. Paterson, M. P. Fontan, A. Ramos, F. Schaefer, and L. Uttley, ISPD Ad Hoc Advisory Committee. *Perit. Dial. Int.,* **25,** 107-131.

36. Gokal R, Ash SR, Helfrich GB, Holmes CJ, Joffe P, Nichols WK, Oreopoulos DG, Riella MC, Slingeneyer A, Twardowski ZJ, 1993: Peritonealcathetersandexit site practices: toward optimum peritoneal access. *Perit. Dial. Int.,* **13,** 29-39.

37. Flanigan, M. J., H. A.Hochstetler, D.Langholdt, and V. S.Lim, 1994: Continuous ambulatory peritoneal dialysis catheter infections: diagnosis and management. *Perit. Dial. Int.,* **14,** 248-254.

38. Lomaestro, B. M., and G. R. Bailie, 1995: Absorption interactions with fluoroquinolones. 1995 update. *Drug Saf.,* 12, 314-333.

39. Warady, B. A., S. Bakkaloglu, J. Newland, M. Cantwell, E. Verrina, A. Neu, V. Chadha, H. K. Yap, and F. Schaefer, 2012: Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. *Perit. Dial. Int.,* **32,** 32-86.

40. Hoshii, S., N. Wada, and M. Honda, 2006: A survey of peritonitis and exit-site and/or tunnel infections in Japanese children on PD. *Pediat. Nephrol.,* **21,** 828–823.

41. Swartz, R. D., 1999: Exit-site and catheter care: review of important issues. *Adv. Petit. Dial.,* **15,** 201-204.

42. Suh, H., N. K. Wadhwa, T. Cabralda, J. Bonanno, A. Wasiluk, and J. Sorrentol, 1997: Persistent exit- site/tunnel infection and subcutaneous cuff removal in PD patients. *Adv Petit. Dial.,* **13,** 233-236.

43. Vychytil, A., M. Lorenz, B. Schneider, W. H. Horl, and M. Haag-Weber, 1998: New criteria for management of catheter infections inperitoneal dialysis patients using ultrasonography. *J. Am. Soc. Nephrol.*, **9,** 290–296.

44. Nichols, W. K., and K. D. Nolph, 1983: A technique for managing exit site and cuff infection in Tenckhoff catheters. *Peril. Dial. Int.,* **3,** 4.

45. Andreoli, S. P., K. W. West, J. L. Grosfeld, and J. M. Bergstein, 1984: A technique to eradicate tunnel infection without peritoneal dialysis catheter removal. *Peril. Dial. Bull.,* **4,** 156.

46. Helfrich, G. B., and J. F. Winchester, 1982: What is the best technique for implantation of a peritoneal catheter? *Peril. Dial. Bull.,* **2,** 132.

47. Ishibashi, Y., H. Kume, and T. Fujita, 2011: Successful treatment of *Mycobacterium gordonae* exit-site and tunnel infection by partial catheter reimplantation of the Tenckhoff catheter. *Perit. Dial. Int.,* **31,** 368-370.

48. Cheung, A., M. Wheeler, W. Limm, L. L. Wong, F. L. Fan, and M. F. Wong, 1995: A salvage technique for CAPD catheters with exit site infections. *Am. J. Sul.,* **170,** 60-61.

49. Piraino, B., J. Bemardini, A. Peitzman, and M. Sorkin, 1987: Failure of peritoneal catheter cuff shaving to eradicate infection. *Peril. Dial. Bull.,* **7,** 179-182.

50. Swartz, R., J. Messana, J. Reynoles, and U. Ranjit, 1991: Simultaneous catheter replacement and removal in refractory PD infections. *Kid. Int.,* **40,** 1160-1165.

51. Lo, C. Y., W. L. Chu, K. M. Wan, S. Y. Ng, W. L. Lee, M. F. Chu, S. W. Cheng, and W. K. Lo, 1993: Pseudomonas exit-site infections in CAPD patients: evolution and outcomes of treatment. *Peri. Dial. Int.,* **18,** 637-653.

52. Gibel, L. J., B. J. Quintana, A. H. Tzamaloukas, and D. L. Garcia, 1989: Soft tissue complications of Tenckhoff catheters. *Adv. Perit. Dial.,* **5,** 229-233.

53. Eisele, G., G. R. Bailie, and B. Lamaestro, 1992: Relationship between peritonitis and exit site infections in CAPD. Adv. Perit. Dial., **8,** 227.

54. Fellin, G., M. G. Gentile, and L. Guerra, 1988: Exit-site infection: a randomized trial on topical *vs.* parenteral therapy. *Adv. Conti. Ambul. Perit. Dial.,* **169**.

55. Scalamogna, A., Castelnovo, A. De Vecchi, L. Guerra, and C. Ponticelli, 1990: *Staphylococcus aureus* exit site and tunnel infection in CAPD. *Adv. Perit. Dial.,* **6,** 130.

56. Tzamaloukas, A. H., M. F. Hartshome, U. Gibel, and G. H. Murata, 1993: Persistence of positive dialysate cultures after apparent cure of CAPD peritonitis. *Adv. Perit. Dial.,* **9,** 198.

57. Gokal, R., S. R. Ash, G. B. Helfrich, C. J. Holmes, P. Joffe, W. K. Nichols, D. G. Oreopoulos, M. C. Riella, A. Slingeneyer, Z. J. Twardowski, and S. Vas, 1993: Peritonealcathetersand exit site practices:toward optimum peritoneal access. *Perit. Dial. Int.,* **13,** 29-39.

58. Davies, S. J., C. S. Ogg, J. S. Cameron, S. Ponton, and W. C. Noble, 1989: *Staphylococcus aureus* nasal carriage, exit-site infection and catheter loss in patients treated with continuous ambulatory peritoneal dialysis (CAPD). *Perit. Dial. Int.,* **9,** 61.

59. Luzar, M. A., G. Coles, B. Faller, A. Slingeneyer, G. D. Dah, C. Brait, C. Wone, Y. Knefati, M. Kessler, and F. Peluso, 1990: *Staphylococcus aureus* nasal carriage and infection in patients on continuous ambulatory peritoneal dialysis. *N. Engl. J. Med.,* **322,** 505.

60. Lye, W. C., S. O. Leong, and E. J. C. Lee, 1993: Methicillin-resistant *Staphylococcus aureus* nasal carriage and infections in CAPD. *Kid. Int.,* **43,** 1357-1362.

61. Piraino, B., J. A. Perlmutter, J. L. HoUey, and J. Bemardini, 1993: *Staphylococcus aureus* peritonitis is associated with *Staphylococcus aureus* nasal carriage in peritoneal dialysis patients. *Peril. Dial. Int.,* **13,** 332.

62. Sesso, R., S. Draibe, A. Castelo, I. Sato, I. Leme, D. Barbosa, and O. Ramos, 1989: *Staphylococcus aureus* skin carriage and development of peritonitis in patients on continuous ambulatory peritoneal dialysis. *Clin. Nephron.,* **31,** 264-268.

63. Sewell, C. M., J. Clarridge, C. Lacke, E. J. Weinman, and E. J. Young, 1982: Staphylococcal nasal carriage and subsequent infection in peritoneal dialysis patients. *JAMA,* **248,** 1493-1495.

64. Selgas, R., M. J. Castro, M. A. Bajo, M.J. Femandez-Reyes, K. Lopez-Revuelta, J.R. Romero, F. de Alvaro, F. Borrego, C. Rifion, 1992: *Staphylococcus aureus* nasal carrier status (SANCS) in CAPD patients; is it induced or favored by subcutaneous rHu-Erythropoietin? *Adv. Peril. Dial.,* **8,** 253.

65. Pcrez-Fontan, M., M. Rosales, A. Rodriguez-Carmona, J. Moncalian, C. Fernandez-Rivera, M. Cao, and F. Valdes, 1992: Treatment of Staphylococcus aureus nasal carriers in CAPD with mupirocin. *Adv. Peril. Dial.,* **8,** 242-245.

66. Holley, J. L., J. Bemardini, and B. Piraino, 1991: Catheter infections in insulin-dependent diabetics on continuous ambulatory peritoneal dialysis. *Peril. Dial.,* **11,** 347.

67. Holley, J. L., J. Bemardini, and B. Piraino, 1991: Risk factors for tunnel infections in continuous peritoneal dialysis. *Am. J. Kid. Dis.,* **18,** 344.

68. Holley, J. L., J. Bemardini, and B. Piraino, 1993: A comparison of peritoneal dialysis related infections in black and white patients. *Peril. Dial. Int.,* **13,** 45.

69. Piraino, B., J. Bemardini, P. K. Centa, J. R. Johnston, and M. I. Sorkin, 1991: The effect of body weight on CAPD related infections and catheter loss. *Peril. Dial. Int.,* **64.**

70. Lindblad, A. S., R. W. Hamilton, K. D. Nolph, and J. W. Novak, 1988: A retrospective analysis of catheter configuration and cuff type: A National CAPD Registry report. *Perit. Dial. Int.,* **8,** 129–133.

71. Eklund, B., E. Honkanen, L. Kyllonen, K. Salmela, and A. R. Kala, 1997: Peritoneal dialysis access: prospective randomized comparison of single-cuff and double-cuff straight Tenckhoff catheters. *Nephrol. Dial. Transplant.*, **12,** 2664–2666.

72. Golper, T. A., M. E. Brier, M. Bunke, M. J. Schreiber, D. K. Bartlett, R. W. Hamilton, F. Strife, and R. J. Hamburger, 1996: Risk factors for peritonitis in long term peritoneal dialysis: the Network 9 Peritonitis and Catheter Survival Studies. Academic Subcommittee of the Steering Committee of the Network 9 Peritonitis and Catheter Survival Studies. *Am. J. Kid. Dis.,* **28,** 428–436.

73. Eklund, B. H., E. O. Honkanen, A. R. Kala, and L. E. Kyllonen, 1994: Catheter configuration and outcome in patients on continuous ambulatory peritoneal dialysis: a prospective comparison of two catheters. *Perit. Dial. Int.,* **14,** 70–74.

74. Eklund, B. H., E. O. Honkanen, A. R. Kala, and L. E. Kyllonen, 1995: Peritoneal dialysis access: prospective randomized comparison of the swan neck and Tenckhoff catheters. *Perit. Dial. Int.,* **15,** 353–356.

75. Lo, W. K., S. L. Lui, F. K. Li, B. Y. Choy, M. F. Lam, K. C. Tse, T. P. S. Yip, F. S. K. Ng, S. C. Lam, W. L. Chu, and S. W. Cheng, 2003: A prospective randomized study on three different peritoneal dialysis catheters. *Perit. Dial. Int.,* **23,** 127–131.

76. Strippoli, G. F. M., A. Tong, D. Johnson, F. P. Schena, and J. C. Craig, 2004: Catheter-related interventions to prevent peritonitis in peritoneal dialysis: a systematic review of randomized controlled trials. *J. Am. Soc. Nephrol.,* **15,** 2735–2746.

77. Luzar, M. A., C. B. Brown, D. Balf, L. Hill, B. Issad, B. Monnier, J. Molart, J. C. Sabatier, J. P. Wauquier, and F. Peluso, 1990: Exit-site care and exit-site infection in continuous ambulatory peritoneal dialysis (CAPD): results of a randomized multicenter trial. *Perit. Dial. Int.,* **10,** 25–29.

78. Jindal, K. K., and D. J. Hirsch, 1994: Excellent technique survival on home peritoneal dialysis: results of a regional program. *Perit. Dial. Int.,* **14,** 324-326.

79. Prowant, B. F., L. M. Schmidt, Z. J. Twardowski, C. K. Griebel, L. K. Burrows, L. P. Ryan, and R. J. Satalowich, 1988: Peritoneal dialysis catheter exit site care. *ANNA J.,* **15,** 219–223.

80. Grosman, M. D., V. M. Mosquera, M. G. Hernandez, S. Agostini, M. Adragna, and E. T. Sojo, 2005: 3% Amuchina is as effective as the 50% concentration in the prevention of exit site infection in children on chronic peritoneal dialysis. *Adv. Perit. Dial.,* **21,** 148–150.

81. Wadhwa, N., and G. Reddy, 2007: Exit-site care in peritoneal dialysis. *Contrib. Nephrol.,* **154,** 117–124.

82. Twardowski, Z. J., 1992: Peritoneal dialysis catheter exit site infections: prevention, diagnosis, treatment, and future directions. *Semin. Dial.,* **5,** 305-315.

83. Khanna, R., and Z. J. Twardowski, 1988: Peritoneal catheter exit site. *Perit. Dial. Int.,* **8,** 119-123.

84. Twardowski, Z. J., B. F. Prowant, B. Pickett, W. K. Nichols, K. D. Nolph, and R. Khanna, 1996: Four-year experience with swan neck presternal peritoneal dialysis catheter. *Am. J. Kid. Dis.,* **27,** 99-105.

85. Twardowski, Z. J., W. K. Nichols, K. D. Nolph, and R. Khanna, 1992: Swan neck presternal (‘‘bath tub’’) catheter for peritoneal dialysis. *Adv. Perit. Dial.,* **8,** 316–324.

86. Gupta, B., J. Bernardini, and B. Piraino, 1996: Peritonitis associated with exit site and tunnel infections. *Am. J. Kid. Dis.,* **28,** 415–419.

87. Bunke, M., M. E. Brier, and T. A. Golper, 1995: Pseudomonas peritonitis in peritoneal dialysis patients: the Network #9 Peritonitis Study. *Am. J. Kid. Dis.,* **25,** 769–774.

88. Piraino, B., J. Bernardini, and M. Sorkin, 1986: The influence of peritoneal catheter exit-site infections on peritonitis, tunnel infections, and catheter loss in patients on continuous ambulatory peritoneal dialysis. *Am. J. Kid. Dis.,* **8,** 436–440.

89. Mujais, S., 2006: Microbiology and outcomes of peritonitis in North America. *Kid. Int.,* **70,** 55–62.

90. Bernardini, J., B. Piraino, J. Holley, J. R. Johnston, and R. Lutes, 1996: A randomized trial of *Staphylococcus aureus* prophylaxis in peritoneal dialysis patients: mupirocin calcium ointment 2% applied to the exit site versus cyclic oral rifampin. *Am. J. Kid. Dis.,* **27,** 695–700.

91. Zeybel, M., A. Ozder, C. Sanlidag, S. Yildiz, C. Cavdar, R. Ersoy, A. Celik, and T. Camsar, 2003: The effects of weekly mupirocin application on infections in continuous ambulatory peritoneal dialysis patients. *Adv. Perit. Dial.,* **19,** 198–201.

92. Bernardini, J., F. Bender, T. Florio, J. Sloand, L. PalmMontalbano, L. Fried, and B. Piraino, 2005: Randomized, double-blind trial of antibiotic exit site cream for prevention of exit site infection in peritoneal dialysis patients. *J. Am. Soc. Nephrol.,* **16,** 539–545.

93. Montenegro, J., R. Saracho, R. Aguirre, I. Martinez, I. Iribar, and J. Ocharan, 2000: Exit-site care with ciprofloxacin otologic solution prevents polyurethane catheter infection in peritoneal dialysis patients. *Perit. Dial. Int.,* **20,** 209–214.

94. B. Piraino, J. Bernardini, T. Florio, and L. Fried, 2003: *Staphylococcus aureus* prophylaxis and trends in gram-negative infections in peritoneal dialysis patients. *Perit. Dial. Int.,* **23,** 456–459.

95. Campbell, D. J., D. W. Johnson, D. W. Mudge, M. P. Gallagher, and J. C. Craig, 2015: Prevention of peritoneal dialysis-related infections. *Nephrol. Dial. Transplant.,* **30,** 1461–1472.

96. Bernardini, J., F. Bender, T. Florio, J. Sloand, L. PalmMontalbano, L. Fried, and B. Piraino, 2005: Randomized, double-blind trial of antibiotic exit site cream for prevention of exit site infection in peritoneal dialysis patients. *J. Am. Soc. Nephrol.,* **16,** 539–545.

97. Johnson, D. W., C. van Eps, D. W. Mudge, K. J. Wiggins, K. Armstrong, C. M. Hawley, S. B. Campbell, N. M. Isabel, G. R. Nimmi, and H. Gibbs, 2005: Randomized, controlled trial of topical exit-site application of honey (Medihoney)

versus mupirocin for the prevention of catheter-associated infections in hemodialysis patients. *J. Am. Soc. Nephrol.,* **16,** 1456–1462.

98. Johnson, D. W., S. V. Badve, E. M. Pascoe, E. Beller, A. Cass, C. Clark, J. de Zoysa, 2014: Antibacterial honey for the prevention of peritoneal-dialysis-related infections (HONEYPOT): a randomised trial. *Lancet Infect. Dis.,* **14,** 23–30.

99. McQuillan, R. F., E. Chiu, S. Nessim, C. E. Lok, J. M. Roscoe, P. Tam, and S. V. Jassal, 2012: A randomized controlled trial comparing mupirocin and polysporin triple ointments in peritoneal dialysis patients: the MP3 Study. *Clin. J. Am. Soc. Nephrol.,* **7,** 297–303.

100. Nunez-Moral, M., E. Sanchez-Alvarez, I. Gonzalez-Diaz, B. Peláez-Requejo, A. Fernández-Viña, A. Quintana-Fernández,and C. Rodríguez-Suárez, 2014: Exit-site infection of peritoneal catheter is reduced by the use of polyhexanide. Results of a prospective randomized trial. *Perit. Dial. Int.,* **34,** 271–277.

101. Nouwen, J., J. Schouten, P. Schneebergen, S. Snijders, J. Maaskant, M. Koolen, A. ven Balkum, H. A. Verbrugh, 2006: *Staphylococcus aureus* carriage patterns and the risk of infections associated with continuous peritoneal dialysis. J. Clin. Microbiol. **44,** 2233–2236.

102. 1996: Nasal mupirocin prevents Staphylococcus aureus exit-site infection during peritoneal dialysis. Mupirocin Study Group. *J. Am. Soc. Nephrol.,* **7,** 2403–2408.

103. Crabtree, J. H., L. L. Hadnott, R. J. Burchette, and R. A. Siddiqi, 2000: Outcome and clinical implications of a surveillance and treatment program for *Staphylococcus aureus* nasal carriage in peritoneal dialysis patients. *Adv. Perit. Dial.,* **16,** 271–275.

104. Strippoli, G. F., A. Tong, D. Johnson, F. P. Schena, and J. C. Craig, 2004: Antimicrobial agents to prevent peritonitis in peritoneal dialysis: a systematic review of randomized controlled trials. *Am. J. Kid. Dis.,* **44,** 591–603.

105. Amato, D., M. V. de Jesus, G. Miranda, B. Leanos, G. Alcantara, M. E. Hurtado, and R. Paniagua, 2001: Staphylococcal peritonitis in continuous ambulatory peritoneal dialysis: colonization with identical strains at exit site, nose, and hands. *Am. J. Kid. Dis.,* **37,** 43–48.

106. Tacconelli, E., Y. Carmeli, A. Aizer, G. Ferriera, M. G. Foreman, and E. M. C. D'Agata, 2003: Mupirocin prophylaxis to prevent *Staphylococcus aureus* infection in patients undergoing dialysis: a meta-analysis. *Clin. Infect. Dis.,* **37,** 1629–1638.

107. Xu, G., W. Tu, and C. Xu, 2010: Mupirocin for preventing exit-site infection and peritonitis in patients undergoing peritoneal dialysis. *Nephrol. Dial. Transplant.,* **25,** 587–592.

108. Rao, S. P., and D. G. Oreopoulos, 1997: Unusual complications of a polyurethane PD catheter. *Perit. Dial. Int.,* **17,** 410–412.

109. Annigeri, R., J. Conly, S. Vas, H. Dedier, K. P. Prakashan,J. M. Bargman,V. Jassal,and D. Oreopoulos, 2001: Emergence of mupirocin-resistant Staphylococcus aureus in chronic peritoneal dialysis patients using mupirocin prophylaxis to prevent exit-site infection. *Perit. Dial. Int.,* **21,** 554–559.

110. Conly, J. M., and S. Vas, 2002: Increasing mupirocin resistance of Staphylococcus aureus in CAPD–should it continue to be used as prophylaxis? *Perit. Dial. Int.,* **22,** 649–652.

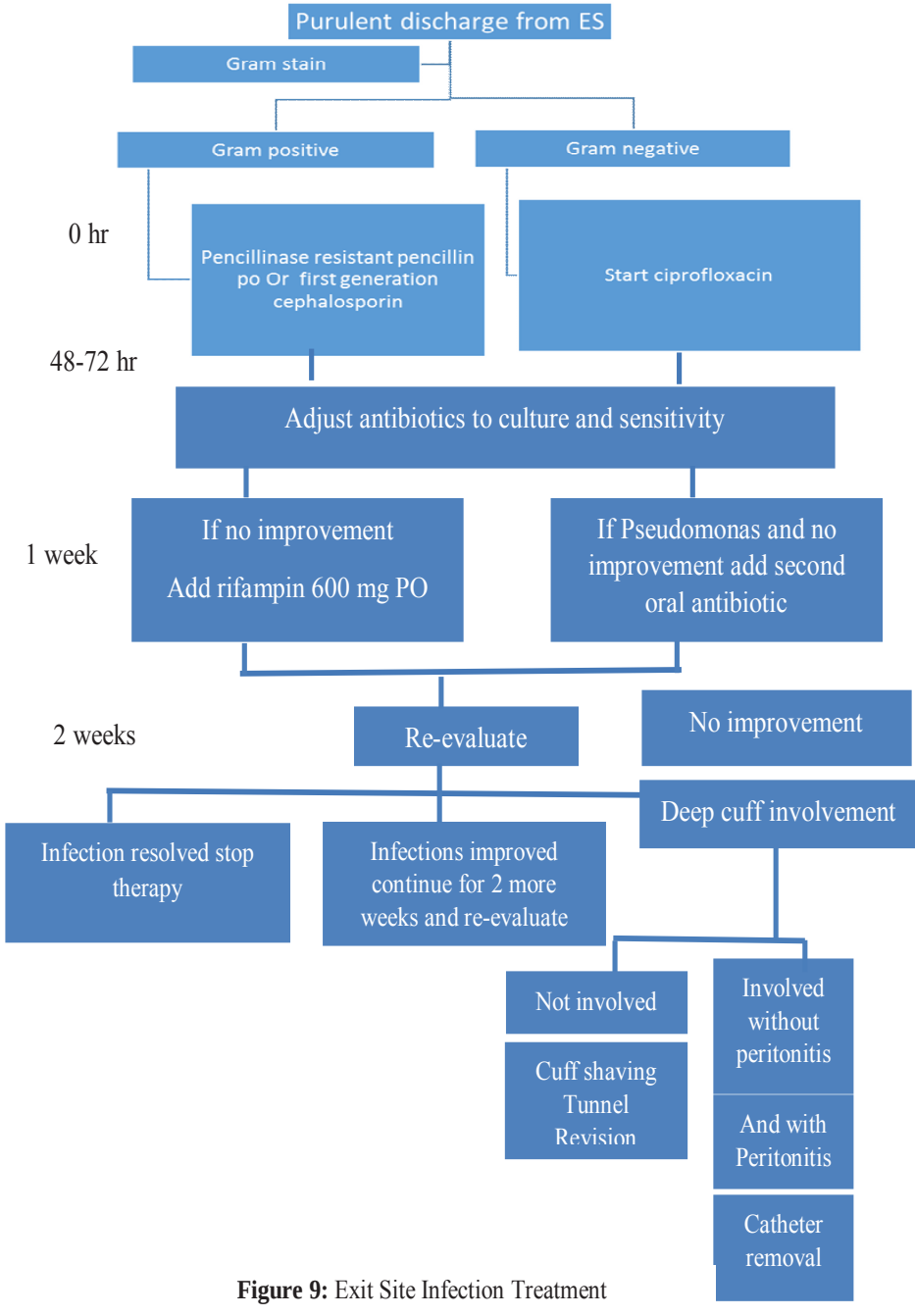

Figure 9: Exit Site Infection Treatment

Chapter 34

Technique Survival in Peritoneal Dialysis

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Technique Survival in Peritoneal Dialysis

Introduction

Peritoneal dialysis (PD) for patients with end stage renal disease (ESRD) has the inherent risk of failure of technique and abandonment of modality, often permanently. The understanding of what constitutes "technique failure" also in unfortunately not uniform and has led to misleading data. A commonly accepted definition is a patient's switch of modality from PD to hemodialysis (HD) for three months or more and excludes patients who die, undergo renal transplantation or recover renal function sufficiently as to stop dialysis [1]. Some reports have included the latter exceptions leading to difficulty in comparison of data [2].

Factors influencing the reported technique survival rates are following (modified from Nakamoto *et al*, 2006):

1. Differences in definition of technique survival (Including or not including death and transplantation).
2. Differences in definition of duration of shift to hemodialysis to diagnose technique failure.
3. Imbalanced allocation of patients.
4. Small sample size.
5. Differences in study design: Monocentric design versus multicentric design; Including/excluding CAPD, APD/CCPD [1].
6. Differences in underlying kidney disease Percentage of diabetics
7. Differences in patient comorbidity
8. Incomplete consideration of certain variables: Age, gender, income, race, medical insurance, therapy costs

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Technique Survival World-Wide

Table 1: Reported Technique Survival Rates worldwide (modified from [2, 11, 13, 16, 18, 43])

Country	Cases (n)	Years	Technique Survival
		Asia	
Japan [3, 4]	235	1980 - 1997	50% at 5.8 years
Japan [5]	807 (children)	1981 - 1997	91% at 3 years 83% at 5 years
Japan [6]	5931	2003	7% per year dropout
Japan [2]	139	1995 – 2004	93.6% at 1 year 96.4% at 2 years 79.1% at 3 years 68.2% at 5 years
Hong Kong [7]	270	1995 – 1998	23.1% at 5 years
Hong Kong [8]	67 (low) 105 (low-avg) 63 (high/high-avg)	2 years	73.5% at 2 years (low) 74.9% at 2 years (low-avg) 77.2% at 2 years (high/high-avg)
Hong Kong [9]	3573	1999 - 2011	31.3% at 5 years 3.1% at 10 years 0.7% at 15-20 years
Korea [10]	229	1986 - 1995	60.4% at 5 years
Korea [11]	1656	1981 - 2005	94.9% at 1 year 83.7% at 3 years 71.9% at 5 years 48.1% at 10 years
Korea [12]	7423	2001 - 2010	93.9% at 1 year 75.2% at 3 years 56.9% at 5 years 32.3% at 10 years
China [13]	339	2005 - 2009	96% at 1 year 82% at 5 years
China [14]	421	2001 - 2011	86.7% at 1 year 55.7% at 5 years 37.4% at 10 years
India [15]	309	1999 - 2004	98.6% at 1 year 93.3% at 5 years 86.6% at 10 years
India [16]	328	2005 - 2009	65.3 pt-months [95%CI 61.5-69]
India [17]	60	2002 - 2011	77% at 1 year 25% at 3 years 10% at 5 years
India [18]	245	2009 - 2013	91.2% at 1 year (diabetics)

			85.4% at 1 years (non-diabetics)
Bangladesh [19]	60	4 years	89% at 1 year
Singapore [20]	1015	2000 - 2008	88.7% at 1 year 39.8% at 5 years 15.4% at 10 years
Taiwan [21]	67	1998 - 2005	58% at 7 years
Taiwan [22]	8430	2000 - 2009	95% at 1 year 60% at 5 years
Turkey [23]	334	1992 - 1999	96.6% at 1 year 90.4% at 3 years 77.4% at 5 years
Thailand [24]	12753	2008 – 2011	92% at 1 year 85% at 2 years 80% at 3 years
Thailand [25]	906	2008 – 2011	92% at 1 year 85% at 2 years
		Europe	
The Netherlands [25]	1324 (< 45 yrs)	1994 - 1999	75% at 2 years
	1736 (45 - 64 yrs)		68% at 2 years
	989 (> 64 yrs)		60% at 2 years
The Netherlands [26]	118[20]	1993 - 1995	64% at 2 years 53% at 3 years
Denmark [27]	57	1990 - 1994	92% at 1 year 81% at 3 years
Belgium [28]	200	1979 – 1994	35.4% at 4 years
Italy [29]	1990	10 years	62% at 4 years 48% at 8 years
Italy [30]	578	1981 – 1993	81% at 3 years 72% at 5 years
Switzerland [31]	50	1982 - 2002	40% at 3 years 20% at 5 years
Europe (EAPOS) [32]	177 (APD)	1999 – 2000	62% at 2 years
		North America	
USA [33]	171	1979-1989	62% at 5 years 40% at 10 years
USA [34]	32135	1991 – 2001	18.65-20.51 – 1st yr dropout rate 16.51-17.58 – 2nd yr dropout rate 16.09 – 3rd yr dropout rate
Canada [35]	7110	1981 – 1997	15.4% dropout rate (Avg)
Canada [36]	155	1987 – 1990	86% at 3 years

Canada [37]	224	1987 – 1991	93% at 1 year 72% at 3 years 44% at 5 years
Canada [38]	895	1983 – 1993	91% at 1 year 73% at 3 years 61% at 5 years
Canada [39]	327	1978 – 1992	79.6% at 1 year 60.2% at 3 years 41.8% at 5 years
South America			
Mexico [40]	627	1985 – 1997	82% at 1 year 61% at 3 years 40% at 5 years 18% at 10 years
Brazil [41]	680	1980 – 2005	85% at 1 year 61% at 3 years 44% at 5 years
Oceania			
Australia [42]	5515	2007 – 2011	85% at 1 year 54.5% at 3 years 36.5% at 5 years
New Zealand [42]	1756	2007 – 2011	91% at 1 year 66.5% at 3 years 44.5% at 5 years

Technique survival is less in patients on PD as compared with patients on HD [43, 44]. World over, HD is the default renal replacement therapy (RRT) modality, especially in the absence of an official "PD first policy". At least three times the number of patients switch from PD to HD than *vice versa*, affecting prevalence of PD further [25, 45]. It is interesting that when technique survival between modalities were compared, in the Cox proportional hazard analysis, PD had a hazard ratio (HR) 10.78 [1.87-62.00]. Other factors including age, gender, body mass index, hemoglobin, albumin, residual renal function, subjective global assessment (SGA) score, comorbidities, etc. did not influence technique survival [46].PD technique survival varies greatly in different centres across the world (**Table 2**).The technique survival rates may not be directly comparable as they include differing populations in terms of race, age, underlying kidney disease, comorbidities, socio-economic status, nutrition and time [22]. Some of these will be looked at separately.

Causes of Technique Failure

The most commonly reported cause of technique failure is peritonitis (over 60% in many studies) which may be responsible for nearly two-thirds of shift to HD [20, 25, 46, 47, 50]. However, multiple other factors may play an added role, *i.e.*, age, diabetes, cardiovascular disease, *etc*. These will be discussed subsequently.

The Y-system, flush before fill technique, increased use of cyclers all play a role in reducing peritonitis rate and improving technique survival [25, 48]. Other causes of technique failure include catheter related infections, ultrafiltration insufficiency, inadequate dialysis, leak and other mechanical complications, compliance to therapy, abdominal surgeries, pancreatitis/malnutrition, cognitive challenges, and abdominal wall defects 20, 47-50]. In Japan, loss of ultrafiltration is the most common cause of technique failure and in a Chinese study, inadequate dialysis was the leading cause. In both these reports too, peritonitis was a close second [2, 4, 5, 14].

Patients' choice also plays a not-insignificant part in technique failure. Patients who choose PD have better compliance to therapy and better technique survival than those who are assigned the therapy [51, 52]. Patients who were forced to do PD due to vascular access problems also were more likely to have technique failure [53]. Technique failure due to social reasons has unfortunately not been reported in most studies but may be vitally important [20]. They are the most common causes cited for technique failure in the Australia and New Zealand Dialysis and Transplantation (ANZDATA) registry [54]. Requirement of abdominal surgery also leads to a temporary halt in PD and may result in a permanent dropout [46].

Other factors affecting technique survival

Diabetes Mellitus / underlying kidney disease / comorbidities / nutrition

Technique survival was significantly lower in patients with diabetic kidney disease and amyloidosis than those with chronic glomerulonephritis [20, 52]. More than three-fourths of the diabetic ESRD were also more likely to have more than one comorbidity and more technique failure on social grounds [20]. Poor glycemic control may be the culprit rather than diabetes *per se* [55, 56]. The risk of technique failure in diabetics increases with time from a RR of 1.8 [95% CI 1.1 – 3] during the first year to 2.2 [95% CI 1.3 – 4] after the second year [57].

A study from Lucknow showed equal technique survival in diabetics and non-diabetics while the study from Vellore reported more mechanical problems in non-diabetics - poor outflow - 4.5% in diabetics and 14.2% in non-diabetics ($p = 0.009$), catheter migration – 1.5% in diabetics and 9.78% in non-diabetics ($p = 0.004$), and primary catheter non-function – 5.3% in diabetics and 15% in non-diabetics ($p = 0.01$) [18, 58].

A Korean study found that diabetics with malnutrition were at highest risk for technique failure. Lean body mass, serum albumin and SGA have positive associations with technique survival [46]. Hypoalbuminemia has a negative effect on technique survival [52, 59]. Increase in lean body mass reduces the HR for technique failure in PD [60]. In the CANUSA study, serum albumin correlated with technique failure but not the other nutritional indicators (normalized protein catabolic rate, SGA score and lean body mass) [60]. Using the Cox proportionate hazard model to ascertain risk of technique failure, only a high BMI was a risk factor in a Korean study with HR 1.34 (95% CI 1.02 to 1.77, p = 0.036). Each 1kg/m^2 increase in BMI translated into 1.3-fold increase in risk of technique failure [46]. Interestingly in patients with BMI < 22.8kg/m^2, there was no difference in technique survival between HD and PD [46]. Data from a study comparing Canadian and Chinese populationsalso showed high BMI to be associated with technique failure but an Indian study did not [16, 62].

Elderly

While it has been clearly seen that age affects patient survival, its effect on technique survival is debated. A study from Spain and one from France showed decreased technique survival with increasing age [63, 64]. Some others have observed that younger patients were more likely to have technique failure and others that age did not impact technique survival [45, 65].

The RR of technique failure increases by 1.13 for every 10 years' increase in age. ($p<0.0001$) [25]. In a Dutch study, a 1-year greater age modestly increased the relative risk of technique failure (RR 1.04; 95% CI 1.003-1.06). Older women with more comorbidities were more likely to switch in the initial three months of PD [57]. This was shown in the NECOSAD study as well where older women preferred HD over PD [26].

In the elderly, usually dialysis is the only RRT modality available. Hence, the choice of therapy must be made after carefully considering both medical and social factors [66]. There are a few differences in medical outcomes between elderly and younger PD patients, *i.e.,* peritonitis and catheter related infections and mechanical complications [66, 67]. They are at a higher risk of malnutrition and need nutritional counselling [66]. Amino-acid-based dialysis solutions may be tried [68]. Surprisingly perhaps, quality of life also may be better in the elderly with similar social functioning and mental health despite poorer physical function [69, 70]. Aging affects their independence which compounded with anxiety, depression, dementia, visual and cognitive impairment make them often unable to perform PD by themselves making nephrologists reluctant to offer them PD [71]. Offering assistance with home-care nurses and / or family members may obviate this hinderance [66]. In the elderly whose fragility mandated that continuous ambulatory PD (CAPD) or automated PD (APD) be performed by trained home-care nurses, the costs incurred were lower than doing in-centre HD [72].

About 45% of France's new patients on PD are on assisted PD [73]. Similarly, in India, just over half do their own PD exchanges [15]. In the well-established PD centres, age may not hinder reasonable technique survival. A report from Toronto reports technique survival of 91.5% at 12 months and 81.4% at 30 months in octogenarians [66]. The long-term usefulness of assisted PD has also been shown in a recent 10-year follow up study [74]. The home-care nurse can help in treating medical complications including peritonitis, substantially reducing hospitalizations [75].

Effect of Treating Centre

Technique survival varies greatly between centres. Data from the Netherlands' comprehensive dialysis registry RENINE, showed that technique failure was, not surprisingly, related to the number of patients on PD in a centre ($r=-0.396$, $p=0.009$) and the percentage of patients with ESRD on PD ($r=-0.410$, $p=0.006$) [25]. On Cox regression analysis, centre size (< 20 patients) was significantly associated with technique failure [25]. (**Table 2**) Similar results were obtained from studies from the USA and Canada [35, 65]. The more experienced the centre is with treating patients on PD, the better the likelihood of technique survival.

Table 2: Cox Multiple Regression Analysis of PD Technique Failure (Modified from Huisman, 2002)

Variables	p	Relative Risk
< 20 patients	p< 0.0001	1.68
PD start in 1994 – 1996	p = 0.0013	1.22
Age (per 10 years)	p< 0.0001	1.13
Sex (male)	not significant	
Diabetes	not significant	

The percentage of patients with ESRD on PD in a centre is mostly influenced by the attitude of physicians and nurses to PD in general. Improved technique survival is centres with a larger percentage of patients with ESRD on PD suggests that opportunity for experience combined with positive attitude is recipe for improving technique survival and may be more important than patient selection criteria [25]. In this Dutch study, there was an increase in the technique survival with time with the 1994 – 1996 cohort having worse technique failure than the later 1997 –1999 cohort (**Table 2**) [25]. The effect of increasing age in this cohort has already been alluded to (See above).

Time Period

Technique survival seems to have improved with time. In a large single centre Korean study that looked at over 25 years' data, technique survival was significantly better in those who start after 1992 compared to those before [76]. The time-dependent improvement in technique survival is not universal. In a recent study from Portugal, despite increased PD utilisation and patient survival, technique survival did not improve over a 20 year period [77]. A study on over 13000 incident patients from Canada over 15 years (1995 to 2009) showed that while technique survival due to peritonitis did not change, technique survival due to inadequate dialysis did improve. Although, it may be imagined to be a result of increasing use of newer PD solutions including Icodextrin and APD, a closer look suggests that it may be merely a reflection in change of guidelines causing us to accept lower targets of adequacy [78]. Whereas the effect of era of PD initiation on risk of technique failure among elderly patients has not been well studied, a recent study fromthe ANZDATA registry reported superior technique survival among patients on PD older than 65 years [79]. But this finding has not been consistently reported. The reason for better technique survival in older patients in recent years is not clear. The benefit was not in reduced peritonitis or adequacy of PD but rather due to other causes of technique failure and may find its answer in increasing home-assisted PD for the elderly [80]. This improvement in PD technique survival in older patients is heartening when we realize that the largest growth in the ESRD population over time is in the ≥65 yrs age group [78, 81].

Follow-up Period

The period that is most critical for technique survival is the first three or perhaps six months after initiation of dialysis as being most vulnerable for dropouts [34, 57]. About 33% to 40% of dropouts are likely to occur in the first three months reducing to about 25% after 2 years [57, 82]. Kolinsky *et al*, analysed the cause of dropout at specific time points, *i.e.*, 0 to 3 months, 3 to 12 months, 12 to 24 months and 24 to 36 months. In the initial three months, psychosocial problems led to the highest dropout rate (52 per 1000 patient-years). Catheter failure related dropout rate was highest in the initial three months (40 per 1000 patient-years) which dropped off rapidly thereafter. Infection related dropouts were high throughout the follow-up period with the highest rate in the second year (57 per 1000 patient-years). Underdialysis and ultrafiltration failure (UFF) causing dropouts increased with time from the second year onwards 14 per 1000 patient-years in the second year and 25 per 1000 patient-years in the third. (**Table 3**) The psychosocial causes of technique failure are perhaps a reflection of improper patient selection [57].

In **Table 4**, the multivariate analysis for probability of PD technique survival showed that age was an important factor irrespective of time on therapy. The risk of technique failure due to diabetes mellitus increased with time. Cardiovascular disease's major effect was seen in the initial three months though the effect persisted throughout follow up.

Table 3 - Incidence rates of each reason for dropout during each period of follow-up

(Rates with 95% CI per 1000 Patient-years) (Modified from Kolesnyk *et al*)

Time	**0 to 3 months**	**3 to 12 months**	**12 to 24 months**	**24 to 36 months**
Patients (n)	709	649	515	327
Rate of infections	35 (13-76)	45 (28-70)	57 (36-85)	36 (18-67)
Rate of catheter failures	40 (16-83)	18 (7-36)	7 (1-20)	3 (0-20)
Rate of psychosocial / unknown	52 (24-99)	18 (7-36)	35 (20-59)	29 (13-58)
Rate of underdialysis / UFF*	5 (0-32)	5 (0-16)	14 (5-31)	25 (10-53)
Rate of abdominal problems	17 (6-51)	14 (5-30)	7 (1-20)	7 (0-26)

*UFF – ultrafiltration failure

Residual Renal Function (RRF)

The loss of as small a value as 1 ml/min RRF predicts technique failure; RR 1.1 (95% 1.04 – 1.25). As seen in **Table 4**, RRF's impact on technique failure was important in the initial three months and continued to be important throughout follow up [57].

Table 4: Multivariate cox proportional hazard model for PD technique survival (modified from Kolesnyk *et al*)

Factor	**0 to 3 months RR (95% CI)**	**3 to 12 months RR (95% CI)**	**12 to 24 months RR (95% CI)**	**24 to 36 months RR (95% CI)**
Age (per 1 year)	1.04 (1.0-1.06)	1.04 (1.02-1.05)	1.03 (1.01-1.04)	1.04 (1.02-1.06)
Gender Diabetes	0.82 (0.3-1.9)	1.8 (1.1-3.0)	1.7 (1.1-2.7)	2.2 (1.3-4.0)
Age (per 1 year) Gender Cardiovascular disease	2.5 (1.2-5.2)	2.0 (1.1-3.0)	2.0 (1.2-3.1)	2.0 (1.1-3.5)
Age (per 1 year) Gender rGFR* (per 1ml/min)	0.93 (0.9-1.2)	1.1 (1.04-1.25)	1.1 (1.01-1.25)	0.97 (0.86-1.1)
Age (per 1 year) Gender Diabetes Cardiovascular disease				

* rGFR – residual glomerular filtration rate

Continuous Ambulatory Peritoneal Dialysis (CAPD) vs Automated Peritoneal Dialysis (APD)

Most published studies suggest that there was no difference between APD and CAPD for risk of technique failure and no change in risk at varying time points on follow up [57]. However, a Taiwanese study suggested that in those younger than 65 years of age, APD was associated with better patient survival and technique survival compared to CAPD, (HR 0.35, 95% CI 0.28-0.95, p=0.034) [83].

Catheter Placement Technique

The blind percutaneous technique of PD catheter insertions is a reliable and safe technique. The ultra-short break in periodof 2.68 (± 2.6) days is suggested as the new standard break in period [18]. The mechanical and infectious complications and technique survival is similar with both the blind percutaneous technique as well as surgical catheter insertion [84].

Failed Allografts

The PD technique failure rates were comparable in patients who switch in both those on PD after a failed allograft and in new patients with ESRD initiated on PD. The high technique survival in those with failed allografts suggests that PD is an excellent modality, and perhaps merits more allograft failure patients to be initiated on PD than is currently practiced [85].

Newer PD Solutions

The usefulness of Icodextrin to improving PD technique survival has been reported from several countries (including India) [17, 86-89]. When Icodextrin was given to diabetics for two years in a randomised controlled trial, it resulted in improved technique survival (71.4%) compared to those on conventional glucose solutions (45%) [87]. In the European Automated Peritoneal Dialysis Outcome Study (EAPOS), there was no decline in ultrafiltration capacity over two years in the group receiving Icodextrin despite worse membrane function at start of therapy [89]. Unlike Icodextrin, the newer biocompatible PD fluids did not have the same advantage of beneficial technique survival [90, 91].

Where Do We Go from Here?

Technique failure increases hospitalisation by about nine days per year, over $7000 in inpatient costs, and increases mortality [92, 93, 94]. It is therefore imperative that maximum attempt is made to improve technique survival. Since, both HD and PD have similar survival, any improvement in PD technique survival is expected to translate into increased number of patients on PD. While most of the efforts are naturally concentrated on increasing PD utilization, it is time we focused on the effect of time on therapy, costs involved in switch to HD and the long-term effects of the change in modality on patient outcomes. If the increasing PD utilization is

offset by a higher rate of technique failure, there would be little or no effect on increasing PD utilization [78].

While age and diabetes status are obviously non-modifiable, the modifiable factors must be attended to [95]. PD centres must aim to have a minimum of 30 patients on PD in order to developand sustain experitise. This number should ideally comprise at least 20% of patients with ESRD on follow up while remembering that having > 40% of patients with ESRD on PD may not increase technique survival further [25]. A higher nurse patient ratio is advantageous in lowering rates of peritonitis and technique survival [96]. Prevention of peritonitis and catheter related infections, adequate nutrition to prevent hypoalbuminemia and optimum use of Icodextrin are some of the methods that can be adopted to increase technique survival. The incorporation of home-visits by nurses and the assisted PD in the elderly are other useful interventions. The role of a highly dedicated PD team in the continued quality improvement of PD is the backbone of improving PD technique survival. It may be justifiably hoped that the hard work of the expert PD team will pay off and result in improved technique survival, and possibly, patient survival also, in the future [97].

Conclusion

Technique survival in PD is a challenging situation in the care of the patients on PD. The causes and risk factors are varied and several of them are amenable to intervention. It is hoped that the concerted efforts of all who practice PD regularly will result in prolonging the ulilization of the modality.

References

1. Blake, P. G., 2000: Trends in patient and technique survival in peritoneal dialysis and strategies: how are we doing and how can we do better? *Adv. Ren. Replace. Ther.,* **7,** 324-337.
2. Nakamoto, H., Y. Kawaguchi, and H. Suzuki, 2006: Is technique survival on peritoneal dialysis better in Japan? *Perit. Dial. Int.,* **26,** 136-143.
3. Kawaguchi, Y., T. Hasegawa, M. Nakayama, H. Kubo, and T. Shigematsu, 1997: Issues affecting the longevity of the continuous peritoneal dialysis therapy. *Kid. Int. Suppl.,* **62,** 105–107.
4. Kawaguchi, Y., 1999: National comparisons: optimal peritoneal dialysis outcomes among Japanese patients. *Perit. Dial. Int.,* **19,** 9–16.
5. Honda, M., 1999: The 1997 reports of the Japanese National Registry data on pediatric peritoneal dialysis patients. *Perit. Dial. Int.,* **19,** 473–478.
6. Kawaguchi, Y., T. Ishizaki, A. Imada, S. Oohira, S. Kuriyama, H. Nakamoto, M. Nakamoto, M. Hiramatu, K. Maeda, and K. Ota, 2003: Study Group for Withdrawal from PD in Japan. Searching for the reasons for drop-out from peritoneal dialysis: a nationwide survey in Japan. *Perit. Dial. Int.,* **23,** 175–177.
7. Szeto, C. C., T. Y. Wong, K. Chow, C. Leung, M. Law, and P. K. Li, 2004: Independent effects of renal and peritoneal clearances on the mortality of peritoneal dialysis patients. *Perit. Dial. Int.,* **24,** 58–63.
8. Szeto, C. C., T. Y. Wong, C. Leung, A. Y. Wang, M. Law, Lui S, and P. K. Li, 2000: Importance of dialysis in mortality and morbidity of Chinese CAPD patients. *Kid. Int.,* **58,** 400–407.
9. Ho, Y. W., K. F. Chau, B. Y. Choy, K. S. Fung, Y. L. Cheng, T. H. Kwan, P. N. Wong, W. M. Lai, S. K. Yuen, S. H. Lo, and C. K. Chan, 2013: Hong Kong renal registry report 2012. *Hong Kong J. Nephrol.,* **15,** 28–43.
10. Choi, S. R., S. C. Lee, B. S. Kim, S. Y. Yoon, H. C. Park, S. W. Kang, K. H. Choi, Y. S. Kim, S. K. Ha, K. Park, and D. S. Han, 2003: Comparative study of renal replacement therapy in Korea diabetic end-stage renal disease patients: a single center study. *Yonsei Med. J.,* **44,** 454–462.
11. Han, S. H., J. E. Lee, D. K. Kim, S. J. Moon, H. W. Kim, J. H. Chang, B. S. Kim, S. W. Kang, K. H. Choi, H. Y. Lee, and D. S. Han, 2008: Long-term clinical outcomes of peritoneal dialysis patients: single center experience from Korea. *Perit. Dial. Int.,* **28,** 21-26.
12. Jin, D. C., I. S. Ha, N. H. Kim, S. W. Lee, J. S. Lee, S. R. Yoon, and B. S. Kim, 2012: Brief report: renal replacement therapy in Korea, 2010. *Kid. Res. Clin. Prac.,* **31,** 62–71.
13. Fang, W., Z. Ni, and J. Qian, 2014: Key Factors for a High-Quality Peritoneal Dialysis Program — The Role of the PD Team and Continuous Quality Improvement. *Perit. Dial. Int.,* **34,** 35–42.
14. Zhang, F., H. Liu, X. Gong, F. Liu, Y. Peng, M. Cheng, and C. Guo, 2015: Risk factors for mortality in Chinese patients on continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **35,** 199–205.

15. Abraham, G., V. Kumar, K. S. Nayak, R. Ravichandran, G. Srinivasan, M. Krishnamurthy, A. K. Prasath, S. Kumar, T. Thiagarajan, M. Mathew, and N. Lesley, 2010: Predictors of long-term survival on peritoneal dialysis in South India: a multicenter study. *Perit. Dial. Int.,* **30,** 29–34.
16. Prasad, N., A. Sinha, A. Gupta, R. K. Sharma, D. Bhadauria, A. Chandra, K. N. Prasad, and A. Kaul, 2014: Effect of body mass index on outcomes of peritoneal dialysis patients in India. *Perit. Dial. Int.,* **34,** 399-408.
17. Vikrant, S., 2014: Long-term clinical outcomes of peritoneal dialysis patients: 9-year experience of a single center from north India. *Perit. Dial. Int.,* **34,** 426-433.
18. George, N., S. Alexander, V. G. David, G. Basu, A. Mohapatra, A. T. Valson, S. Jacob, H. K. Pathak, A. Devasia, V. Tamilarasi, and S. Varughese, 2016: Comparison of Early Mechanical and Infective Complications in First Time Blind, Bedside, And Midline Percutaneous Tenckhoff Catheter Insertion with Ultra-Short Break-In Period in Diabetics and Non-Diabetics: Setting New Standards. *Perit. Dial. Int.,* **36,** 655-661.
19. Iqbal, M. M., M. N. Islam, H. Sattar, M. A. Samad, R. M. Hossain, S. Islam, M. R. Alam, M. H. Rahman, and H. U. Rashid, 2004: Outcome of continuous ambulatory peritoneal dialysis in a group of elderly patients from Bangladesh. *Adv. Perit. Dial.,* **20,** 101–104.
20. Choo, J. C. J., S. Y. Ong, T. Krishnasamy, and M. W. Y. Foo, 2012: The Singapore general hospital peritoneal dialysis programme from 2000 – 2008. *Proc. Singapore Healthcare,* **21,** 132-139.
21. Shiao, C. C., T. W. Kao, K. Y. Hung, Y. C. Chen, M. S. Wu, T. S. Chu, K. D. Wu, and T. J. Tsai, 2009: Seven-year follow-up of peritoneal dialysis patients in Taiwan. *Perit. Dial. Int.,* **29,** 450–457.
22. Wu, M. S., I. W. Wu, and K. H. Hsu, 2012: Survival analysis of Taiwan Renal Registry Data System (TWRDS) 2000–2009. *Acta. Nephrol.,* **26,** 104–108.
23. Utas, C., 2001: Patient and technique survival on CAPD in Turkey. *Perit. Dial. Int.,* **21,** 602–606.
24. Dhanakijcharoen, P., D. Sirivongs, S. Aruyapitipan, P. Chuengsaman, and A. Lumpaopong, 2011: The 'PD First' policy in Thailand: three-years experiences (2008–2011). *J. Med. Assoc. Thai.,* **94,** 153–161.
25. Huisman, R. M., M. G. Nieuwenhuizen, and F. Th de Charro, 2002: Patient related and center-related factors influencing technique survival of peritoneal dialysis in The Netherlands. *Nephrol. Dial. Transplant.,* **17,** 1655–1660.
26. Jager, K. J., M. P. Merkus, F. W. Dekker, E. W. Boeschoten, J. G. Tijssen, P. Stevens, W. J. Bos, and R. T. Krediet, 1999: Mortality and technique failure in patients starting chronic peritoneal dialysis: results of The Netherlands Cooperative Study on the Adequacy of Dialysis. NECOSAD Study Group. *Kid. Int.,* **55,** 1476-1485.
27. Bistrup, C., A. Holm-Nielsen, and R. S. Pederson, 1996: Technique survival and complication rates in a newly started CAPD center (five years of experience). *Perit. Dial. Int.,* **16,** 90–98.

28. Lambert, M. C., D. Vijt, R. De Smet, and N. Lameire, 1996: Patients and technique survival after treatment shifts between CAPD and haemodialysis in a single center. *EDTNA ERCA J.,* **22,** 4–7.
29. Lupo, A., R. Tarchini, G. C. Cancarini, L.Catizone, R. Cocchi, A. De Vecchi, G. Viglino, M. Salomone, G. Segoloni, and A. Giangrande, 1994: Long-term outcome in continuous ambulatory peritoneal dialysis: a 10-year survey by the Italian Cooperative Peritoneal Dialysis Study Group. *Am. J. Kid. Dis.,* **24,** 826–837.
30. Maiorca, R., G. C. Cancarini, R. Zubani, C. Camerini, L. Manili, G. Brunori, and E. Movilli, 1996: CAPD viability: a long-term comparison with hemodialysis. *Perit. Dial. Int.,* **16,** 276–287.
31. Gloor, H. F., S. Pandolfi, and S. Ruttimann, 2003: 20 years of peritoneal dialysis in a mid-sized Swiss hospital. *Swiss Med. Wkly.,* **133,** 619–624.
32. Brown, E. A., S. J. Davies, P. Rutherford, F. Meeus, M. Borras, W. Riegel, J. C. Divino Filho, E. Vonesh, and M. Van Bree, 2003: EAPOS Group. Survival of functionally anuric patients on automated peritoneal dialysis: the European APD Outcome Study. *J. Am. Soc. Nephrol.,* **14,** 2948–2957.
33. Rotellar, C., J. Black, J. F. Winchester, T. A. Rakowaski, W. F. Mosher, M. J. Mazzoni, M. Amiranzavi, V. Garagusi, M. R. Alijani, and W. P. Argy, 1991: Ten years' experience with continuous ambulatory peritoneal dialysis. *Am. J. Kid. Dis.,* **17,** 158–164.
34. Guo, A., and S. Mujais, 2003: Patient and technique survival on peritoneal dialysis in the United States: evaluation in large incident cohorts. *Kid. Int. Suppl.,* **88,** 3–12.
35. Schaubel, D. E., P. G. Blake, and S. S. A. Fenton, 2001: Trend in CAPD technique failure: Canada, 1981-1997. *Perit. Dial. Int.,* **21,** 365–371.
36. Jindai, K. K., and D. J. Hirsch, 1994: Excellent technique survival on home peritoneal dialysis: results of a regional program. *Perit. Dial. Int.,* **14,** 324–326.
37. Passadakis, P., E. Thodis, V. Vargemezis, and D. G. Oreopoulos, 2001: Longterm survival with peritoneal dialysis in ESRD due to diabetes. *Clin. Nephrol.,* **56,** 257–270.
38. Marcelli, D., D. Spotti, F. Conte, A. Tagliaferro, A. Limido, F. Lonati, F. Malberti, and F. Locatelli, 1996: Survival of diabetic patients on peritoneal dialysis or hemodialysis. *Perit. Dial. Int.,* **16,** 283–287.
39. Domrongkitchaiporn, S., M. Karim, L. Watson, and M. Moriarty, 1994: The influence of continuous ambulatory peritoneal dialysis connection technique on peritonitis rate and technique survival. *Am. J. Kid. Dis.,* **24,** 50–58.
40. Cueto-Manzano, A. M., E. Quintano-Pina, and R. Correa-Rotter, 2001: Long term CAPD survival and analysis of mortality risk factors: 12-year experience of a single Mexican center. *Perit. Dial. Int.,* **21,** 148–153.
41. Moraes, T. P., R. Pecoits-Filho, S. C. Ribeiro, M. Rigo, M. M. Silva, C. M. Teixiera, D. D. Pasqual, R. Fuerbringer, and M. C. Riella, 2009: Peritoneal dialysis in Brazil: twentyfive years of experience in a single center. *Perit. Dial. Int.,* **29,** 492–498.
42. McDonald, S., and K. Hurst, 2012: ANZDATA registry report 2012. Adelaide, South Australia. Australia and New Zealand Dialysis and Transplant Registry 2012.

43. Maiorca, R., E. Vonesh, G. C. Cancarini, A. Cantaluppi, L. Manili, G. Brunori, C. Camerini, P. Feller, and A. Strada, 1988: A six-year comparison of patient and technique survivals in CAPD and HD. *Kid. Int.,* **34,** 518–524.
44. Serkes, K. D., C. R. Blagg, K. D. Nolph, E. F. Vonesh, and F. Shapiro, 1990: Comparison of patient and technique survival in continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis: A multicenter study. *Perit. Dial. Int.,* **10,** 15–19.
45. Maiorca, R., and G. C. Cancarini, 1994: Outcome of peritoneal dialysis: comparative studies. *Textbook of Peritoneal Dialysis.* In: Gokal, R., and K. D. Nolph, Eds. Kluwer Academic Publishers, Dordrecht, 712–734.
46. Lee, J. H., S. H. Park, J. H. Lim, Y. J. Park, S. U. Kim, K. H. Lee, K. H. Kim, S. C. Park, H. Y. Jung, O. Kwon, and J. Y. Choi, 2016: Impact of dialysis modality on technique survival in end-stage renal disease patients. *Korean J. Intern. Med.,* **31,** 106-115.
47. Davies, S. J., L. Phillips, A. M. Griffiths, L. H. Russell, P. F. Narish, and G. I. Russell, 1998: What really happens to people on long-term peritoneal dialysis? *Kid. Int.,* **54,** 2207–2217.
48. Klaus, G., 2005: Prevention and treatment of peritoneal dialysis-associated peritonitis in pediatric patients. *Perit. Dial. Int.,* **25,** 117-119.
49. Jaar, B. G., L. C. Plantinga, D. C. Crews, N. E. Fink, N. Hebah, J. Coresh, A. S. Kliger, and N. R. Powe, 2009: Timing, causes, predictors and prognosis of switching from peritoneal dialysis to hemodialysis: a prospective study. *BMC Nephrol.,* **10,** 3-14.
50. Mujais, S., and K. Story, 2006: Peritoneal dialysis in the US: Evaluation of outcomes in contemporary cohorts. *Kid. Int. Suppl.,* **103,** 21–26.
51. Koc, Y., A. Unsal, T. Basturk, T. Sakaci, E. Ahbap-Dal, A. Sinangil-Arar, S. Kose-Budak, and H. Kayabasi, 2012: Is there impact of mortality prior hemodialysis therapy in peritoneal dialysis patients? *Nefrologia*, **32,** 335-342.
52. Gulcan, E., V. Kıdır, M. Keles, E. Cankaya, A. Uyanik, and F. Saatci, 2017: Factors affecting patient survival and technical survival in patients undergoing peritoneal dialysis. *Int. J. Clin. Exp. Med.,* **10,** 1004-1014.
53. Sipahioglu, M. H., A. Aybal, A. Unal, B. Tokgoz, O. Oymak, and C. Utas, 2008: Patient and technique survival and factors affecting mortality on peritoneal dialysis in Turkey: 12 years' experience in a single center. *Perit. Dial. Int.,* **28,** 238-245.
54. Brown, F., A. Gulyani, H. Dent, K. Hurst, and S. McDonald, 2011: Chapter 6 peritoneal dialysis [Internet]. North Terrace (AU): Australia & New Zealand Dialysis & Transplantation (ANZDATA), 2011 [cited 2015 Sep 20].
55. Sekercioglu, N., C. Dimitriadis, C. Pipili, R. M. Elias, J. Kim, D. G. Oreopoulos, and J. M. Bargman, 2012: Glycemic control and survival in peritoneal dialysis patients with diabetes mellitus. *Int. Urol. Nephrol.,* **44,** 1861-1869.
56. Tzamaloukas, A. H., Z. Y. Yuan, G. H. Murata, E. Balaskas, P. S. Avasthi, and D. G. Oreopoulos, 1993: Clinical associations of glycemic control in diabetics on CAPD. *Adv. Perit. Dial.,* **9,** 291-294.

57. Kolesnyk, I., F. W. Dekker, E. W. Boeschoten, and R. T. Krediet, 2010: Time-dependent reasons for peritoneal dialysis technique failure and mortality. *Perit. Dial. Int.,* **30,** 170-177.
58. Prasad, N., A. Gupta, A. Sinha, A. Singh, R. K. Sharma, A. Kumar, and A. A. Kaul, 2008: A comparison of outcomes between diabetic and nondiabetic CAPD patients in India. *Perit. Dial. Int.,* **28,** 468-476.
59. Isla, R. A., D. Mapiye, C. R. Swanepoel, N. Rozumyk, J. E. Hubahib, and I. G. Okpechi, 2014: Continuous ambulatsry peritoneal dialysis in Limpopo province, South Africa: predictors of patient and technique survival. *Perit. Dial. Int.,* **34,** 518-525.
60. Huang, J. W., Y. C. Lien, H. Y. Wu, C. J. Yen, C. C. Pan, T. W. Hung, C. T. Su, C. K. Chiang, H. T. Cheng, and K. Y. Hung, 2013: Lean body mass predicts long-term survival in Chinese patients on peritoneal dialysis. *PLoS One*, **8,** e54976.
61. Canada-USA (CANUSA) Peritoneal Dialysis Study Group, 1996: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: association with clinical outcomes. *J. Am. Soc. Nephrol.,* **7,** 198-207.
62. Fang, W., J. Qian, A. Lin, F. Rowaie, Z. Ni, Q. Yao, J. M. Bargman, and D. G. Oreopoulos, 2008: Comparison of peritoneal dialysis practice patterns and outcomes between a Canadian and a Chinese centre. *Nephrol. Dial. Transplant.,* **23,** 4021-4028.
63. Gentil, M. A., A. Carriazo, M. I. Pavon, M. Rosado, D. Castillo, B. Ramos, G. R. Algarra, F. Tejuca, V. P. Banasco, and J. A. Milan, 1991: Comparison of survival in CAPD and hospital haemodialysis: a multicentric study. *Nephrol. Dial. Tranplant.,* **6,** 444 –451.
64. Genestier, S., G. Hedelin, P. Schaffer, and B. Faller, 1995: Prognostic factors in CAPD patients: a retrospective study of a 10-year period. *Nephrol. Dial. Tranplant.,* **10,** 1905–1911.
65. Port, F. K., P. J. Held, K. D. Nolph, M. N. Turenne, and R. A. Wolfe, 1992: Risk of peritonitis and technique failure by CAPD connection technique: a national study. *Kid. Int.,* **42,** 967–974.
66. Dimkovic, N., and D. G. Oreopoulos, 2008: Assisted peritoneal dialysis as a method of choice for elderly with end-stage renal disease. *Int. Urol. Nephrol.,* **40,** 1143–1150.
67. Jagose, J. T., I. E. Afthentopoulos, A. Shetty, and D. G. Oreopoulos, Successful use of continuous ambulatory peritoneal dialysis in octogenarians. *Geriatr. Nephrol. Urol.,* **5,** 135-141.
68. Joner, M. R., T. W. Gehr, J. M. Burkart, R. J. Hamburger, A. P. Kraus, B. M. Piraino, T. Hagen, F. G. Ogrinc, and M. Wolfson, 1998: Replacement of aminoacid and protein loses with 1.1% aminoacid peritoneal dialysis solution. *Perit. Dial. Int.,* **18,** 210–216.
69. Harris, S. A., D. L. Lamping, E. A. Brown, and N. Constantinovici, 2002: Clinical outcomes and quality of life in elderly patients on peritoneal dialysis versus hemodialysis. *Perit. Dial. Int.,* **22,** 463–470.
70. Povlsen, J. V., and P. Ivarsen, 2006: Assisted automated peritoneal dialysis (AAPD) for functionally dependent and elderly patients. *Perit. Dial. Int.,* **25,** 60–64.

71. Li, J. S. C., 2004: Prevalence of cognitive impairment among elderly Chinese continuous ambulatory peritoneal dialysis patients. *Hong Kong J. Nephrol.,* **6,** 22–30.
72. Cogny-Van Weydevelt, F., K. Bacquaert-Dufour, D. Benevent, S. Lavaud, J. M. Beaud, B. Allard, P. Riberi, and R. Dandavino, 1999: A cost effectiveness analysis of continuous ambulatory peritoneal dialysis vs. self care in centre hemodialysis in France. *Dial. Transplant.,* **28,** 70–74.
73. Lobbedez, T., R. Moldovan, M. Lecame, B. H. de Ligny, W. El Haggan, and J. P. Ryckelynck, 2006: Assisted peritoneal dialysis. Experience in a French renal department. *Perit. Dial. Int.,* **26,** 671–676.
74. Querido, S., P. Q. Branco, E. Costa, S. Pereira, M. A. Gaspar, and J. D. Barata, 2015: Results in Assisted Peritoneal Dialysis: A Ten-Year Experience. *Int. J. Nephrol.,* **2015,** 712539.
75. Gokal, R., J. King, S. Bogle, F. Marsh, D. Oliver, C. Jakubowski, L. Hunt, R. Baillod, C. Ogg, M. Ward, and R. Wilkinson, 1987: Outcome in patients on CAPD and haemodialysis: 4 year analysis of a prospective multi centre study. *Lancet*, **2,** 1105–1109.
76. Han, S. H., S. C. Lee, S. V. Ahn, J. E. Lee, H. Y. Choi, B. S. Kim, S. W. Kang, K. H. Choi, D. S. Han, and H. Y. Lee, 2007: Improving outcome of CAPD: twenty-five years' experience in a single Korean center. *Perit. Dial. Int.,* **27,** 432–440.
77. Aguiar, A., L. Rodrigues, A. Borges, H. Sá, R. Alves, and M. Campos, 2016: Increased peritoneal dialysis utilization and improved patient survival over a 20-year period: data from a Portuguese Peritoneal Dialysis Unit. *Port. J. Nephrol. Hypert.,* **30,** 113- 120.
78. Perl, J., R. Wald, J. M. Bargman, Y. Na, S. V. Jassal, A. K. Jain, L. Moist, and S. J. Nessim, 2012: Changes in patient and technique survival over time among incident peritoneal dialysis patients in Canada. *Clin. J. Am. Soc. Nephrol.,* **7,** 1145-1154.
79. Lim, W. H., G. K. Dogra, S. P. McDonald, F. G. Brown, and D. W. Johnson, 2011: Compared with younger peritoneal dialysis patients, elderly patients have similar peritonitis-free survival and lower risk of technique failure, but higher risk of peritonitis-related mortality. *Perit. Dial. Int.,* **31,** 663–671.
80. Oliver, M. J., R. R. Quinn, E. P. Richardson, A. J. Kiss, D. L. Lamping, and B. J. Manns, 2007: Home care assistance and the utilization of peritoneal dialysis. *Kid. Int.,* **71,** 673–678.
81. Canadian Organ Replacement Register, 2008: CORR Preliminary Report: Preliminary Statistics for Renal Failure and Solid Organ Transplantation in Canada. Ottawa, ON, Canadian Organ Replacement Register, 2008.
82. Descoeudres, B., M. T. Koller, D. Garzoni, T. Wolff, J. Steiger, S. Schaub, and M. Mayr, 2008: Contribution of early failure to outcome on peritoneal dialysis. *Perit. Dial. Int.,* **28,** 259-267.
83. Sun, C. Y., C. C. Lee, Y. Y. Lin, and M. S. Wu, 2011: In younger dialysis patients, automated peritoneal dialysis is associated with better long-term patient and technique survival than is continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **31,** 301-307.

84. Ozener, C., A. Bihorac, and E. Akoglu, 2001: Technical survival of CAPD catheters: comparison between percutaneous and conventional surgical placement techniques. *Nephrol. Dial. Transplant.,* **16,** 1893-1899.
85. Mujais, S., and K. Story, 2006: Patient and technique survival on peritoneal dialysis in patients with failed renal allograft: a case-control study. *Kid. Int. Suppl.,* **103,** 133-137.
86. Takatori, Y., S. Akagi, H. Sugiyama, J. Inoue, S. Kojo, H. Morinaga, K. Nakao, J. Wada, and H. Makino, 2011: Icodextrin increases technique survival rate in peritoneal dialysis patients with diabetic nephropathy by improving body fluid management: a randomized controlled trial. *Clin. J. Am. Soc. Nephrol.,* **6,** 1337-1344.
87. Wang, I. K., Y. F. Li, J. H. Chen, C. C. Liang, Y. L. Liu, H. H. Lin, C. T. Chang, W. C. Tsai, T. H. Yen, and C. C. Huang, 2015: Icodextrin Decreases Technique Failure and Improves Patient Survival in Peritoneal Dialysis Patients. *Nephrol.,* **20,** 161-167.
88. Han, S. H., S. V. Ahn, J. Y. Yun, A. Tranaeus, and D. S. Han, 2012: Effects of icodextrin on patient survival and technique success in patients undergoing peritoneal dialysis. *Nephrol. Dial. Transplant.,* **27,** 2044-2050.
89. Davies, S. J., E. A. Brown, N. E. Frandsen, A. S. Rodrigues, A. Rodriguez-Carmona, A. Vychytil, E. Macnamara, A. Ekstrand, A. Tranaeus, and J. C. Divino Filho, 2005: Longitudinal membrane function in functionally anuric patients treated with APD: data from EAPOS on the effects of glucose and icodextrin prescription. *Kid. Int.,* **67,** 1609-1615.
90. Ke, C. L., Y. P. Hsieh, and Y. Yang, 2013: Mortality and technique failure in peri-toneal dialysis patients using different dialysate characteristics. *Acta Nephrologica,* **27,** 90-98.
91. Cho, Y., D. W. Johnson, S. V. Badve, J. C. Craig, G. F. Strippoli, and K. J. Wiggins, 2013: The impact of neutral-pH peritoneal dialysates with reduced glucose degradation products on clinical outcomes in peritoneal dialysis patients. *Kid. Int.,* **84,** 969–979.
92. Boissinot, L., I. Landru, E. Cardineau, E. Zagdoun, J. P. Ryckelycnk, and T. Lobbedez, 2013: Is transition between peritoneal dialysis and hemodialysis really a gradual process? *Perit. Dial. Int.,* **33,** 391–397.
93. Chui, B. K., B. Manns, N. Pannu, J. Dong, N. Wiebe, K. Jindal, and S. W. Klarenbach, 2013: Health care costs of peritoneal dialysis technique failure and dialysis modality switching. *Am. J. Kid. Dis.,* **61,** 104–111.
94. Pajek, J., A. J. Hutchison, S. Bhutani, P. E. Brenchley, H. Hurst, M. P. Perme, A. M. Summers, and A. Vardhan, 2014: Outcomes of peritoneal dialysis patients and switching to hemodialysis: A competing risks analysis. *Perit. Dial. Int.,* **34,** 289–298.
95. Ersoy, F. F., 2009: Improving technique survival in peritoneal dialysis: what is modifiable? *Perit. Dial. Int.,* **29,** 74-77.
96. Kavanagh, D., G. J. Prescott, and R. A. Mactier, 2004: Peritoneal dialysis–associated peritonitis in Scotland (1999–2002). *Nephrol. Dial. Transplant.,* **19,** 2584–2591.

97. Fang, W., Z. Ni, and J. Qian, Lessons from a high-quality PD program-the role of the PD team and the CQI.

Chapter 35

Reinitiation of Peritoneal Dialysis

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Reinitiation of Peritoneal Dialysis

The proportion of patients on peritoneal dialysis (PD) in our country is 18-20% [1]. The concept of reinitiation of PD has not gained in our country. For a patient undergoing PD, catheter removal during the course of a severe peritonitis is to prevent the two major consequences of uncontrolled peritonitis, namely death and irreversible injury to the peritoneal membrane, the latter precluding future continuation of PD therapy [2].The indications for catheter removal are refractory peritonitis, relapsing peritonitis, refractory exit-site and tunnel infection and fungal peritonitis. Catheter removal may also be considered for repeat peritonitis, Mycobacterial peritonitis and multiple enteric organisms [3].

Catheter removal for peritonitis renders fair to good results when indicated for reasons other than the clinical aggressiveness of the infection, as in uncomplicated relapsing or catheter-dependent peritonitis. These settings allow a chance to induce clinical remission of the infection with antibiotics, permitting removal or even one-step catheter exchange [4] in the absence of peritoneal inflammation. Thus, removal of the catheter may be lifesaving in several patients of severe peritonitis, yet peritonitis with catheter removal is usually associated with significantly higher mortality rates than those reported for PD-related peritonitis overall [5-11]. Patients who survive this serious (in terms of both risk and suffering) complication find themselves in a poor clinical and psychological condition [2]. The available information suggests, a high proportion of patients whose catheters were removed were unable to successfully reinitiate PD, due to irreversible peritoneal injury or to decisions by the patient or the nephrologist, the latter for empiric reasons [2].

A recollection of some of the definitions

1.*Peritonitis:* Presence of any two of the following a. symptoms and signs of peritoneal inflammation, b. cloudy peritoneal fluid with an elevated peritoneal fluid leucocyte count (more than 100/ μL) due predominantly (more than 50%) to neutrophils and c. demonstration of bacteria in the peritoneal fluid by Gram's stain or culture.

2.*Refractory peritonitis:* Failure of the peritoneal fluid to clear after five days of appropriate antibiotics [3].3. *Technique failure*: Permanent transfer to haemodialysis (HD).

Reinitiation of PD

The decision of reinitiation of PD should be entirely of the patient. The nephrology team treating the patient should limit the influence only to inform them the option of possibility of reinitiation of PD. Only after patients had convinced themselves

and expressed willingness for PD, further investigations should be done. In all the patients, a minimum of four weeks should be allowed between the catheter removal and reinsertion. In one study, the reported mean interval after the removal of catheter and attempt of reinsertion was 50.4 days [12]. After 2009, all the patients were subjected to peritoneal scintigraphy and computerized tomography to assess the presence of adhesions in the abdomen.

Peritoneal scintigraphy

The peritoneal scintigraphy is performed by mixing 2.0 m Citechnetium-99m sulfur colloid in 2 L 2.5% dextrose PD solution and then infusing the dialysate using a 14-gauge intravenous cannula under aseptic conditions. Scintigraphic views are obtained using a large field of view scintillation camera set at 140 keV photopeak, with a 20% window, and equipped with a lowenergy parallel-hole collimator. Starting at the time of infusion, a dynamic series of 1 minute/frame images centered on the diaphragmatic region were obtained for 15 minutes. Static

anterior, posterior, and lateral views of the abdomen were then obtained at post infusion and post ambulatory phases and after draining out the radiolabeled dialysate. A normal scan should demonstrate free flow of dialysate fluid throughout the peritoneal cavity, outlining the intraperitoneal recesses (**Figure1**). A non-uniform distribution of the dialysate fluid, with most of it confining to the central part of the abdomen in several loculations (**Figure 2**) suggests the presence of adhesions. The loculated tracer accumulation persistent even after draining of dialysate fluid, confirms the presence of adhesions [13].

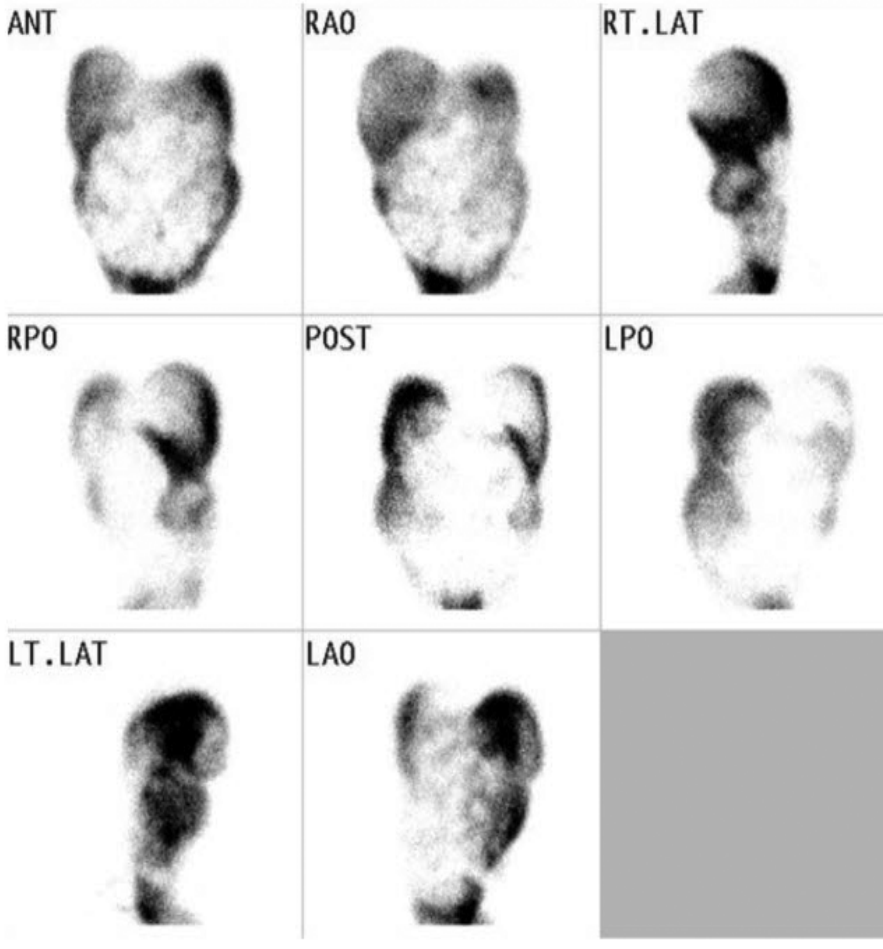

Figure 1: Free Flow of Dialysate Fluid Throughout the Peritoneal Cavity, Outlining the Intraperitoneal Recesses

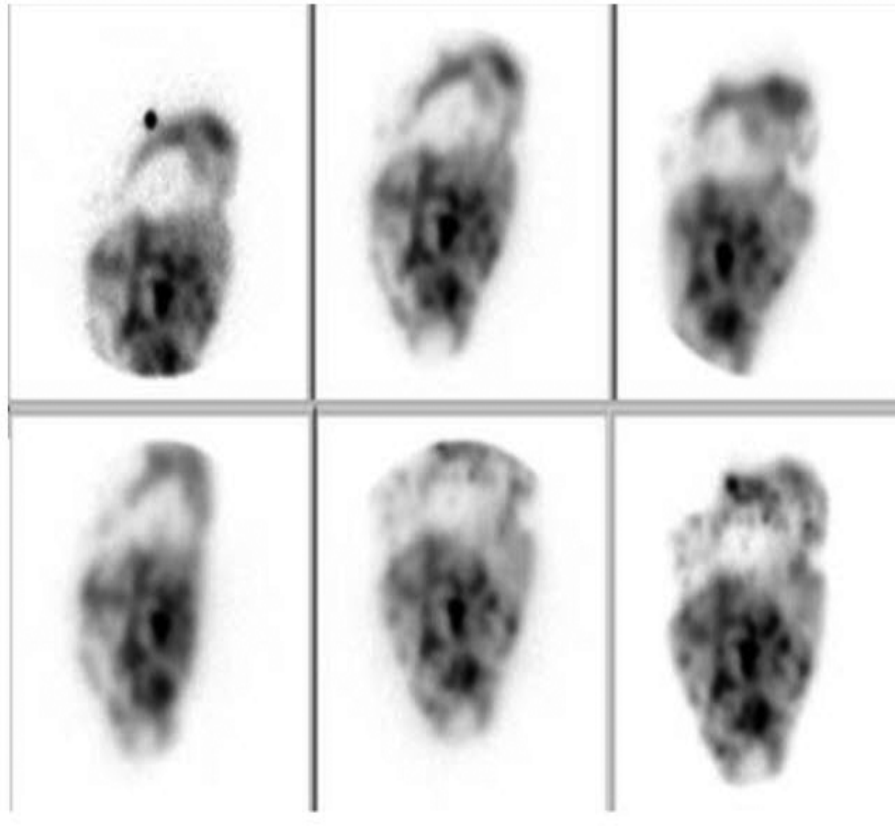

Figure 2: Non-Uniform Distribution of Dialysate Fluid.

The reinsertion of catheter should be either be done by open surgery or by laparoscopy. The previous studies [6, 8, 12, 14, 15] on reinsertion of PD are reported in the **Table 1**. The previous studies identified severe peritonitis, dialysis vintage and increasing patient age as factors that predicted the technique failure.

Table 1: Previous Studies

	Szeto *et al.* [6]	**Cox *et al.* [14]**	**Troidle *et al.* [8]**	**Sahu *et al.* [15]**	**Ram *et al.* [12]**
Year of publication	2002	2006	2005	2003	2014
Day on which catheter removed for refractory peritonitis	10	6.6 to 8.9	-	-	5 to 6
Number of patients reinitiated on PD	51	42	88	Total reinitiations: 106; After peritonitis: 50	31[c]
Follow up period after reinitiation of PD (months)	18.5 ± 16.8	20 ± 7.3	15.4 ± 15.4	48	24
Number of days between Tenckhoff catheter removal and reinsertion (mean)	40 days	10 ± 5.9 weeks in success group; 12 ± 7.3 weeks in failed group	-	-	50.4
Predictors of technique failure after reinitiation of PD	Severe peritonitis requiring temporary haemodialysis	Dialysis vintage	-	Increasing patient age	None identified
Outcome	At 2 years: Patient survival: 80.3%at 2 years, Technique survival: 56.3%	At the end of follow up Successful PD: 23 of 42 (54.7%), PD technique failure: 19 of 42 (45.2%)	At 12 months: On PD: 37 (42%), On PD for less than 12 months: 51 (58%)	At 48 months: Continued with PD: 65 (61.3%) patients. Second catheter removed: 41 patients.[b]	Patients on regular follow up without peritonitis: 13 (41.9 %), died while on PD: 11 (35.4 %), ultrafiltration failure:1 (3.2 %), catheter removed due to refractory peritonitis:6 (19.3%) In 6 patients with catheter removed (technique failure), PD was continued for 18. ± 9.6 months.[d]

a: In another 49 patients, the reinsertion failed due to intraoperative finding of peritoneal sclerosis and bowel adhesions.

b: The study did not specify the outcomes of the patients who had second catheter placed after the removal of catheter for the peritonitis.
c: In another seven patients, the reinsertion failed due to intraoperative finding of bowel adhesions.
d: In addition, five patients had the catheter inserted for a third time, after a second episode of refractory peritonitis. The duration of PD on the third catheter was 13.2 ± 5.0 months (range 6–18).
e: See the text for further information

In our programme, the organisms which caused refractory peritonitis were fungal: 7 (22.5%), *Pseudomonas aeruginosa*: 4 (12.9%), *Escherichia coli*: 3 (9.6%), *Staphylococcus aureus*, Coagulase negative staphylococcus and *Mycobacterium tuberculosis*: 2 (6.4%) each, *Acinetobacter baumnii* and *Klebsiella pneumonia*: 1 (3.2%) each. It was culture negative in 9 (29%) patients. Also, in our programme the decision of reinitiation of PD was not influenced by us. The decision was taken by the patient. Removal of catheter on day 5 or 6, a mean interval of 50.4 days after the removal of catheter, use of peritoneal scintigraphy to rule out adhesions and reinsertion of catheter by open surgery might have contributed to successful reintiation of PD in our patients. We could not find any difference in the effect of organism causing peritonitis on reinitiation of PD. But it was opined that the agents with aggressive and/or persistent infections (yeast and surgical enteric peritonitis) might impede reinitiation of PD [2]. A previous study has reported an increase in D/P creatinine ratio after reinitiation of PD [6]. We also observed a similar increase in the proportion of high and high average transporters after reinitiation (47.61%) than before (33.33%). This change from low and low average transporter to high and high average transporter status could due to be long term PD resulting in high solute transport status (Type 1 UFF). The change from high and high average transport status to low and low average transporter status appeared due either to mild degrees of peritoneal sclerosis or lesser degrees of adhesions (**Table 2**).

Table 2: Peritoneal equilibration test

Transport category (D/P Cr reference ranges)	PET during first phase of PD (n= 27)	PET after reinitiation of PD (n=21)	D/P Cr after reinitiation of PD (mean ± SD)
Low (0.34-0.49)	1	2	0.45 ± 0.05
Low average (0.50-0.64)	17	9	0.50 ± 0.06
High average (0.66-0.81)	9	7	0.72 ± 0.01
High (0.82-1.03)	0	3	0.88 ± 0.01

D/P Cr: Dialysate plasma creatinine ratio

In our study, the PD technique survival in the patients reinitiated on PD was 77.41% (24 out of 31) and patient survival was 67.72% (21 out of 31) at the end of

two years [12]. The technique and patient survival of the overall PD patient population was better than the reinitiated group. The technique survival was 81.3% and patient survival was 80.1% at the end of two years, for the overall PD population. In the previous studies the PD technique survival after reinitiation was between 42% and 56.3% [6, 8, 14].

References

1.Reddy, Y. N. V., G. Abraham, M. Mathew, and R. Ravichandran, 2011: An Indian model for cost-effective CAPD with minimal man power and economic resources. *Nephrol. Dial. Transplant.,* **26,** 3089–3091.

2.Pérez-Fontán, M., and A. Rodríguez-Carmona, 2007: Peritoneal catheter removal for severe peritonitis: landscape after a lost battle. *Perit. Dial. Int.,* **27,** 155-158.

3.Li, P. K., C. C. Szeto, B. Piraino, J. Bernardini, A. E. Figueiredo, A. Gupta, D. W. Johnson, E. J. Kuijper, W. C. Lye, W. Salzer, and F. Schaefer, 2010: Peritoneal dialysis-related infections recommendations: 2010 update. ISPD. *Perit. Dial. Int.,* **30,** 393-423.

4.Mitra, A., and I. Teitelbaum, 2003: Is it safe to simultaneously remove and replace infected peritoneal dialysis catheters? Review of the literature and suggested guidelines. *Adv. Perit. Dial.,* **19,** 255–259.

5.Choi, P., E. Nemati, A. Banerjee, E. Preston, J. Levy, and E. Brown, 2004: Peritoneal dialysis catheter removal for acute peritonitis: a retrospective analysis of factors associated with catheter removal and prolonged postoperative hospitalization. *Am. J. Kid. Dis.,* **43,** 103–111.

6.Szeto, C. C., K. M. Chow, T. Y. H. Wong, C. B. Leung, A. Y. M. Wang, S. F. Lui, and P. K. T. Li, 2002: Feasibility of resuming peritoneal dialysis after severe peritonitis and Tenckhoff catheter removal. *J. Am. Soc. Nephrol.,* **13,** 1040–1045.

7.Fontán, P. M., A. Rodríguez-Carmona, R. García-Naveiro, M. Rosales, P. Villaverde, and F. Valdés, 2005: Peritonitis-related mortality in patients undergoing chronic peritoneal dialysis. Perit. Dial. Int., **25,** 274–284.

8.Troidle, L., N. Gorban-Brennan, and F. O. Finkelstein, 2005: Outcome of patients on chronic peritoneal dialysis undergoing peritoneal catheter removal because of peritonitis. *Adv. Perit. Dial.,* **21,** 98–101.

9.Krishnan, M., E. Thodis, D. Ikonomopoulos, E. Vidgen, M. Chu, J. M. Bargman, S. I. Vas, and D. G. Oreopoulos, 2002: Predictors of outcome following bacterial peritonitis in peritoneal dialysis. *Perit. Dial. Int.,* **22,** 573–581.

10. Digenis, G. E., G. Abraham, E. Savin, P. Blake, N. Dombros, K. Sombolos, S. Vas, R. Mathews, and D. G. Oreopoulos, 1990: Peritonitis-related deaths in continuous ambulatory peritoneal dialysis patients. *Perit. Dial. Int.,* **10,** 45–47.

11. Fried, L. F., J. Bernardini, J. R. Johnston, and B. Piraino, 1996: Peritonitis influences mortality in peritoneal dialysis patients. *J. Am. Soc. Nephrol.,* **7,** 2176–2182.

12. Ram, R., G. Swarnalatha, and K. V. Dakshinamurty, 2014: Reinitiation of peritoneal dialysis after catheter removal for refractory peritonitis. *J. Nephrol.,* **27,** 445-449.

13. Gudit, S., P. Sudhakar, R. Ram, N. Prasad, V. V. Prabhakar,and K.V. Dakshinamurty, 2010: Peritoneal scintigraphy in the diagnosis of adhesions. *Perit. Dial. Int.,* **30,** 112-113.

14. Cox, S. D., S. B. Walsh, M. M. Yaqoob, and S. L. S. Fan, 2006: Predictors of survival and technique success after reinsertion of peritoneal dialysis catheter following severe peritonitis. *Perit. Dial. Int.,* **27,** 67–73.

15. Sahu, K. M., A. Walele, V. Liakopoulos, and J. M. Bargman, 2003: Analysis of factors predicting survival of a second peritoneal dialysis catheter. *Adv. Perit. Dial.,* **19,** 252-254.

Chapter 36

Non-Infectious Complications of Peritoneal Dialysis

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Non-Infectious Complications of Peritoneal Dialysis – Abdominal Hernia

Peritoneal dialysis (PD) is gaining popularity as a home dialysis therapy. However, it is associated with various mechanical and metabolic complications. The mechanical complications include abdominal wall and pericatheter leak, genital edema, hydrothorax, back pain and hernias.

Types of hernias reported in patients on PD

1. Pericatheter.
2. Inguinal (direct and indirect).
3. Umbilical.
4. Incisional / Ventral.
5. Epigastric.
6. Femoral.
7. Foramen of Morgagni.
8. Lateral wall hernias through the aponeurotic layer between rectus abdominis muscle and semilunar line – Spigelian hernia.
9. Antimesenteric wall of intestine protrudes through the defect in anterior abdominal wall - Richter's hernia.
10. Enterocele.
11. Cystocele.

Incidence

Abdominal wall hernia is a common mechanical complication of PD [1, 2]. Its incidence ranges from 2.0 - 31. 4% in adults and 11.8 to 40% in children on PD [3, 4].

Incisional hernia or the pericatheterhernia are the most common hernia [5, 6]. Some have reported inguinal or umbilical hernias as the most common ones [7, 8]. Cystocele and enterocele are very rare. In the recent reports, there was an increasing incidence of umbilical hernias [9]. In about 5 - 12% of patients, hernias are present even before starting PD [10-12].

Aetiology and Pathogenesis

According to Laplace's law, with the instillation of dialysate, the tension on the abdominal wall increases due to the rise in intra abdominal pressure (IAP) and larger radius of the abdomen. Increased IAP and abdominal wall tension imposes mechanical stress on the abdominal wall and thus, leads to hernia formation in the patients with congenital or acquired weakness or defects in the abdomen. In the presence of dialysate in the peritoneal cavity, IAP rises and this rise in IAP is

proportional to the volume of the dialysis fluid instilled into the peritoneal cavity [13-15].

The increase in IAP also depends on the posture of the patient and the conditions associated with transient high pressures, *i.e*, coughing and straining. Supine posture is associated with least IAP and highest IAP is seen with sitting posture.

Midline abdominal incision for the implantation of dialysis catheter has a predilection for the development of incision hernia because it is anatomically weak area [8]. In a study, change to paramedian incision was associated with less pericatheter leak and hernia formation [16]. However, in a meta-analysis, there was no difference in the catheter related complications with a paramedian versus midline incision [17].

Processus vaginalis is another area of potential weakness for hernia formation. In the absence of obliteration of processus vaginalis, increased IAP during PD pushes bowel and dialysate into this processus vaginalis leading to formation of indirect inguinal hernia. It is commonly seen in boys. Prophylactically it should be repaired on both the sides even for unilateral inguinal hernia [18].

The role of intra peritoneal pressure or fill-volume in the development of hernia is still controversial. Bleyer studied 244 patients on PD and found that there was no significant difference in the incidence of hernia formation between the patients using 1.5 L, 2.0 L or 3.0 L dialysis fluid. Exchange volumes can be increased to improve the clearances [19].

The risk of hernias is more in children when compared to adults despite higher IAP in adults when compared to children. This was because of presence of anatomically weak areas of abdominal wall in children [4, 20].

Other risk factors contributing to the development of hernia in patients on PD include uraemia, poor nutrition, anemia, previous hernia repair, sites of previous abdominal surgeries, obesity and those who have experienced a postoperative leak at the time of catheter insertion. Older patients and those with an increased body mass index also show increased risk of herniation. Multiparous women due to weakness of supporting structures of abdominal wall are also at high risk. Patients with polycystic kidney disease show increased incidence of hernia formation due to the large kidney size leading to increased IAP and defects in the connective tissue integrity [21].

PD modality *per se* has not been shown to be an independent risk factor for hernia formation. In a study by Sagrario, continuous ambulatory peritoneal dialysis (CAPD) was associated with higher percentage of hernias when compared to automated peritoneal dialysis (APD) (63% Vs 47%) [22]. Transplant patients also showed higher risk of herniation, probably due to the steroid effects on the abdominal musculature.

Clinical Features

Time to development of hernia after CAPD initiation is varied. Von Lilien has reported highest rate of hernia development within first 3 months of PD initiation [4]. Tsang has reported more hernias within 7 months of initiation of PD [23]. In most of the studies, it was usually within one year after initiation of PD. Clinical manifestations may vary from asymptomatic swelling to patient discomfort, pain and alteration of body image (**Figure 1 and Figure 2**). Sequestration of the dialysate into the hernia sac leads to low ultrafiltration and unpredictable dialysis clearance.

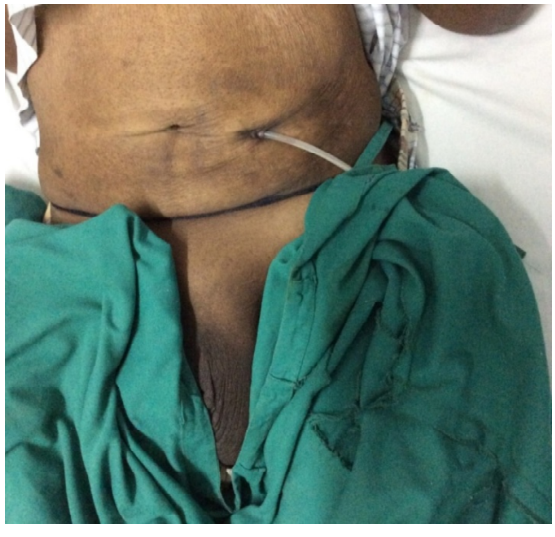

Figure 1: Left Inguinal Hernia

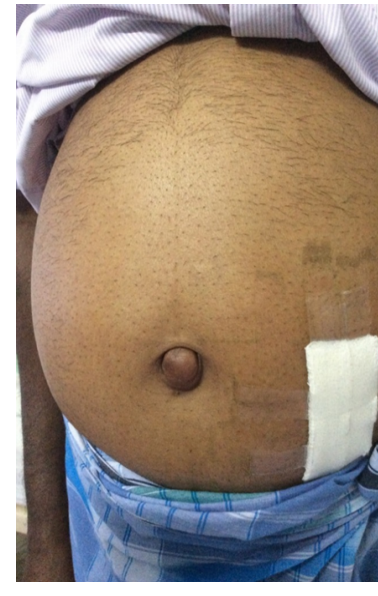

Figure 2: Umblical Hernia

Other complications include incarceration and strangulation of bowel. This complication is especially seen with small hernias. Umbilical hernia has more predilections for bowel strangulation [24]. This condition can even mimic peritonitis [25].

Diagnosis

Early detection of hernia may prevent technique failure and there by improve the outcomes on peritoneal dialysis.In patients planned for CAPD, careful search for hernia at susceptible sites is warranted. It can be accomplished by thorough physical examination of the patient [26]. Juergenson evaluated CAPD patients with abdominal, inguinal, genital and pleuroperitoneal leaks, and ultrafiltration

problemsby using scintigraphy. So, prophylactic use of scintigraphy may aid in early detection and offer patients an early surgical intervention [27].

Diagnostic methods

1. Peritoneal scintigraphy: It is an important diagnostic test to evaluate a patient on PD with abdominal wall swelling and inguinal swelling. Several radio pharmaceuticals have been described, including ^{99m}Tc sulfur colloid, ^{99m}MAA (^{99m}Tc macro aggregated albumin), and ^{99m}Tc DTPA. At our centre, we use 2.0 Mci of ^{99m}technetium sulfur colloid mixed with two liters of 2.5% PD solution. In the presence of hernia, tracking of sulfur colloid into the hernial sac is visualized in anterior, posterior, lateral and oblique images.
2. CT Peritoneography/ Dye assisted computed tomography: A 100 ml of Omnipaque 300 is added to 2.0 L of PD solution and is instilled into the peritoneal cavity. To facilitate the entry of the dye into the hernia sac, patient is made ambulatory for the next 2 hours. CT scanning is then performed. This is used to differentiate abdominal wall leaks from abdominal wall hernias. It can also diagnose whether the scrotal edema is because of fluid tracking down the processusvaginalis or along the anterior abdominal wall.
3. Ultrasonography: It is a non-invasive test used to differentiate solid appearing hernias from fluid collections due to leaks or hydroceles.

4. Magnetic resonance imaging: It is indicated in patients who are allergic to the radiologic dye. It can also differentiate hernias from fluid collections

Treatment

Hernia repair is warranted because of patient discomfort, pain, and unsightliness of the growing hernia complications related to hernia, *i.e*., bowel incarceration and strangulation, and ultrafiltration failure. However, patients with high surgical risk, hernias can be externally supported with truss and PD may be continued with low IAP maneuvers i.e., frequent low volume exchanges carried out in supine posture.

Hernia diagnosed before the start of PD can be repaired on the day of catheter insertion [10, 12]. The disadvantages seen when hernia repair and CAPD catheterization were done as two separate procedures included the delay in PD initiation due to the time required for wound healing after hernioplasty and increased post operative morbidity due to two separate procedures and also due to anesthesia.

There is scarce data whether to stop or continue PD after hernia repair [28, 29]. In the initial days, at the time of hernia repair, PD was usually changed to haemodialysis. This was associated with morbidity due to the insertion of temporaryvascular access and its complications i.e. sepsis and thrombosis. Patient can be started on PD after one or two days after surgery.

In the present era, PD therapy is based on principles of low IAP, *i.e.*, frequent exchanges (6 times a day) with lower volume (1-1.5 L) and in supine position if the patient is on CAPD. Patient on APD may be kept day dry and can continue low volume night exchanges.

Martinez-Mier reported that more than one third of these patients continued PD even on the day of surgery and the rest of the patients resumed to PD within 72 hrs. This study has supported early restoration of PD with low volume exchanges after hernioplasty [30].

Mettang and colleagues have reported no leaks or hernia recurrences in nine PD patients who underwent herniotomy. PD was paused for 1-3 days postoperatively depending on the residual renal function [29].

A good postoperative recovery with early resumption (as early as 24 hours after surgery) of PD was observed by Lewis and Guzman- Valdivia [31, 32]. Crabtree has recommended low volume (1.0-1.5 L till volume) automated PD exchanges post operatively and resumption of usual dialysis regimen after second week [33].

In the presence of hernias with compromised bowel like bowel incarceration and strangulation, patient may be temporarily transferred to haemodialysis as there is increased risk of peritonitis due to the breach in the intestinal mucosal integrity [34].

The surgical techniques include

1. Herniorrhaphy: In this procedure, primary closure is done by simple or continuous sutures. It is associated with high recurrence rates as pulling the fascia together during repair can lead to increased tension at the incision, thus weakening the incision site [33].
2. Technique involving the use of prosthetic materials in the form of mesh. Polypropylene is one of the most common prosthetic materials used for the repair. Based on the better results with mesh hernioplasty, this procedure has become the treatment of choice for hernia in patients on PD. It is done by fixing the mesh to the aponeurosis in order to give mechanical support to the hernia defect. This procedure is associated with low recurrences [35, 36]. There is no reported risk of peritonitis seen when the mesh is infected as the mesh would develop “neoperitoneum” that prevents bacterial invasion and spread [37].

Experience at SVIMS

At our institute, 160 CAPD catheter insertions were done. Of these, 96(60%) were men. Diabetes was the leading cause of ESRD (63.7%). Out of 160 CAPD catheter insertions, 15 patients developed hernias. Out of these 15patients, 3 developed hernias (inguinal hernia – 2, umbilical hernia – 1) even before initiation of PD. All these three underwent hernia repair at the time of catheter insertion. The remaining 12 patients (Umblical - 8, Inguinal -5, Incisional – 2) developed hernias after CAPD

initiation. The duration to the development of hernia for 12 patients ranged from 2 months to 12 months after CAPD initiation. All these 12 patients underwent mesh hernioplasty. They were resumed to low volume frequent exchanges with a cycler within 3rd postoperative day. They were shifted to their previous PD regimen within 10-14 day of hernia repair.

References

1. Nelson, H., M. Lindner, E. S. Schuman, G. F. Gross, and J. F. Hayes, 1983: Abdominal wall hernias as a complication of peritoneal dialysis. *Surg. Gynecol. Obstet.,* **157,** 541-544.

2. Pauls, D. G., B. B. Basinger, and C. F. Shield, 1992: Inguinal herniorrhaphy in the continuous ambula tory peritoneal dialysis patient. *Am. J. Kid. Dis.,* **20,** 497-499.

3. Stone, M. M., E. W. Fonkalsrud, I. B. Salusky, H. Takiff, T. Hall, and R. N. Fine, 1986: Surgical management of peritoneal dialysis catheters in children: five-year experience with 1,800 patient-month followup. *J. Pediat. Surg.,* **21,** 1177-1181.

4. Von Lilien, T., I. B. Salusky, H. K. Yap, E. W. Fonkalsrud, and R. N. Fine, 1987: Hernias: a frequent complication in children treated with continuous peritoneal dialysis. *Am. J. Kid. Dis.,* **10,** 356-360.

5. O'Connor, J. P., R. J. Rigby, I. R. Hardie, D. R. Wall, R. W. Strong, P. W. Woodruff, and J. J. Petrie, 1986: Abdominal hernias complicating continuous ambulatory peritoneal dialysis. *Am. J. Nephrol.,* **6,** 271–274.

6. Harries, S. R., K. D. Farmer, L. R. Gellett, and P. A. Dubbins, 2000: Incisional hernia: an unusual cause of acute pain and swelling following renal transplant. *J. Clin. Ultrasound,* **28,** 187–189.

7. Kauffman, H. M. Jr., and M. B. Adams, 1986: Indirect inguinal hernia in patients undergoing peritoneal dialysis. *Surgery,* **99,** 254–256.

8. Apostolidis, N. S., P. J. Tzardis, A. J. Manouras, M. D. Kostenidou, and A. N. Katirtzoglou, 1988: The incidence of postoperative hernia as related to the site of insertion of permanent peritoneal catheter. *Am. Surg.,* **54,** 318–319.

9. Dabbas, N., K. Adams, K. Pearson, and G. Royle, 2011: Frequency of abdominal wall hernias: is classical teaching out of date? *JRSM Short Rep.,* **2,** 1-6.

10. Garcia–Urena, M. A., C. R. Rodriguez, V. V. Ruiz, F. J. Carnero Hernandez, E. Fernandez–Ruiz, J. M. Vazquez Gallego, and M. W. Garcia, 2006: Prevalence and management of hernias in peritoneal dialysis patients. *Perit. Dial. Int.,* **26,** 198–202.

11. Afthentopoulos, I. E., S. Panduranga Rao, R. Mathews, and D. G. Oreopoulos, 1998: Hernia development in CAPD patients and the effect of 2.5 L dialysate volume in selected patients. *Clin. Nephrol.,* **49,** 251–257.

12. Nicholson, M. L., A. M. Madden, P. S. Veitch, and P. K. Donnelly, 1989: Combined abdominal hernia repair and continuous ambulatory peritoneal dialysis (CAPD) catheter insertion. *Perit. Dial. Int.,* **9,** 307–308.

13. Twardowski, Z. J., R. Khanna, K. D. Nolph, A. Scalamogna, M. H. Metzler, T. W. Schneider, B. F. Prowant, and L. P. Ryan, 1986: Intraabdominal pressures during natural activities in patients treated with continuousambulatory peritoneal dialysis. *Nephron,* **44,** 129–135.

14. de Jesus Ventura, M., D. Amato, R. Correa-Rotter, and R. Paniagua, 2000: Relationship between fill volume, intraperitoneal pressure, body size, and subjective discomfort perception in CAPD patients. Mexican Nephrology Collaborative Study Group. *Perit. Dial. Int.,* **20,** 188–193.

15. Dejardin, A., A. Robert, and E. Goffin, 2007: Intraperitoneal pressure in PD patients: relationship to intraperitoneal volume, body size and PD related complications. *Nephrol. Dial. Transplant.,* **22,** 1437–1444.

16. Spence, P., R. Mathews, R. Khanna, and D. G. Oreopoulos, 1985: Improved results with a paramedian technique for the insertion of peritoneal dialysis catheters. *Surg. Gynecol. Obstet.,* **161,** 585–587.

17. Strippoli, G. F., A. Tong, D. Johnson, F. P. Schena, and J. C. Craig, 2004: Catheter type, placement and insertion techniques for preventing peritonitis in peritoneal dialysis patients. *Cochrane Database Syst. Rev.,* CD004680.

18. Khoury, A. E., J. Charendoff, J. W. Balfe, G. A. McLorie, and B. M. Churchill, 1991: Hernias associated with CAPD in children. *Adv. Perit. Dial.,* **7,** 279–282.

19. Bleyer, A. J., M. J. Casey, G. B. Russell, M. Kandt, and J. M. Burkart, 1998: Peritoneal dialysate fill-volumes and hernia developmentin a cohort of peritoneal dialysis patients. *Adv. Perit. Dial.,* **14,** 102-104.

20. Aranda, R. A., J. E. Roma Jr., E. Kakehashi, W. Domingos, E. Sabbaga, M. Marcondes, and H. Abensur, 2000: Intraperitoneal pressure and hernias in children on peritoneal dialysis. *Ped. Nephrol,* **14,** 22-24.

21. Del Peso, G., M. A. Bajo, O. Costero, C. Hevia, F. Gil, C. Diaz, A. Aguilera, and R. Selgas, 2003: Risk factors for abdominal wall complications in peritoneal dialysis patients. *Perit. Dial. Int.,* **23,** 249–254.

22. Balda, S., A. Power, and V. Papalois, 2013: Impact of hernias on peritoneal dialysis technique survival and residual renal function. *Perit. Dial. Int.,* **33,** 629–634.

23. Lap-Yuen, T., H. Chun-Ying, and P. Sheng-Jeng, 2002: Hernia in ESRD patients receiving peritoneal dialysis. *Acta. Nephrologica,* **16,** 57-61.

24. Suh, H., N. K. Wadhwa, T. Cabralda, D. Sokunbi, and B. Pinard, 1994: Abdominal wall hernias in ESRD patients receiving peritoneal dialysis. *Adv. Perit. Dial.,* **10,** 85–88.

25. Engeset, J., and G. G. Youngson, 1984: Ambulatory peritoneal dialysis and hernial complications. *Surg. Clin. North Am.,* **64,** 385–392.

26. Rubin, J., S. Raju, N. Teal, E. Hellems, and J. D. Bower, 1982: Abdominal hernia in patients undergoing CAPD. *Arch. Intern. Med.,* **142,** 1453-1455.

27. Juergensen, P. H., H. Rijvi, V. J. Caride, A. S. Kliger, and F. O. Finkelstein, 1999: Value of scintigraphy in chronic peritoneal dialysis patients. *Kid. Int.,* **55,** 111-119.

28. Cherney, D. Z., Z. Siccion, M. Chu, and J. M. Bargman, 2004: Natural history and outcome of incarcerated abdominal hernias in peritoneal dialysis patients. *Adv. Perit. Dial.,* **20,** 86-89.

29. Mettang, T., H. Stoeltzing, D. M. Alscher, S. Magadum, R. Dunst, and U. Kuhlmann, 2001: Sustaining continuous ambulatory peritoneal dialysis after herniotomy. *Adv. Perit. Dial.,* **17,** 84-87.

30. Martínez-Mier, G., E. Garcia-Almazan, H. E. Reyes-Devesa, V. Garcia-Garcia, S. Cano-Gutierrez, Y. Mora, R. Fermin, J. Estrada-Oros, L. F. Budar-Fernandez, S. F. Avila-Pardo, and G. F. Mendez-Machado, 2008: Abdominal wall hernias in end-stage renal disease patients on peritoneal dialysis. *Perit. Dial. Int.,* **28,** 391-396.

31. Lewis, D. M., C. Bingham, M. Beaman, A. J. Nicholls, and H. N. Riad, 1998: Polypropylene mesh hernia repair-an alternative permitting rapid return to peritoneal dialysis. *Nephrol. Dial. Transplant,* **13,** 2488-2489.

32. Guzman-Valdivia, G., and I. Zaga, 2001: Abdominal wall hernia repair in patients with chronic renal failure and a dialysis catheter. *Hernia,* **5,** 9-11.

33. Crabtree, J. H., 2006: Hernia repair without delay in initiating or continuing peritoneal dialysis. *Perit. Dial. Int.,* **26,** 178-182.

34. Swarnalatha, G., R. Rapur, S. Pai, and K. V. Dakshinamurty, 2012: Strangulated umbilical hernia in a peritoneal dialysis patient. *Indian J. Nephrol.,* **22,** 381-384.

35. Amid, P. K., and I. L. Lichtenstein, 1996: Retromuscularalloplasty for large scar hernias: A simple staple attachment technique. *Chirurg,* **67,** 648-652.

36. Grolleau, J. L., and P. Micheau, 1999: Incisional hernia repair techniques for abdominal wall. *Ann. Chir. Plast. Esthet.,* **44,** 339-355.

37. Imvrios, G., D. Tsakiris, D. Gakis, D. Takoudas, P. Koukoudis, M. Papadimitriou, and A. A. Antoniadis, 1994: Prosthetic mesh repair of multiple recurrent and large abdominal hernias in continuousambulatory peritoneal dialysis patients. *Perit. Dial. Int.,* **14,** 338–343.

Chapter 37

Non-infectious Complications of Peritoneal Dialysis: Hydrothorax

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Non-infectious Complications of Peritoneal Dialysis: Hydrothorax

Introduction

Peritoneal dialysis (PD), a life sustaining procedure for ESRD patients is simple in technology, convenient to do and relatively less costlier [1]. However, it is associated with a number of infectious and non infectious complications that require timely diagnosis and appropriate management; the failure to do so may lead to technique failure and sometimes loss of life.

Whenever the dialysate fluid is introduced into the peritoneal cavity, it results in elevation of intra abdominal pressure, the magnitude of which in turn depends on the dialysate volume and the patient position [2]. The increase in the intra abdominal pressure results in various mechanical complications including hydrothorax and it is described in this section.

Approximately, 2% of CAPD patients develop hydrothorax [3] which is also known as sweet hydrothorax [4, 5] owing to the presence of glucose in the collected fluid. The condition was first described in 1967 [5]. In more than 80% of the cases, it occurs on the right side although rarely, it can occur on the left side or both the sides [6, 7, 8].

Pathophysiology

Congenital diaphragmatic defects, increased peritoneal pleural pressure gradient leading to acquired diaphragmatic defects and abnormal lymphatic drainage can contribute to hydrothorax in CAPD [9, 10, 11]. Elevated intra abdominal pressure during exchanges leads to the diaphragm collagen fibres separation and weakening. This results in the formation of pleural blebs which eventually rupture to open pleuroperitoneal communications [12, 13]. The predominant right side involvement has several explanations like covering of left side diaphragmatic surface by heart and pericardium, presence of processes vaginalis peritoneii, an embryonic remnant connecting the right chest with the peritoneum [14]. The other postulated mechanisms are role of the intestinal circulation in sweeping fluid preferentially to the right upper quadrant of abdomen [15], outward movement of ribs contributing to reduced hydrostatic pressure in suprahepatic region leading to collection of dialysatel [16], piston action of liver capsule in driving fluid through the pores of the right diaphragm [17]. Patients with underlying connective tissue disorders and previous episodes of peritonitis may also develop this condition because of the weakening of the diaphragmatic tissue
[18].

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Clinical features

The most common complaint is dyspnea initially with exertion that may later on progress to orthopnea. However, 25 % of the patients may remain asymptomatic [19]. When it develops acutely there may be a reduction in the ultrafiltration volume which leads to prescription of more hypertonic PD fluids and further aggravation of the condition [20].The time to onset of symptoms may vary from days to years after initiation of the PD. About 50% of cases may occur within one month of initiation of PD. Those with congenital defects of diaphragm present early whereas with acquired defects the presentation may occur at a later date [9, 21]. Clinical examination often reveals a right sided pleural effusion.

Diagnosis

Imaging

A simple chest x ray shows the presence of hydrothorax (**Figure 1a, 1b, 1c**). CT peritoneography demonstrates pleuro peritoneal communication or the presence of diaphragmatic defects. It is performed by mixing the PD fluid with contrast and instilling into the peritoneal cavity and subsequently imaging with a CT scanner [11]. The other imaging modality is MRI. Tc-99m DTPA scintigraphy can also demonstrate the anatomical defects. Peritoneal scintigraphy with Tc-99m macro-aggregated albumin with simultaneous single-photon-emission computed tomography and computed tomography (SPECT/CT) was also described by some authors [22]. Peritoneal scintigraphy is performed by infusing a PD bag mixed with 5 mCi of Technetium labelled albumin colloid into the peritoneal cavity, patient is made ambulatory followed by serial imaging at 0, 10, 20, 30 minutes (posterior views and one anterior view at 30 minutes). Sometimes delayed view after 2 to 3 hrs may be necessary [23].

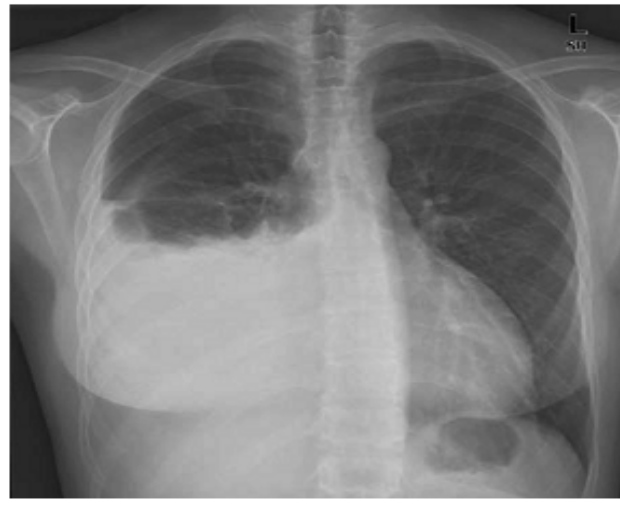

Figure 1a: Chest X ray Showing Right Pleural Effusion

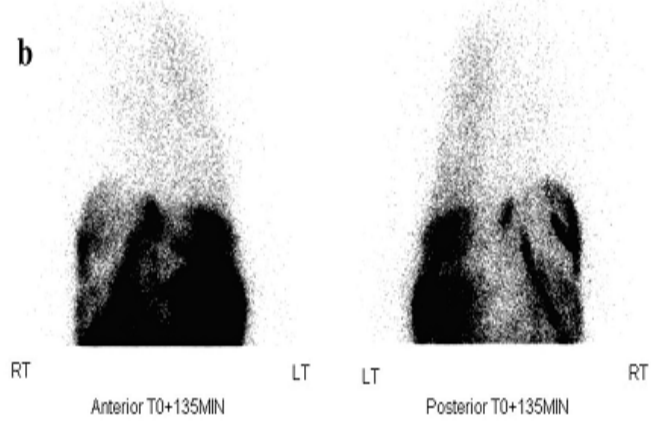

Figure 1b: CT Peritoneography- Sagittal Section Showing Iaphragmatic Hernia of Morgagni (Krivokuca *et al*, 2008)

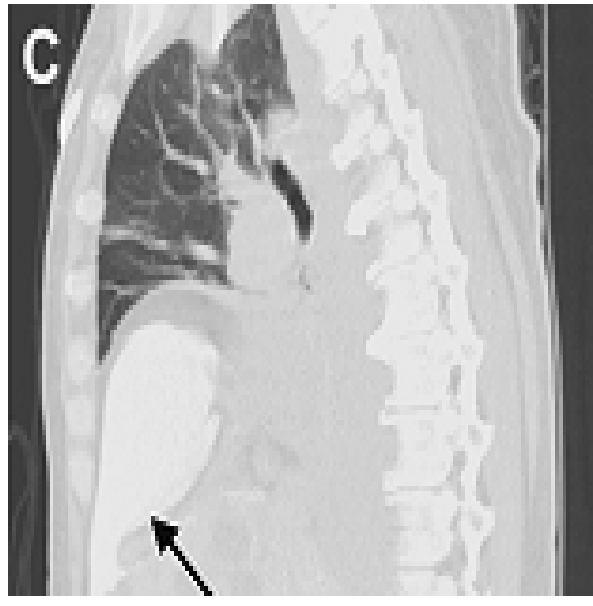

Figure 1c: Tc-99m DTPA scintigraphy showing **left-sided** pleuroperitoneal leak (Chow *et al,* 2003)

Pleural Fluid Analysis

Although, the advanced imaging techniques described above are useful in their own way, a simple pleural fluid analysis almost establishes the diagnosis. It is typically a clear transudate with high glucose concentration and a high pleural fluid serum glucose gradient (>50 mg/dl) [3]. However, sometimes the glucose concentration may be lower because of the absorption by the pleural mesothelium [13].

Differential diagnosis

Apart from sweet hydrothorax, the other possibilities to consider in a patient on CAPD with pleural effusion are pulmonary infarction, congestive cardiac failure, pericardial disease, hypothyroidism, neoplasm and pneumonia (bacterial/tuberculous) [24]. Fluid overload state because of low ultrafiltration volume should also be considered, however, it frequently leads to bilateral pleural effusions.

Treatment

Emergency situation

In patients with severe dyspnea, it is necessary to remove the large volume of pleural fluid along with complete drainage of the peritoneal fluid [21].

Conservative/ PD rest

Withholding CAPD temporarily for 4-6 weeks followed by initiation with low dwell volumes and increasing the frequency or switching over to automated peritoneal dialysis (APD; PD Cycler) can ameliorate symptoms and lead to continuation of The CAPD in 50 to 60% of the patients [25, 26, 27]. Temporary withholding of CAPD may result in healing of the diaphragmatic defects. Rarely, the dialysate itself may lead to pleurodesis by acting as an irritant in the pleural cavity. However, recurrent effusions after re- initiation may require other modalities of management as described below.

Pleurodesis

Chemical Pleurodesis

It is performed through the placement of an intercostal tube and with one of the agents like talc, autologous blood or tetracycline. Talc pleurodesis can also be performed under video assisted thoracoscopic guidance [13]. The success rate was about 50% [25]. CAPD can be resumed in 3-4 weeks. No data is available regarding the superiority of one agent over the other in chemical pleurodesis.

Surgical Pleurodesis

Thoracotomy and suturing of the diaphragmatic defects followed by pleurectomy or pleural abrasion could be performed resulting in surgical pleurodesis [11].

Video assisted thoracoscopic surgery

Video assisted thoracoscopic surgery (VATS) aids in direct visualization of the defects in diaphragm followed by repair [25]. One study described successful long term continuation of CAPD in 88% of patients [28].

Prevention

Measures to prevent abrupt rise in the intraabdominal pressure like prescription of low dwell volumes initially, avoiding sitting position, identification of at risk individuals, e.g., ADPKD patients may prevent this complication.

Conclusion

With the various modalities of management described above for CAPD related hydrothorax, only 50 to 60 % of patients can continue long term CAPD. The

remaining patients require a conversion to HD. Therefore, before initiation of CAPD this complication should be kept in mind and the patient should be educated about the management and possible outcomes of the same.

References

1. Blake, P. G., and J. T. Daugridas, 2006: Physiology of Peritoneal Dialysis. Handbook of Dialysis, J. T. Daugridas, P. G. Blake and T. S., Eds., Lippincott Williams and Wilkins, Philadelphia, 323.

2. Bargman, J. M., 2006: Mechanical complications of Peritoneal Dialysis. Handbook of Dialysis, John T Daugridas, P. G. Blake and T. S., Eds., Lippincott Williams and Wilkins, Philadelphia, 440.

3. Szeto, C. C., and K. M. Chow, 2004: Pathogenesis and management of hydrothorax complicating peritoneal dialysis. *Curr. Opin. Pulm. Med.,* **10,** 315-319.

4. Michel, C., A. Devy, S. Lavaud, and F. A. Lebargy, 2001: "sweet" hydrothorax. *Press Med.;* **30,** 1401-1403.

5. Chow, K. M., C. C. Szeto, T. Y. Wong, and P. K. Li, 2002: Hydrothorax complicating peritoneal dialysis: diagnostic value of glucose concentration in pleural fluid aspirate. *Perit. Dial. Int.,* **22,** 525-528.

6. Nomoto, Y., T. Suga, K. Nakajima, H. Sakai, G. Osawa, K. Ota, Y. Kawaguchi, T. Sakai, S. Sakai, M. Shibat, S. Takahashi, 1989: Acute hydrothorax in continuous ambulatory peritoneal dialysis—a collaborative study of 161 centers. *Am. J. Nephrol.*, **9,** 363–367.

7. Mak, S. K., K. Nyunt, P. N. Wong, 2002: Long-term follow-up of thoracoscopic pleurodesis for hydrothorax complicating peritoneal dialysis. *Ann. Thorac. Surg.,* **74,** 218–221.

8. Tang, S., W. H. Chui, A. W. Tang, W. C. T. Anthony, F. K. Li, W. S. Chau, Y. W. Ho, T. M. Chan, and K. N. Lai, 2003: Video-assisted thoracoscopic talc pleurodesis is effective for maintenance of peritoneal dialysis in acute hydrothorax complicating peritoneal dialysis. *Nephrol. Dial. Transplant.,* **18,** 804–808.

9. Kennedy, C., C. McCarthy, S. Alken, J. McWilliams, R. K. Morgan, M. Denton, P. J. Conlon, and C. Magee, 2011: Pleuroperitoneal Leak Complicating Peritoneal Dialysis: A Case Series. *Int. J. Nephrol,* **2011,** 4.

10. Cho, Y., V. D'Intini, and D. Ranganathan, 2010: Acute hydrothorax complicating peritoneal dialysis: a case report. *J. Med. Case Rep.,* **4,** 355.

11. Szeto, C. C., and K. M. Chow, 2004: Pathogenesis and management of hydrothorax complicating peritoneal dialysis. *Curr. Opin. Pulm. Med.,* **10,** 315–319.

12. Rajnish, A., M. Ahmad, and P. Kumar, 2003: Peritoneal scintigraphy in the diagnosis of complications associated with continuous ambulatory peritoneal dialysis. *Clin. Nucl. Med.,* **28,** 70.

13. Krivokuca, I., J. W. J. Lammers, and J. Kluin, 2008: Peritoneal dialysis – An unusual cause of pleural effusion ("sweet hydrothorax"). Resp Med CME, **4**, 197–200.

14. Gagnon, R. F., and E. Daniels, 2004: The persisting pneumatoenteric recess and the infracardiac bursa: possible role in the pathogenesis of right hydrothorax complicating peritoneal dialysis. *Adv Perit Dial.,* **20,** 132-136.

15. Guest, and Steven, 2015: The Curious Right-Sided Predominance of Peritoneal Dialysis-Related Hydrothorax. *Clin. Kidney J.,* **8.2,** 212–214.

16. Overholt, R. H., 1931: Intraperitoneal pressure. *Arch. Surg.* **22,** 691–703.

17. Kirschner, P. A., 1998: Porous diaphragm syndromes. *Chest Surg. Clin. N. Am.* **8:** 449–472.

18. Chow, C. C., Y. J. Sung, C. K. Cheung, C. Hamilton-Wood, and K. N. Lai, 1988: Massive hydrothorax in continuous ambulatory peritoneal dialysis: diagnosis, management and review of the literature. *New Zealand Med. J.* **101,** 475–477.

19. Lew, S. Q., 2010: Hydrothorax: pleural effusion associated with peritoneal dialysis. *Perit Dial Int.,* **30**, 13-18.

20. Edwards, S. R. and A. M. Unger, 1967: Acute hydrothorax—a new complication of peritoneal dialysis. *J. Am. Med. Ass.,* **199,** 853–855.

21. Kei nishiyama, K. Fukushima, T. Jo, T. Miyai, S. Kanda, N. Sugawara, K. Ishizuka, H. Chikamoto, Y. Akioka, and M. Hattori, 2015: SPECT/CT to diagnose pleuroperitoneal communication-associated hydrothorax in peritoneal dialysis. *Kid. Int.,* **87,** 866.

22. Bargman, J. M., 2011: Mechanical complications of Peritoneal Dialysis. Handbook of Dialysis, John T Daugridas, Peter G Blake, Todd S, Eds., Lippincott Williams and Wilkins, Philadelphia, 443.

23. Hari, W., 2015: Atypical Pleural Effusions in Patients on Peritoneal Dialysis. *World J. Nephrol. Urol.,* **4,** 256-259.

24. Chow, K. M., C. C. Szeto, and P. K. T. Li, 2003: Management options for hydrothorax complicating peritoneal dialysis. *Seminars Dial.,* **16,** 389–394.

25. Soyaltin, U. E., F. Ekinci, D. Ayatan, C. Turemis, M. Yildirim, and H. Akar, 2015: Successful Continuation of Peritoneal Dialysis after "Sweet" Hydrothorax. *BANTAO J.,* **13,** 42-45.

26. Ing, A., J. Rutland, and S. Kalowski, 1992: Spontaneous resolution of hydrothorax in continuous ambulatory peritoneal dialysis. *Nephron.*, **61,** 247-248.

27. Tang, S., W. H. Chui, A. W. C. Tang, F. K. Li , W. S. Chau, Y. W. Ho, T. M. Chan, and K. N. Lai, 2003: Video-assisted thoracoscopic talc pleurodesis is effective for maintenance of peritoneal dialysis in acute hydrothorax complicating peritoneal dialysis. *Nephrol. Dialysis Transplant.,* **18,** 804–808.

Chapter 38

Non - infectious Complications of Peritoneal Dialysis: Genital and Abdominal Wall Edema

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Non - infectious Complication of Peritoneal Dialysis: Genital Edema and Abdominal Wall Edema

Introduction

Genital and anterior wall edema are relatively common and distressful complications for patients on peritoneal dialysis (PD). Approximately, 10% of patients on PD develop labial, scrotal and penile edema. Female patients have considerably lower incidence of this complication than men. This unequal distribution is due to embryonic remnant known as patent processus vaginalis [1]. Patent processus vaginalis is present in approximately 80-95 % of all the newborn males, however, its incidence decreases drastically in the first three years of age. About 20 % of those in whom the processus vaginalis remains patent will manifest signs and symptoms during their lifetime [2]. Genital edema is commonly associated with anterior wall edema.

Pathogenesis

The presence of dialysis fluid in the abdominal cavity increases intra-abdominal pressure and may lead to the dialysis fluid leaking from acquired or congenital defects in the abdominal leads to genital or abdominal wall edema. Dialysate can reach the genitalia by two routes [1, 3]. Firstly, the dialysate can find its path through the soft-tissue plane from: a). the catheter insertion site; b). soft-tissue defect; c). peritoneal-fascial defect; and d). dialysate can also dissect through the walls of the tunica vaginalis causing edema of scrotum. Dialysate fluid can also traverse the peritoneal membrane into the soft tissues of the anterior abdominal wall, leading to abdominal wall edema.

Patients with this complication often present with increasing abdominal girth in conjunction with decreased peritoneal fluid drainage volume. Secondly, the dialysate can travel *via* a patent processus vaginalis to the tunica vaginalis, resulting in hydrocele. In case viscera follows or accompanies the dialysate in its path through the processus vaginalis, an associated inguinal hernia will be present.

Risk Factors

The risk factors include:

1. Large dialysate volume

2. Sitting position

M. Desai

3. Isometric exercise

4. Valsalva maneuver

5. Recent abdominal surgery

6. Pericatheter leak and hematoma

5. Obesity

6. Multiparity

7. Congenital anatomical defects

Clinical Manifestations

Although genital edema is not harmful to the patient, it does cause considerable distress and discomfort. Typically, the patients complain of (a) abdominal swelling or bogginess, scrotal or labial edema (**Figure1**) (b) diminished effluent return (with unchanged PET results) (c) weight gain without peripheral edema. (d) abdominal wall edema - abdominal skin can look pale and boggy (**Figure 2**), indentations made by clothing (**Figure 3**), or by the catheter lying across the abdomen appear more prominent and deeper. It is best to examine the patient in a standing position to detect edema or asymmetry of abdomen. Always look for associated inguinal hernias in case of genital edema.

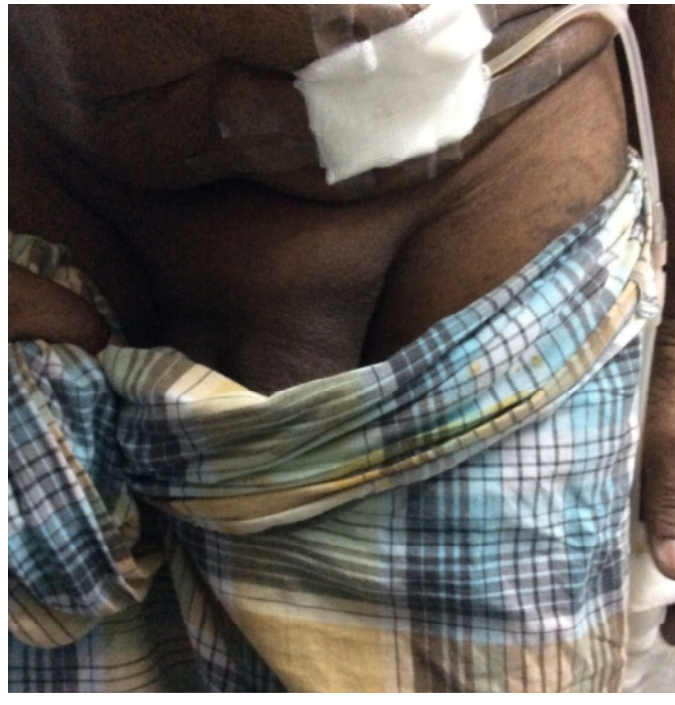

Figure1: Genital Edema

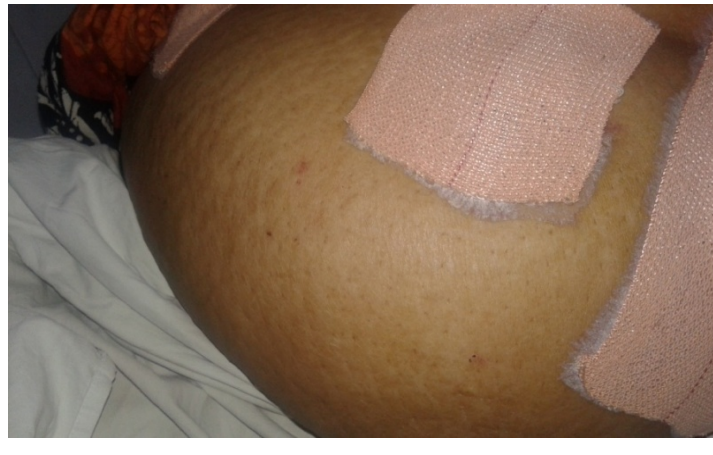

Figure 2: Abdominal Wall Edema

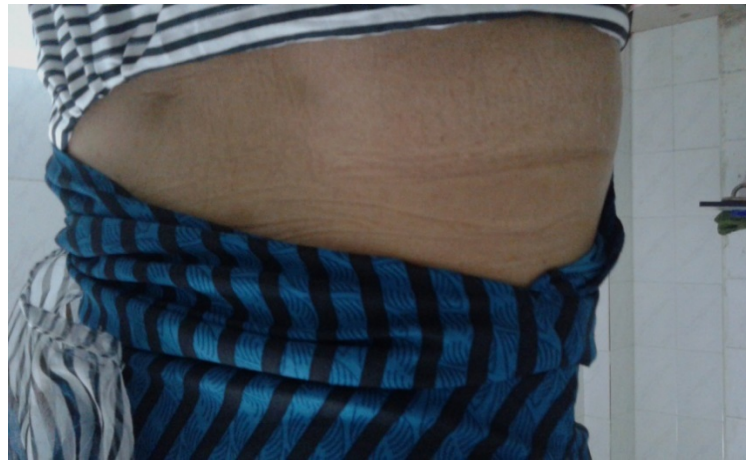

Figure 3: Abdominal Wall Edema. Arrows Show Indentation Made by Clothing

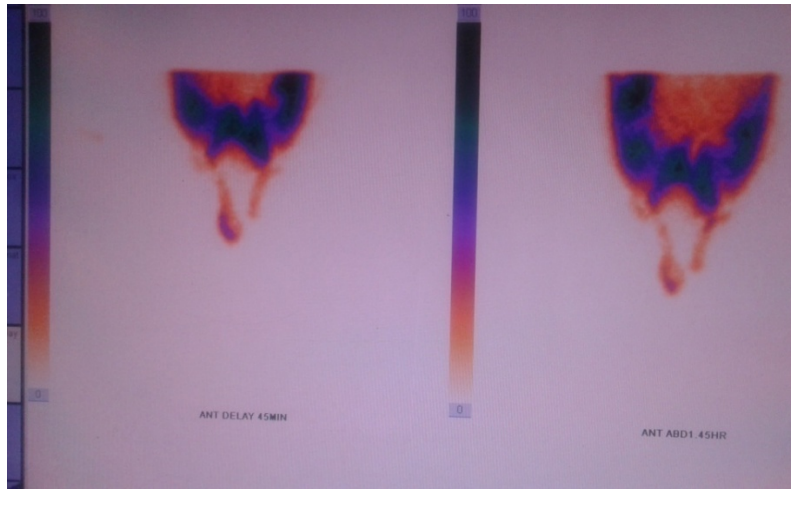

Figure 4: Peritoneal Scintigraphy.

Diagnosis

The following diagnostic imaging techniques are used to diagnose genital edema and abdominal edema - peritoneal scintigraphy, computed tomography and magnetic resonance [3].

Peritoneal Scintigraphy: Peritoneal scintigraphy (**Figure 4**) is a safe, accurate, and rapid way of diagnosing leaks in the peritoneal cavity [5-8]. About 3 to 5 millicuries of technetium 99m isotope per 0.5 to 2.0 L of dialysis solution is injected into the abdominal cavity. Multiple projections (anterior, lateral, posterior, and oblique) are then taken to help separate a leak in the abdominal wall from the peritoneal fluid posterior to it [9]). Isotope is not absorbed from the peritoneum. The net dose of radiation is therefore only a fraction of the total dose instilled into the peritoneal cavity [10]. To facilitate fluid egress out of the peritoneal cavity, a variety of measures can be employed to increase intra-abdominal pressures [11]. The patient should ambulate or (if non-ambulatory) be made to roll from side to side. Use of larger volumes of dialysate during procedure, if tolerated, should be advocated. Images are subsequently taken at regular time intervals, with most leaks being detected in two to six hours. Delayed scans (24 to 48 hours later) are advocated in small leaks or in initially equivocal studies [9, 12].

CT Peritoneography: CT peritoneography is an accurate and reliable method of diagnosing even small peritoneal defects. About 100-150 mL of iodinated contrast is mixed per bag of dialysate. After infusing dialysate into patient, ambulate the patient for 30 to 60 minutes to increase the intra-abdominal pressure to facilitate the egress of dialysate into the leaks.

MR Peritoneography: MR Peritoneography helps to diagnose anatomic defects or leaks [13-15]. Gadolinium-based dye was most commonly used. However, among patients with moderate to advanced renal failure (estimated glomerular filtration rate [eGFR] less than 30 mL/min), the administration of gadolinium has been associated with the nephrogenic systemic fibrosis. In such patients, gadolinium-based imaging should be avoided. If possible saline, or the dialysis solution itself, has also been used as contrast medium [15]. These fluids show up as a hyperintense image on T2 weighted images owing to its electrolyte content.

Treatment

The patient with uncomplicated abdominal wall or genital edema (but without an associated hernia) should be treated conservatively with bed rest and scrotal elevation. Scrotal elevation may help reduce the edema. If patient requires dialysis, frequent, low volume exchange on cycler in supine position or nocturnal dialysis with dry days to minimize intra-abdominal pressure [1, 16] should be employed. If these measures fail, hemodialysis (HD) can be instituted temporarily. A rest period of three to seven days may be sufficient for the tissue defect to heal and allow for the reinstitution of PD. Recurrent abdominal wall edema can be treated with a more prolonged course of HD (at least four to six weeks) or surgical repair. The outcome

of conservative management is variable. In one study, patients with uncomplicated peritoneal leaks (leaks without associated hernia), who were initially treated with either low volume supine PD or with a dry day or HD for four weeks had a 52% risk of relapse. However, repeating this technique for an additional four weeks resulted in resolution of the leak in 86% of the remaining patients [17]. In contrast, the treatment of recurrent genital edema is dependent upon the etiology of the edema: A patent processus vaginalis should be surgically repaired or by exploratory laparotomy [18, 19]. Leakage from anterior abdominal wall may be managed by catheter replacement [1, 16].

References

1. Bargman, J. M., 2009: Noninfectious Complications of Peritoneal Dialysis. *Nolph and Gokal's Textbook of Peritoneal Dialysis*. R. Khanna, and R. T. Krediet, Eds. Springer, New York, 571-609.
2. Rahman, N., and K. Lakhoo, 2009: Patent *Processus vaginalis*: a window to the abdomen. *Afr. J. Paediat. Surg.,* **6,** 116-117.
3. Haggerty, S. P., and J. M. Jorge, 2013: Laparoscopy to evaluate scrotal edema during peritoneal dialysis. *JSLS,* **17,** 429-432.
4. Blake, P. G., J. T. Daugirdas, and T. S. Ing, 2007: Handbook of Dialysis. 4th ed. (P. G. Blake, J. T. Daugirdas, and T. S. Ing, Eds.). Philadelphia, PA: Lippincott Williams & Wilkins.
5. Juergensen, P. H., H. Rizvi, V. J. Caride, A. S. Kliger, and F. O. Finkelstein, 1999: Value of scintigraphy in chronic peritoneal dialysis patients. *Kid. Int.,* **55,** 1111.
6. Walker, J. V., and M. B. Fish, 1988: Scintigraphic detection of abdominal wall and diaphragmatic peritoneal leaks in patients on continuous ambulatory peritoneal dialysis. *J. Nucl. Med.,* **29,** 1596.
7. Goh, A. S., G. S. Lee, S. G. Kee, E. S. Ang, and F. X. Sundram, 1994: Radionuclide detection of dialysate leakage in patients on continuous ambulatory peritoneal dialysis. *Ann. Acad. Med. Singapore,* **23,** 315.
8. Johnson, J., S. Baum, and R. D. Smink Jr., 1987: Radionuclide imaging in the diagnosis of hernias related to peritoneal dialysis. *Arch. Surg.,* **122,** 952.
9. Berman, C., M. G. Velchik, N. Shusterman, and A. Alavi, 1989: The clinical utility of the Tc-99m SC intraperitoneal scan in CAPD patients. *Clin. Nucl. Med.,* **14,** 405.
10. Johnson, B. F., Segasby CA, Holroyd AM, C. B. Brown, G. L. Cohen, and A. T. Raftery, 1987: A method for demonstrating subclinical inguinal herniae in patients undergoing peritoneal dialysis: the isotope 'peritoneoscrotogram'. *Nephrol. Dial. Transplant.,* **2,** 254-257.
11. Twardowski, Z. J., R. J. Tully, F. F. Ersoy, and N. M. Dedhia, and M. Narendra, 1990: Computerized tomography with and without intraperitoneal contrast for determination of intraabdominal fluid distribution and diagnosis of complications in peritoneal dialysis patients. *ASAIO Trans.,* **36,** 95.
12. Sissons, G. R., S. M. Jones, C. Evans, and A. R. Richards, 1991: Scintigraphic detection of abdominal hernias associated with continuous ambulatory peritoneal dialysis. *Br. J. Radiol.,* **64,** 1158.
13. Prokesch, R. W., W. Schima, E. Schober, A. Vychytil, V. Fabrizil, and T. R. Bader, 2000: Complications of continuous ambulatory peritoneal dialysis: findings on MR peritoneography. *AJR Am. J. Roentgenol.,* **174,** 987-991.
14. Arbeiter, K. M., C. Aufricht, T. Mueller, E. Balzar, and R. W. Prokesch, 2001: MRI in the diagnosis of a peritoneal leak in continuous ambulatory peritoneal dialysis. *Pediat. Radiol.,* **31,** 745-747.
15. Prischl, F. C., T. Muhr, E. M. Seiringer, S. Funk, G. Kronabethleitner, M. Wallner, W. Artmann, and R. Kramar, 2002: Magnetic resonance imaging of the

peritoneal cavity among peritoneal dialysis patients, using the dialysate as "contrast medium". *J. Am. Soc. Nephrol.,* **13,** 197-203.
16. Bargman, J. M., 2015: Hernias, Leaks, and Encapsulating Peritoneal Sclerosis. *Handbook of Dialysis.* J. T. Daugirdas, P. G. Blake, and T. S. Ing, Eds., Wolters Kluwer, 515-516.
17. Peso, G. D., M. A. Bajo, O. Costero, C. Hevia, F. Gil, C. Díaz, A. Aguilera, and R. Selgas, 2003: Risk factors for abdominal wall complications in peritoneal dialysis patients. *Perit. Dial. Int.,* **23,** 249-254.
18. Cobelo, C., S. Ros, C. Trujillo, and P. Garcia, 2010: An unusual case of vaginal leak in a patient on peritoneal dialysis. *Perit. Dial. Int.,* **30,** 665.
19. Shavit, L., M. Lifschitz, J. Plaksin, 2006: Postcoital peritonitis associated with transvaginal leak of dialysate in a CAPD patient. *Perit. Dial. Int.,* **26,** 720.

Chapter 39

Non - Infectious Complications of Peritoneal Dialysis - Gastrointestinal and Hepatic Complications

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Non - Infectious Complications of Continuous Ambulatory Peritoneal Dialysis – Gastrointestinal and Hepatic Complications

In continuous ambulatory peritoneal dialysis (CAPD) the fluid is present in the abdomen, which leads to an increased intra-abdominal pressure that causes complications like abdominal hernias and leak of dialysis fluids. Other complications include, encapsulating peritoneal sclerosis and other mechanisms of damage to the peritoneal membrane, complications similar to those encountered in the patients on hemodialysis (HD) including dialysis – associated amyloidosis and acquired cystic disease of the kidney.

Hernia Formation

Dialysis fluid in the peritoneal cavity leads to an increased intra- abdominal pressure (IAP). The pressure within the abdomen increases in proportion to the volume of dialysated instilled [1-3]. The supine patient generates the lowest IAP for a given volume of intraperitoneal fluid. Even in the supine patient on automated peritoneal dialysis, intraperitoneal pressure correlates with the volume of instilled dialysate [4, 5]. Intermittent events such as coughing and straining result in transient high pressures. In addition, patients who are older, more obese generate higher IAP for a given activity [1, 3].

Different types of Hernias

1. Ventral
2. Epigastric
3. Pericatheter
4. Umbilical
5. Inguinal –Direct and Indirect
6. Femoral
7. Foramen of morgagni
8. Cystocele
9. Spigelian
10. Richters

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11. Enterocoele

Indirect inguinal hernias are the result of bowel and /or dialysate tracking through the processus vaginalis, which in some individuals has remained patent rather than undergoing normal obliteration. It is much more common in the men. In boys, it is very likely that if one processus vaginalis is patent (causing inguinal hernia), then the other side is also patent, and repair should be done bilaterally.

Asymptomatic hernias are probably quite common and may not be detected until some complication such as bowel strangulation occurs. Different centers report a cumulative incidence of 10-15% of hernias in their patients on PD [6]. The most worrisome complications are incarceration and strangulation of bowel [7- 9].

Risk factors for hernia include large dialysate volumes, sitting position, isometric exercises, coughing, straining at stool, recent abdominal surgery, pericatheter leak or hematoma, obesity, multiparity and congenital anatomical defect.

Diagnosis.

1. Stand and bear down makes a hernia more obvious

2. Ultrasonography

3. Dye- assisted computed tomography (CT)

4. Magnetic resonance imaging

Treatment

The patient should be warned that if a hernia stops being reducible and tender; then they should approach the doctor on an immediate basis.Patient with peritonitis can have small strangulated hernias andthis can lead to transmural leakage of bacteria and peritonitis.*Surgical repair*

It is not usually necessary for the patient to be converted to HD around the surgical repair of a hernia [10, 11]. The patient can be maintained temporarily on “low – pressure” PD (smaller volumes in CAPD, day dry in APD) postoperatively to allow time for wound healing. An alternative is to hemodialyse the patient until wound healing is more complete (2-3 weeks). Conventional hernioplasty may be followed by the insertion of an overlying polypropylene mesh to reinforce the hernia repair [12, 13- 15].

If the patient is too ill or refuses surgery, mechanical support of the hernia can be effected with a corset or truss

Genital and Abdominal Wall Oedema

1. Edema of the labia majora, scrotum and penis is a distressing complication of PD. Early reports suggested that up to 10% of CAPD patients could experience genital oedema [16, 17]

2. Dialysate can reach the genitalia by two routes

i. Patent processus vaginalis to the tunica vaginalis, resulting in hydrocele.

ii. The second route is through a defect in the abdominal wall, often associated with the catheter tract.

3. It appears that women have a much lower incidence of genital oedema compared to men [18, 19].

4. Diagnosis is often clinical as it is painful and distressing to the patient

5. Other methods are, CT peritoneography and 3-5 mCi of Technetium – labeled albumin colloid scintigraphy.

Treatment

1. PD should be temporarily stopped.

2. Bed rest and scrotal elevation are helpful.

3. Temporary APD with low volumes and with the patient supine

4. HD can be used temporarily.

5. Repaired surgically.

6. Replacement of the catheter.

Abdominal Wall and Pericatheter Leak

1. Poor surgical technique may play a role in the development of pericatheter leak.

Diagnosis is done when

2. There is decreased effluent volumes, weight gain, protuberant abdomen, and absence of generalised edema.

3. Asymmetry of the abdomen.

4. Boggy look and impressions over abdomen

5. Pericatheter leak is diagnosed by wetness on the exit site dressing. A urine dipstick placed on the wet part will test strongly positive for glucose. A CT scan also can be done.

Treatment

1. The patient should be drained and PD stopped for at least 24 to 48 hours.

2. HD

3. In most cases, the leak seals spontaneously.

4. In persisting leak, the catheter should be removed and reinserted at another site

5. Antibiotic prophylaxis is not usually necessary for pericatheter leak unless there are obvious signs of infection.

In Abdominal wall leak, APD in the supine position usually allows the dialysate accumulation to resolve. If the leak is the result of disruption of abdominal wall integrity, the patient should be converted to a day dry APD regimen or to HD. Surgical repair is an alternative when feasible.

Encapsulating Peritoneal Sclerosis

Encapsulating peritoneal sclerosisoccurs in 1%-3% of patients. The outcome is generally poor with a high mortality, probably on the basis of severe malnutrition and recurrent bowel obstruction. It is usually seen after 5years and even more so after 10 years. Younger age at onset of PD is an independent risk factor. Thepatients who have transitioned to HD or renal transplant are also vulnerable.

No reliable association of EPS has been reported with the type or number of episodes of PD peritonitis, or with the type or strength of PD solutions used. Patients with underlying auto- immune/ inflammatory disease such as lupus or vasculitis may be predisposed. There are two phases of encapsulation- early inflammatory phase and late sclerosing phase with a fibrotic cocoon. The signs and symptoms include vague abdominal discomfort, a change to a rapid transport status, bloody effluent, and signs of inflammation, including erythropoietin – resistant anemia and elevated C- reactive protein, peritonitis, weight loss and recurrent bowel obstruction. The name of encapsulation should not be exchanged with peritoneal sclerosis.

Imaging is helpful in the sclerosing phase, where cocooning of the bowel is seen, in conjunction with thickening, tethering, enhancement, and calcification of the peritoneal membrane. The inflammatory phase of EPS is best treated with modest doses of corticosteroid Tamoxifen or m Tor inhibitors as their antifibrotic effects may be beneficial. There is no clarity on reducing the incidence on changing the patient to HD. In established abdominal cocoon and recurrent bowel obstruction, surgery may be necessary.

Calcifying Peritonitis may be a variant of EPS that is found very rarely**.** Benign course is observed as compared to that of EPS. Parietal peritoneum shows fibrous thickening and few cells. Bands of ossification and calcium deposits are also observed. It is most commonly seen in patients with hemoperitoneum, hyperparathyroidism, acetate buffer, high calcium - phosphate product. Since, it is a very rare condition, no proper recommendations for its treatment are available.Some of the measures include stopping PD, changing to HD, avoiding hypocalcemia, minimising calcium phosphate product and parathyroidectomy.

Gastrointestinal Complications of PD

Pancreatitis

Peritoneal dialysate can enter the peritoneal cavity through epiploic foramen which irritates the pancreas. Some of the irritants are high glucose concentration of dialysis fluid, unidentified toxic byproduct of the dialysate, bags, or tubing acidity of nonbiocompatible dialysate infected dialysate in a recurred episode of pancreatitis hypertriglyceridemia, adynamic bone disease, and hypercalcemia [20, 21, 22] Diagnosis is made when severe epigastric pain remains even after investigations are negative for peritonitis. Serum amylase values greater than three times the upper limit of normal are suggestive of acute pancreatitis. However, serum amylase may be falsely high in renal failure patients and negative with pancreatitis with use of Icodextrin.

Icodextrin may have inappropriately low levels of serum amylase during pancreatitis because metabolites of icodextrin interfere with the serum assay for amylase [23]. In them serum lipase, should be used.

Pancreatitis can also occur as a complication of peritonitis. Usually drain fluid is clear. It can be brown black in hemmorhagic pacreatitis due to methemalbumin, and cloudy due to the presence of triglycerides and fibrin.

Ultrasound and CT scanning can demonstrate an engorged, edematous pancreas, or pseudocyst formation [21, 22].

Mortality is high especially in patients with acute hemorrhagic pancreatitis and conversely, the persistence of clear dialysis fluid throughout the course of pancreatitis is a good prognostic sign. Treatment is conservative management.

Hepatic Complications

1. Fatty deposits under the hepatic capsule, which are nodular in shape seen in patients using intraperitoneal insulin and rapid transporters

2. Thickness of deposit correlates with obesity, and dose of intraperitoneal insulin.

3. Insulin in higher concenteration in subcapsular hepatocytes of abdomen in an obese patient with relative peripheral insulin deficiency, free fatty acids are re-esterified and cause steatonecrosis, but usually liver function remains normal.

4. If the patient changes from intraperitoneal to subcutaneous insulin, the steatotic lesions regress [24, 25].

5. The liver is also at risk for abscess formation as a result of dialysis – associated peritonitis

6. Ultrasound of the liver may be normal and exploratory laparotomy may be necessary. Needle aspiration and drainage under CT guidance is a less invasive alternative.

7. Portal vein thrombosis as a complication of *Staphylococcus aureus* peritonitis in a patient with alcoholic cirrhosis [26] and ascites after discontinuation of PD.

8. Post – PD ascites due to portal hypertension and other unknown causes is also a rare complication [27, 28].It usually resolves over the first year after discontinuation of PD.

Other Gastrointestinal Complications

1. Abdominal bloating and reflux may be due to an increased IAP and volume, diminished lower esophageal sphincter pressure and delayed gastric emptying.

2. Gastroesophageal reflux may also be responsible for cough, especially at night, in many patients on PD [29, 30].

Treatment includes frequent small meals, avoidance of foods that reduce sphincter pressure (chocolate, alcohol), decreased dialysis volumes, and the use of histamine – 2 blockers and proton – pump inhibitors. Pro – motility agents may be helpful, including oral domperidone and intraperitoneal erythromycin [31].

3. The small bowel perforation as a result from pressure necrosis from the dialysis catheter is also a rare complication

4. There are rare reports of ischemic colitis and necrotizing enteritis as complications of PD [32- 34]. The likeliest cause is hypotension with consequent hypoperfusion of the bowel.

5. Marked gastrointestinal bleeding from dialted submucosal vessel in the bowel has been reported in association with the use of hypertonic dextrose solutions. Other causes might be angiodysplastic bleeding vascular ectasia of the stomach.

6. Pneumoperitoneum can be seen due to air infused along with dialysis fluid particularly with “flush before fill” systems. The outcome is benign and the air

should gradually resorb. In a patient with severe abdominal pain, free air under the diaphragm on a chest x – ray suggest the possibility of perforation of an abdominal viscus and urgent measure should be taken in such cases.

Chyloperitoneum

1. Chylomicrons rich in triglycerides into the peritoneal cavity are referred to as chylous ascites, or as chyloperitoneum in the patient on PD. It occurs due to the blockage of lymphatic drainage from the gut to the main lymphatic trunks. Compromise of the integrity of these lymphatic channels is most commonly the result of neoplasm, particularly lymphoma. The diagnosis is suggested by the white, milky appearance of the dialysate in conjunction with the absence of any indication of peritonitis. Lipoprotein electrophoresis shows lipid staining at the origin, characteristic of chylomicrons [35]. The dialysate layer stains positive for fat with Sudan black and dissolves with ether [35, 36]. The triglyceride level of the dialysate is greater than the plasma triglyceride level, a characteristic of the intestinal lymph.

It is seen as a complication of tuberculous peritonitis, superior venacaval syndrome, lymphomas, intraabdominal malignancy, and use of calcium channel – blocker [37-39].

2. The treatment consists of a temporary cessation of PD. A diet of medium – chain fatty acids may be helpful until its resolution [35, 40]. Octreotide has also been reported to resolve chyloperitoneum in a patient on PD [41].

Hemoperitoneum

Some of the causes of hemoperitoneum are menstruation, ovulation, ovarian cysts in females, renal cell carcinoma, malignancy of colon, ADPKD, Pancreatitis, hepatic metastasis and malignancy, splenic rupture, anticoagulation therapy, ITP, sclerosing peritonitis, peritoneal calcification and cholecystitis A common and benign cause of blood in the peritoneal cavity is menstruation. In retrospective reviews of hemoperitoneum, menstrual bleeding is the single most common cause, accounting for more than one – third of the benign episodes, [42, 43] the majority of regularly menstruating women on CAPD experience recurrent hemoperitoneum [44].

The episodes of hemoperitoneum associated with menstruation and ovulation are recognized by their periodicity and occurrence in the women of reproductive age. It is usually benign except in rarely increasing anemia of chronic disease. The bloody dialysate may provide a rich growth medium for intraperitoneal bacteria especially *Staphylococcus epidermidis* peritonitis. If patient has a painful abdomen, and localised tenderness with the bloody effluent, urgent surgical consultation should be taken.

Due to the risk of catheter block, use of intraperitoneal heparin 500- 1,000 U/L has been recommended for as long as the dialysate still has visible blood or fibrin. The

use of rapid exchanges with dialysate at room temperature may lead to a rapid resolution of the bleeding. It is postulated that the relatively cool dialysate induces peritoneal vasoconstriction, and this leads to hemostasis [45]. The women of reproductive age should be educated about hemoperitoneum.

References

1. Twardowski, Z. J., R. Khanna, K. D. Nolph, A. Scalamonga, M. H. Metzler, T. W. Schneider, B. F. Prowant, and L. P. Ryan, 1986: Intraabdominal pressures during natural activities in patients treated with continuous ambulatory peritoneal dialysis. *Nephron,* **44,** 129- 135.

2. De Jessus, V. M., D. Amato, R. Correa – Rotter, and R. Paniagua, 2000: Relationship between fill volume, intraperitoneal pressure, body size, and subjective discomfort perception in CAPD patients. *Mexican Nephrol. Collaborative Study Group, Perit. Dial. Int.,* **20,** 188-193.

3. Dejardin, A., A. Robert, and E. Goffin, 2007: Intraperitoneal pressure in PD patients; relationship to intraperitoneal volume, body size and PD – related complications. *Nephrol. Dial. Transplant.,* **22,** 1437 – 1444.

4. Durand, P. Y., J. Chanliau, J. Gamberoni, D. Hestin, and M. Kessler, 1996: Measurement of Hypdrostatic to intraperitoneal pressure: A necessary routine test in peritoneal dialysis. *Perit. Dial. Int.,* **16,** 84-87.

5. Aranda, R. A., J. E. Romao, E. Kakehashi, W. Domingos, E. Sabbaga, M. Marcondes, and H. Abensur, 2000: Intraperitoneal pressure and hernias in children on peritoneal dialysis. *Pediat. Nephrol.,* **14,** 22-24.

6. Sush, H., N. K. Wadhwa, T. Cabralda, D. Sokunbi, and B. Pinard, 1994: Abdominal wall hernias in ESRD patients receiving peritoneal dialysis. *Adv. Perit. Dial.,* **10,** 58-88.

7. Griffin, P. J., and G. A. Coles, 1982: Strangulated hernias through Tenckhoff cannula sites. *Br. Med. J. (Clin. Res. ED),* **284,** 1837.

8. Shohot, J., Z. Shapira, D. Shmueli, and G. Boner, 1985: Intestinal incarceration in occult abdominal wall hernia in continuous ambulatory peritoneal dialysis. *Isr. J. Med. Sci.,* **21,** 985-987.

9. Wong, K. K., L. C. Lan, S. C. Lin, and P. K. Tam, 2003: Small bowel herniation and gangrene from peritoneal dialysis catheter exit site. *Pediatr. Nephrol.,* **18,** 301-302.

10. Carbtree, J. H., 2006: Hernia repair without delay in intimating or continuing peritoneal dialysis. *Perit. Dial. Int.,* **26,**178-182.

11. Shah, H., M. Chu, and J. M. Bargman, 2006: Perioperative management of peritoneal dialysis patients undergoing hernia surgery without the use of interim hemodialysis. *Perit. Dial. Int.,* **26,** 684-687.

12. Guzaman–Valdivia, G., and I. Zaga, 2001: Abdominal wall hernia repair in patients with chronic renal failure and dialysis catheter. *Hernia*, **5,** 9-11.

13. Imvrious, G., D. Tsakirits, D. Gakis, D. Takoudas, P. Koukoudis, M. Papadimitriou, and A. A. Antoniadis, 2005: Prosthetic mesh repair of multiple recurrent and large abdominal hernias in continuous ambulatory peritoneal dialysis patients. *Perit. Dial. Int.,* **25,** 295 – 296.

14. Kantartzi, K., A. Polychronidis, S. Perente, V. Vargemezis, and C. Simopoulos, 2005: Prolene hernia system: An innovative method for hernia repair in patients on peritoneal dialysis. *Perit. Dial. Int.,* **25,** 295-296.

15. Kantartzi, K., A. Polychronidis, M. Theodoridis, S. Perente, V. Vargemezis, and C. Simopoulos, 2005: Prolene hernia system: an innovative method for hernia repair in patients on continuous ambulatory peritoneal dialysis. *Clin. Nephrol.,* **63,** 325 – 326.

16. Kopecky, R. T., P. A. Frymoyre, L. S. Witanowaski, and F. D. Thomas, 1987: Complications of continuous ambulatory peritoneal dialysis: diagnostic value of peritoneal scintigraphy. *Am. J. Kid. Dis.,* **10,** 123-132.

17. Capelouto, C. C., and W. C. DeWolf, 1993: Genital Swelling secondary to leakage from continuous ambulatory peritoneal dialysis: computerized tomography diagnosis. *J. Urol.,* **150,** 196-198.

18. Tzallaloukasl, A. H., L. J. Gibel, B. Eisenberg, R. S. Goldllian, S. P. Kanig, P. G. Zager, L. Elledge, B. Wood, and D. Sillons, 1990: Early and late peritoneal dialysate leaks in patients on CAPD. *Adv. Perit. Dial.,* **6,** 61-64.

19. Abraham, G., P. G. Blake, R. E. Mathews, J. M. Bargman, S. Izatt, and D. G. Oreopoulos, 1990: Genital swelling as a surgical complication of continuous ambulatory peritoneal dialysis. *Surg. Gynecol. Obstet.,* **170,** 306-308.

20. Caruana, R. J., N. T. Wolfman, N. Karstaedt, and D. J. Wilson, 1986: Pancreatitis: an Important cause of abdominal symptoms in patients on peritoneal dialysis. *Am. J. Kid. Dis.,* **7,** 135–140.

21. Rutsky, E. A., M. Robards, J. A. Van Dyke, and S. G. Rostand, 1986: Acute pancreatitis in Patient with end stage renal disease without transplantation. *Arch. Intern. Med.,* **146,** 1741 -1745.

22. Flynn, C., P. Chandran, and C. Shadur, 1986: Recurrent pancreatitis in a patient on CAPD (letter). *Perit. Dial. Bull.,* **6,** 106.

23. Schoenicke, G., B. Grabensee, and J. Plum, 2002: Dialysis with icodextrin interferes with measurement of serum alpha- amylase activity. *Nephrol. Dial. Transplant.,* **17,** 1988-1992.

24. Kalili, K., F. P. Lan, A. E. Hanbidge, D. Muradali, D. G. Oreopoulos, and I. R. Wanless, 2003: Hepatic subcapsular statosis in response to intraperitoneal insulin delivery: CT finding and prevalence. *AJR Am. I. Roetgenal.,* **180,** 1601–1614.

25. Demir, S., D. Torun, N. Tokmak, U. Ozkan, and L. Oguzkurt, 2007: Resolution of heapatic subcapsular steatosis after discontinuation of CAPD. *Nephrol. Dial. Transplant.,* **22,** 1247 – 1249.

26. Lambrecht, G. L., M. L. Malbrain, P. Zachee, R. Daelemans, and R. L. Lins, 1994: Protal vein thrombosis complicating peritonitis in a patient on chronic ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **14,** 282-283.

27. Haq, M. Z., A. H. Tzamaloukas, D. Malhotra, and L. J. Gibel, 1997: Symptomatic ascites after discontinuation of continuous peritoneal dialysis. *Perit. Dial. Int.,* **17,** 568 -572.

28. Malagon, M., and R. J. Hogg, 1987: Renal transplantation after prolonged dwell peritoneal dialysis in children. *Kid. Int.,* **31,** 981 – 985.

29. Min, F., S. M. Tarlo, J. Bargman, N. Poonai, R. Richardson, and D. G. Oreopoulos, 2000:

Prevalence and cause of cough in chronic dialysis patients: a comparison between hemodialysis and peritoneal dialysis patients. *Adv. Perit. Dial.,* **16,** 129-133.

30. Tarlo, S. M., 2006: Peritoneal dialysis and cough. ACCP evidence – based clinical practice guidelines. *Chest,* **129,** 202-203.

31. De Graaf – Strukowska, L., C. A. van Hees, J. Ferwerda, N. H. Schut, and W. T. van Drop, 1995: Two non – diabetic patients with delayed gastric emptying during CAPD effectively treated with erythromycin. *Nephrol. Dial. Transplant.,* **10,** 2349-2350.

32. Steiner, R. W., and N. A. Halasz, 1990: Abdominal catastrophes and other unusual events in continuous ambulatory peritoneal dialysis patients. *Am. J. Kid. Dis.,* **15,** 1-7.

33. Rottembourg, J., G. M. Gahl, J. L. Poignet, E. Mertani, P. Strippoli, P. Langlois, P. Tranbaloc, and M. Legrain, 1983: Severe abdominal complications in patients undergoing continuous ambulatory peritoneal dialysis. *Proc. Eur. Dial. Transplant. Assoc.,* **20,** 236-242.

34. Koren, G., M. Aladjem, J. Militiano, B. Seegal, A. Jonash, and H. Boichis, 1984: Ischemic colitis in chronic intermittent peritoneal dialysis. *Nephron.,* **36,** 272-274.

35. Porter, J., W. M. Wang, and D. B. Oliveira, 1991: Chylous ascites and continuous ambulatory peritoneal dialysis. *Nephrol. Dial. Transplant.,* **6,** 659-661.

36. Humayun, H. M., J. T. Daugirdas, T. S. Ing, and D. J. Leehey, 1984: Chylous ascites in a patient treated with intermittent peritoneal dialysis. *Artif. Organs,* **8,** 358-360.

37. Yostimoto, K., S. Saima, Y. Nakamura, N. Nakayama, H. Kubo, Y. Kawaguchi, H. Nishitani, A. Yasui, K. Yokoyama, S. Kuriyama, D. Shirai, A. Kugiyama, K. Hayano, H. Fukui, I. Horigome, Y. Amagasaki, Y. Tsubakihara, T. Kamekawa, R. Ando, S. Tomura, R. Okamoto, S. Miwa, T. Koyama, and H. Echizen, 1994: Dihydropyridine type calcium channel blocker –induced turbid dialysate in patients undergoing peritoneal fluid cytology. *Am. J. Kid. Dis.,* **23,** 747 -750.

38. Bargman, J. M., R. Zent, P. Ellis, M. Auger, and S. Wilson, 1994: Diagnosis of lymphoma in a continuous ambulatory peritoneal dialysis patients by peritoneal fluid cytology. *Am. J. Kid. Dis.,* **23,** 747 -750.

39. Jain, S., L. Cropper, and P. Rutherford, 2003: Chylous ascites due to bile duct tumour in a patient receiving automated peritoneal dialysis. *Nephrol. Dial. Transplant.,* **18,** 224.

40. Melnick, J. Z., C. M. McCarty, M. P. Hunchik, and S. R. Alexander, 1995: Chylous ascites complicating neonatal peritoneal dialysis. *Pediatr. Nephrol.,* **9,** 753-735.

41. Lee, P. H., C. L. Lin, P. C. Lai, and C. W. Yang, 2005: Octreotide therapy for chylous ascites in a chronic dialysis patient. *Nephrol.,* **10,** 344-347.

42. Greenbag, A., J. Bernardini, B. M. Piraino, J. R. Johnston, and J. A. Perlmutter, 1992: Hemoperitoneum in women undergoing chronic peritoneal dialysis: single – center experience and literature review. *Am. J. Kid. Dis.,* **19,** 252-256.

43. Tse, K. C., P. S. Yip, M. F. Lam, F. K. Li, B. Y. Choy, T. M. Choy, and K. N. Chai, 2002: Recurrent hemoperitoneum complicating continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **22,** 488-491.

44. Holley, J. L., M. Schiff, R. J. Schmidt, F. H. Bender, and F. Dumler, 1996: Hemoperioneum occurs in over half of menstruating women on peritoneal dialysis. *Perit. Dial. Int.,* **16,** 650.

45. Goodkin, D. A., and M. G. Benning, 1990: An outpatient maneuver to treat bloody effluent during continuous ambulatory peritoneal dialysis (CAPD). *Perit. Dial. Int.,* **10,** 227-229.

Chapter 40

Non - Infectious Complications of Peritoneal Dialysis – Respiratory and Cardiovascular Complications

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Non - Infectious Complications of Peritoneal Dialysis – Respiratory and Cardiovascular Complications

Peritoneal dialysis (PD) can have deleterious effects not just on the mechanics of breathing and cardiovascular contractility by an increase in the intra-abdominal pressure (IAP) but can also influence these systems adversely by the high concentration of glucose in the PD fluid.

Effects on pulmonary gas exchanges

Early studies conducted on acutely ill patients and the more recent studies conducted on stable patients initiated on continuous ambulatory peritoneal dialysis (CAPD) showed a reduction in most of the lung volumes [1-3]. Many of these patients regained their baseline lung function after 2 weeks when they were on CAPD. These changes are no worse in patients on COPD [4]. It is also observed in some studies that at the initiation of PD, the PaO_2 may reduce by 8 mm of Hg and this would recover to baseline values in the ensuing months despite a persistent reduction of FRC.This is postulated to happen due to the redistribution of blood from the less ventilated areas to the more ventilated areas. In the long term, persistent subclinical pulmonary edema leading to the development of interstitial lung disease makes the diffusion capacity of carbon monoxide worse (DLCO less than 70%) in patients on CAPD in comparison to patients who are on hemodialysis or have undergone renal transplantation [5].

Indeed, it is interesting to note that the presence of fluid in the abdomen may in fact improve the pulmonary function. The contractility of the diaphragm is enhanced after infusion of the PD fluid due to the stretch of the diaphragm muscles (Starling's law) and the increase in the curvature of the diaphragm leading to a reduction of the radius reduction in the radius of the diaphragm (Laplace law) [6]. This may be the reason why there is no statistical difference in the results of the pulmonary function tests done with or without the fluid in the abdomen [7].

Persistent subclinical pulmonary edema leading to the development of interstitial lung disease makes the diffusion capacity of carbon monoxide worse (DLCO less than 70%) in patients on CAPD in comparison to patients who are on hemodialysis (HD) or have undergone renal transplantation [5].

A. Sashi Kiran

Buffer metabolism and respiratory dynamics

It is seen in patients receiving total parenteral nutrition that there is an increase in the minute ventilation, carbon dioxide excretion and oxygen consumption [8]. Studies in the patients on CAPD have shown similar changes [9]. Because some of the glucose is metabolized in a manner that does not require oxygen but produces carbon dioxide, we see that the respiratory quotient increases. The PCO_2 is kept normal by the compensatory hyperventilation that ensures but in patients who are too ill to hyperventilate or have a respiratory muscle weakness this may lead to respiratory acidosis every time a high glucose PD fluid is infused [10].

Hydrothorax

In about 5% of the people on PD, it could be seen that the dialysis fluid is getting accumulated into the pleural cavity and most frequently on the right [11, 12]. The incidence may be much higher as most of the times it is asymptomatic. Majority of the patients are women making us implicate pregnancy induced stretch of the diaphragm as a possible contributing factor [13]. It is interesting to note that patients with ADPKD have a disproportionately high incidence either due to the higher IAP due to presence of large kidneys or due to the weakness of the diaphragm seen in this condition [14].

Pathogenesis

Studies involving surgery or pleuroscopy showed that the instillation of dialysate fluid into the abdomen can reveal blebs on the pleural side of the diaphragm which may swell and rupture as the IAP increases [13]. Based on these studies, it can be implied that the cause of hydrothorax can be either a localized deficiency of muscle fibers or a defect in the musculotendinous part of the diaphragm. These defects may not be rare occurrences and may be detected only in situations where there is a raised IAP.

Patients with clear rent in the diaphragm may develop hydrothorax after the first few cycles of PD but in patients who have attenuated tissue it may take repeated cycles of PD or an episode of peritonitis to disrupt the tissue before hydrothorax develops [15, 16].

Clinical features

Half of the patients developing hydrothorax present within a month of starting CAPD and a quarter of the remaining within a year, but there are reports where it was detected as late as 8 years after the initiation of CAPD [17]. Dyspnea and persistent ultrafiltration failure should make one suspect the presence of hydrothorax [17]. Other less common symptoms can be weight gain, chest pain or hypotension [18]. However, in a quarter of patients on CAPD, hydrothorax is an incidental finding, it being recognized on routine physical examination or chest radiograph [17].

Diagnosis

A chest radiograph will reveal a pleural effusion. A thoracentesis can sometimes be used to ascertain the nature of the pleural fluid by estimating the glucose content [19].

Modalities for evaluation of the defects

Erstwhile investigations like methylene blue instillation and contrast catheterograms are no longer necessary. The ones that are used currently are mentioned below.

Peritoneal scintigraphy

This method which is commonly used to demonstrate the inflow and distribution pattern of PD fluid can also be used to identify the leaks in the peritoneal cavity [20]. About 5 millicurie of Technetium 99 is added to 2 liters of PD fluid and is injected into the peritoneal cavity. The patient is encouraged to ambulate or roll over to facilitate the movement of fluid into the pleural space. Multiple projections are taken periodically for about 6 hours following the instillation to help identify the site of leak [21]. The net exposure of radiation to the patient is minimal since most of the administered isotope is not absorbed and is eventually drained from the body.Hence, this is a safe and accurate method of diagnosis of peritoneal leaks (**Figure 1**).

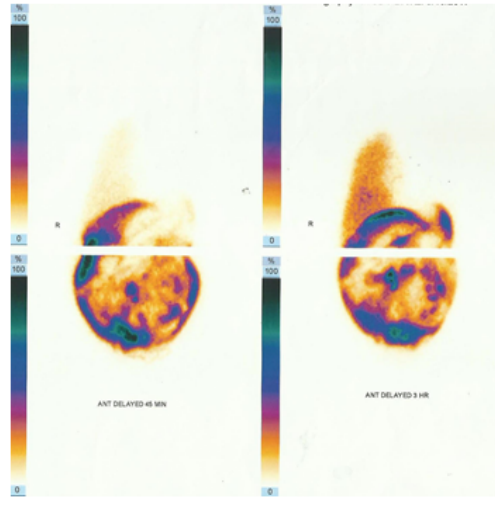

Figure 1: Peritoneal Scintigraphy Showing Pleuroperitoneal Communication on Right Side.

CT Peritoneography (CTP)

This is an accurate method to detect peritoneal leaks. Like in scintigraphy, about 50 ml of iodinated contrast is mixed with PD fluid and is infused into the peritoneal cavity. A major concern with this procedure is the intense radiation exposure to children.

MR Peritoneography

MR peritoneography can be a useful tool in instances where peritoneal scintigraphy or CTP cannot be used. The PD fluid itself can act as a contrast material due to the presence of electrolytes obfuscating the need for using Gadolinium, thus avoiding nephrogenic systemic fibrosis [22].

Treatment of Hydrothorax

In the rare patient with acute respiratory distress, a thoracentesis can be performed but in most instances draining the abdominal cavity itself would provide relief. Subsequent management in a patient who desires to remain on PD would be as follows:

Short course hemodialysis with subsequent return to CAPD

In instances where an episode of peritonitis disrupts the mesothelium leading to the appearance of hydrothorax, it would be ideal for the patient to remain on HD for 4 weeks to allow the mesothelium to repair. Later the patient may resume CAPD as before.

Short course hemodialysis with subsequent CCPD

Most of the patients who develop hydrothorax would do well with a PD by cycler for quite some time. The smaller dialysis volumes with more frequent exchanges would minimize the occurrence of hydrothorax [23].

Pleurodesis

Pleurodesis with autologous blood or talc or oxytetracycline (20 mg/kg) can be offered to patients with recurrent episodes of hydrothorax [24, 25]. The benefit of this therapy may be seen in two-third of the patients [26].

Operative repair

The defects in the pleural or peritoneal space can be visualized during a visual-assisted thoracoscopy procedure and repaired [27]. Surgical repair can beoffered to children with eventration of diaphragm before initiating them on PD.

Cardiovascular disease (CVD)

It is observed that the right and left atrial pressures are increased in conditions of elevated intra-abdominal pressure like cirrhosis and these pressures improve following the removal of fluid from the abdominal cavity. But, in the patients on CAPD a similar phenomenon is not observed consistently. Results from various studies have revealed that the infusion of as much as 3liters of dialysis fluid would have no effect on the cardiac index (CI) in most patients but may reduce the CI by 20% in some [28, 29]. Hence, it appears that the presence of 2 liters of intraperitoneal dialysate does not have a significant effect on the cardiovascular system.

Cardiovascular morbidity and mortality including not just ischemic heart disease, but, also new onset congestive heart failure (CHF), peripheral vascular disease and stroke is 10 to 30 % more prevalent in ESRD population on CAPD. The development of CVD appears to be complex interplay between the uremic risk factors (uremic toxins, volume overload, vascular calcifications, hyperparathyroidism) and novel risk factors (inflammation, oxidative stress, endothelial dysfunction, malnutrition, epigenetic changes) along with the traditional risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking, male sex and a sedentary life style). Factors like hypokalemia and low blood pressures, unique to be seen in a patient on PD but not seen in patients on HD would contribute additionally for the CVD.

Evaluation

There is no evidence to suggest that universal screening for coronary disease is beneficial [30]. In patients at risk of developing CVD, cardiac perfusion studies like Dobutamine stress echography and Thallium scintigraphy may be useful. Echocardiography would help in evaluating left ventricular hypertrophy, valvular calcification, systolic and diastolic dysfunction. A 12 lead electrocardiography would ideally be performed at the initiation of PD and repeated once a year to detect any arrhythmias.

It is difficult to define a reference range for cardiac troponins in patients with renal failure hence serial measurement of troponin I and troponin T are important in diagnosing acute myocardial infarction. An increase in troponin level of more than 20% within 4 to 6 hours should be diagnosed as acute coronary syndrome [31]. Care should be taken that at least one of the troponin value is above the 99 percentile.

Carotid duplex ultrasonography needs to be performed in patients who have suffered a transient ischemic attack or an acute thromboembolic stroke to identify the presence of carotid artery stenosis [32].

An ankle-brachial index of less than 0.9 and a toe-brachial index less than 0.6 would suggest the presence of peripheral vascular disease [33].

Management

Integral to the management are regular physical activity at least 5 times per week, saltrestriction to less than 5 gm of NaCl per day and cessation of smoking [34, 35]. Patients with ESRD with a good residual kidney function (RKF) have a better survival advantage. Hence, the RKF needs to be estimated using a 24 hour urinary clearance for urea and creatinine at least once every 6 months. The rate of loss of RKF should not be more than 4 ml/min/1.73m^2/year [36]. The RKF can be better preserved with the use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) along with a neutral pH and low GDP containing PD fluid.

Volume overload contributes significantly to the mortality in patients on HD as well as PD. Along with the clinical assessment of volume status, monitoring of timed ultrafiltrate collection once in 6 months is necessary. Advising once daily icodextrin in a long dwell would be ideal, if patients have a difficulty in maintaining euvolemia.

To prevent the microvascular complications of diabetes, the HbA1C levels need to be less than 7% but the target can be relaxed to 8.5% in older patients with a single end stage chronic illness as a stage 3-4 CHF or an oxygen dependent lung disease [37, 38]. If insulin and oral hypoglycemic drugs prove insufficient to achieve this target, then once daily icodextrin may be advised.

Home blood pressure measurements at least once a week are necessary to ensure that the blood pressure is consistently below 140/90 mm hg but care must be taken as systolic pressure less than 110 mm hg is associated with an increased mortality. This target can be met with the use of diuretics, fluid control, salt restriction, use of glucose free PD solutions in addition to the antihypertensive medications preferably ACEI or ARB.

Patients undergoing PD are particularly at risk of developing hypokalemia. Low extracellular potassium increases the likelihood of re-entrant arrhythmia where as high potassium concentration would cause ventricular fibrillation [39]. Hence, it is prudent to maintain the potassium level between 3.5 and 5.5 meq/L.

Patients on PD have a worse lipid profile than those on HD due to the systemic glucose absorption and peritoneal protein loses. Statins effectively reduce the cholesterol levels but it remains to be proven conclusively if this helps in reducing the cardiovascular mortality. A study involving patients treated with a combination of simvastatin and ezetimibe showed a reduction in cardiovascular events but had no effect on cardiovascular mortality.

Patients with ischemic heart disease need antiplatelet agents and those with LVH benefit with ACEI or ARBs. Spironolactone too has shown to reduce the progression of left ventricular mass index. Beta blockers would benefit patients with dilated cardiomyopathy or systolic heart failure.

Dialysis patients have a very high mortality rate due to CVD. Recent focus is on the contribution of the nontraditional and uremia specific risk factors. Evidence shows that these factors are at play from an early stage of declining renal function making it prudent to evaluate and initiate treatment early.

References

1. Berlyne, G., H. Lee, and A. Ralston, 1966: Pulmonary complications of peritoneal dialysis.*Lancet*, **2,** 75-78.

2. da Silva, T., W. B. Davis, and D. E. Coleman, 1985: Peritonitis, dialysate infusion and lung infection in continuous ambulatory peritoneal dialysis. *Clin. Nephrol.,* **24,** 79-83.

3. Gokbel, H., M. Yeksan, and E. Dogan, 1998: Effects of CAPD application on pulmonary function. *Perit. Dial. Int.,* **18,** 344-345.

4. Singh, S., Dale, A., and B. Morgan, 1984: Serial studies of pulmonary functionin continuous ambulatory peritoneal dialysis: A prospective study. *Chest*, **86,** 874-877.

5. Bush, A., and R. Gabriel, 1991: Pulmonary function in chronic renal failure: effects of dialysis and transplantation. *Thorax*, **46,** 424-428.

6. Gomez-Fernandez, P., L. Sanchez Agudo, J. M. Calatrava, F. Escuin, R. Selgas, M. E. Martinez, and L. Sanchez-Sacilia, 1984: Respiratory muscle weakness in uremic patients under continuous ambulatory peritoneal dialysis. *Nephron,* **36,** 219-223.

7. Ulubay, G., S. Sezer, and S. Ulasli, 2006: Respiratory evaluation of patients on continuous ambulatory peritoneal dialysis prior to renal transplantation. *Clin. Nephrol.,* **66,** 269-274.

8. Eiser, A. R., 1985: Pulmonary gas exchange during hemodialysis and peritoneal dialysis: interaction between respiration and metabolism. *Am. J. Kid. Dis.,* **6,** 131-142.

9. Fabris, A., S. Biasioli, C. Chiaramonte, M. Feriani, E. Pisani, C. Ronco, G. Cantarella, and G. La Greca, 1982: Buffer mechanisms in continuous ambulatory peritoneal dialysis (CAPD): Relationship with respiratory dymanics. *Trans. Am. Soc. Artif. Intern. Organs,* **28,** 270-275.

10. Cohn, J., R. A. Balk, and R. C. Bone, 1990: Dialysis-induced respiratory acidosis. *Chest,* **98,** 1285-1288.

11. Duffy, J. P., S. M. Allen, and H. R. Matthews, 1994: Hydrothorax due to dialysate leakage. *Clin. Nephrol.,* **42,** 65.

12. Garcia, R. R., and A. M. Carrasco, 1998: Hydrothorax in peritoneal dialysis. *Perit. Dial. Int.,* **18,** 5-10.

13. Boeschoten, E. W., R. T. Krediet, C. M. Roos, J. J. Kloek, M. E. I. Scipper, and L. Arisz, 1986: Leakage of dialysate across the diaphragm: an important complication of continuous ambulatory peritoneal dialysis. *Neth. J. Med.,* **29,** 242-246.

14. Fletcher, S., J. H. Turney, and A. M. Brownjohn, 1994: Increased incidence of hydrothorax complicating peritoneal dialysis in patients with adult polycystic kidney disease. *Nephrol. Dial. Transplant.,* **9,** 832-833.

15. Bundy, J. T., and P. J. Pointer, 1994: Cough induced hydrothorax in peritoneal dialysis. *Perit. Dial. Int.,* **14,** 293.

16. Huang, J. J., J. S. Wu, and W. C. Chi, 1999: Hydrothorax in continuous ambulatory peritoneal dialysis: therapeutic implications of Tc-99m MAA peritoneal scintigraphy. *Nephrol. Dial. Transplant.,* **14,** 992-997.

17.Nomoto, Y., T. Suga, K. Nakajima, H. Sakai, G. Osawa, K. Ota, Y. Kawaguchi, T. Sakai, S. Sakai, M. Shibat, and S. Takahashi, 1989: Acute hydrothorax in continuous ambulatory peritoneal dialysis--a collaborative study of 161 centers. *Am. J. Nephrol.,* **9,** 363-367.

18. Abraham, G., A. Shokker, P. Blake, and D. G. Oreopoulos, 1988: Massive hydrothorax in patients on peritoneal dialysis: A literature review. *Adv. Perit. Dial.,* **4,** 121.

19. Tang, S., W. H. Chui, A. W. Tang, F. K. Li, W. S. Chau, Y. W. Ho, T. M. Chan, and K. N. Lai, 2003: Video-assisted thoracoscopic talc pleurodesis is effective for maintenance of peritoneal dialysis in acute hydrothorax complicating peritoneal dialysis. *Nephrol. Dial. Transplant.,* **18,** 804-808.

20. Gudit, S., P. Sudhakar, R. Ram, N. Prasad, V. V. S. Prabhakar, and K. V. Dakshinamurthy, 2010: Peritoneal scintigraphy in the diagnosis of adhesions. *Perit. Dial. Int.,* **30,** 112-113.

21. Berman, C., M. G. Velchik, N. Shusterman, and A. Alavi, 1989: The clinical utility of the Tc-99m SC intraperitoneal scan in CAPD patients. *Clin. Nucl. Med.,* **14,** 405.

22. Prischl, F. C., T.Muhr, E. M.Seiringer, S. Funk, G. Kronabethleitner, M. Wallner, W. Artmann, and R. Kramar, 2002: Magnetic resonance imaging of the peritoneal cavity among peritoneal dialysis patients, using the dialysate as "contrast medium". *J. Am. Soc. Nephrol.,* **13,** 197-203.

23. Christidou, F., and G.Vayonas, 1995: Recurrent acute hydrothorax in a CAPD patient: successful management with small volumes of dialysate. *Perit. Dial. Int.,* **15,** 389.

24. Hidai, H., S. Takatsu, and T. Chiba, 1989: Intrathoracic instillation of autologous blood in treating massive hydrothorax following CAPD. *Perit. Dial. Int.,* **9,** 221-223.

25. Kanaan, N., T. Pieters, F. Jamar, and E. Goffin, 1999: Hydrothorax complicating continuous ambulatory peritoneal dialysis: successful management

with talc pleurodesis under thoracoscopy. *Nephrol. Dial. Transplant.,* **14,** 1590-1592.

26. Sudduth, C. D., and S. A. Sahn, 1992: Pleurodesis for nonmalignant pleural effusions: Recommendations. *Chest*, **102,** 1855-1860.

27. Yen, H. T., H. Y. Lu, and H. P. Liu, 2005: Video-assisted thoracoscopic surgery for hydrothorax in peritoneal dialysis patients-check-air-leakage method. *Eur. J. Cardiothorac. Surg.,* **28,** 648-649.

28. Schurig, R., G. Ghal, M. Schartl, H. Becker, and M. Kessel, 1979: Central and peripheral hemodynamics in long term peritoneal dialysis patients. *Proc. Eur. Dial. Transplant. Assoc.,* **16,** 165-170.

29. Swartz, C., G. Onesti, L. Mailloux, M. Neff, O. Remirez, P. Germon, I. Kazem, and L. W. Luther, 1969: The acute hemodynamic and pulmonary function effects of peritoneal dialysis. *Trans. Am. Soc. Artif. Intern. Organs,* **15,** 367-372.

30. Friedman, S. E., R. T. Palac, D. M. Zlotnick, M. C. Chobanian, and S. P. Costa, 2011: A call to action: variability in guidelines for cardiac evaluation before renal transplantation. *Clin. J. Am. Soc. Nephrol.,* **6,** 1185–1191.

31. Wu, A. H., A. S. Jaffe, F. S. Apple, R. L. Jesse, G. L. Francis, D. A. Morrow, L. K. Newby, J. Ravkilde, W. H. W. Tang, and R. H. Christenson, 2007: National Academy of Clinical Biochemistry laboratory medicine practice guidelines: use of cardiac troponin and B-type natriuretic peptide or N-terminal proB-type natriuretic peptide for etiologies other than acute coronary syndromes and heart failure. *Clin. Chem.,* **53,** 2086–2096.

32. Furie K. L., S. E. Kasner, R. J. Adams, G. W. Albers, R. L. Bush, S. C. Fagan, J. L. Helperin, S. C. Johnston, I. Katzan, W. N. Kernan, P. H. Mitchell, B. Ovbiagele, Y. Y. Palesch, R. L. Sacco, L. H. Schwamm, S. W. Smoller, T. N. Turan, and D. Wentworth, 2011: Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, **42,** 227–276.

33. Hirsch, A. T., Z. J. Haskal, N. R. Hertzer, C. W. Bakal, M. A. Creager, and J. L. Halperin, 2006: ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood

Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation*, **113,** 463–654.

34. de Brito-Ashurst, I., L. Perry, T. A. Sanders, J. E. Thomas, H. Dobbie, M. Varagunam, and M. M. Yakoob, 2013: The role of salt intake and salt sensitivity in the management of hypertension in South Asian people with chronic kidney disease: a randomised controlled trial. *Heart*, **99,** 1256–1260.

35. Braatvedt, G., B. Rosie, W. Bagg, and J. Collins, 2006: Current and former smoking increases mortality in patients on peritoneal dialysis. *N. Z. Med. J.,* **119,** 1–10.

36. Fan, S. L., T. Pile, S. Punzalan, M. J. Raftery, and M. M. Yaqoob, 2008: Randomized controlled study of biocompatible peritoneal dialysis solutions: effect on residual renal function. *Kid. Int.,* **73,** 200–206.

37. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease: Chapter 3: Management of progression and complications of CKD. *Kid. Int.,* **3,** 73–90.

38. American Diabetes Association, 2014: Standards of medical care in diabetes—2014. *Diabetes Care,* **37,** 14–80.

39. Osadchii, O. E., 2010: Mechanisms of hypokalemia-induced ventricular arrhythmogenicity. *Fundamental Clin. Pharmacol.,* **24,** 547–559.

Chapter 41

Non-infectious Complications of Peritoneal Dialysis: Haemoperitoneum and Chyloperitoneum

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Introduction

Chronic peritoneal dialysis (PD) as a viable modality of renal replacement therapy (RRT) has been utilised in clinical practice for more than three decades in India. Initial challenges for practicing nephrologists were the infectious complications of the procedure. [1] As we bring down the rates of peritonitis in our patients, patient survival with PD increases. This makes non infectious complications relatively more important, of which mechanical catheter complications and metabolic derangements like dyslipidemia *etc.* are quite common [2].

Hemoperitoneum and chyloperitoneum are rare non infectious complications in patients with PD [3] are often benign but can pose difficult management problems and can lead to serious outcomes if the underlying cause is not diagnosed early and treated appropriately.

Hemoperitoneum

Blood in the peritoneal dialysate fluid is defined as hemoperitoneum (**Figure 1**). It is an infrequent occurrence in PD patients. Sometimes, it is procedure related, in other occasions it reflects the presence of serious underlying pathology as the PD catheter is a window to the intraabdominal structures.

Epidemiology

In a large series of PD patients from USA, hemoperitoneum was seen complicating PD in 6.15% of patients. Overall, 65% of these patients were women (9.7% incidence in women with PD *vs* 3.6% men with PD). There was no racial predilection [4].

U. Anand

Figure 1: Hemoperitoneum

The mean age at first episode of hemoperitoneum in this cohort was 43.4 ± 16.8 years. The mean interval at first episode of hemoperitoneum was 17.8 ± 22.7 months (range, 0.6-83.2 months) after starting PD. Hemoperitoneum can be seen immediately after insertion of the catheter and commencement of the dialysis procedure. It can also manifest as late as 72 months after starting PD.

Etiology and clinical features

Majority of the episodes of hemoperitoneum are related to gynecologic causes and often benign. Menstruation and ovulation are the major cause of bloody dialysate. Usually, there is a mild pink discolouration of the dialysate, in some instances though, grossly bloody dialysate is obtained. All women patients of the reproductive age group on PD should be informed about this complication [5]. Hemoperitoneum in such a situation is related to the reproductive cycle and is self limiting. These women may present with mild abdominal tenderness secondary to blood induced peritoneal irritation. The blood in the peritoneal cavity is because of retrograde menstruation or rupture of a follicular cyst during ovulation. Rarely, endometriosis in the peritoneal cavity can be responsible for the bloody dialysate [6]. The hemoperitoneum in ruptured follicular cyst happens mid cycle. It is important to note that amenorrhoic PD patients may resume menstruation with the improvement of the uremic milieu on starting dialysis. The obstetric causes of hemoperitoneum are mentioned in **Table 1** along with other reported causes of hemoperitoneum.

The other causes of hemoperitoneum can be broadly classified as:

1. Catheter related.

2. Intra-abdominal Pathology.

3. Intra-abdominal vascular catastrophes.

4. Procedure related.

5. Bleeding diathesis.

6. Infections.

7. Sclerosing peritonitis.

Catheter related bloody dialysate is often noted immediately after insertion of the catheter. Bleeding happens because of trauma to the peritoneal vessels during the procedure. Also, the patient who is yet to be dialysed has a bleeding predisposition because of uremia. Occasionally, bleeding during catheter placement can happen in patients who have undergone previous abdominal surgery (appendectomy, ovarian resection, hysterectomy, caesarean section, open cholecystectomy, segmental resection of the small intestine *etc*.) [7]. In these patients, laparoascopic assisted catheter placement is often associated with adhesiolysis which increases the risk of bleeding. The catheter was also responsible for intra-abdominal visceral injury and hemoperitoneum. Review of literature showed two case reports of catheter induced mesenteric vascular injury and splenic injury [8, 9]. In pregnant women, the pelvic PD catheter was responsible for a serosal tear of the uterus and serious intra-abdominal bleeding [10].

Hemoperitoneum secondary to underlying intra-abdominal pathology can be a serious medical problem if not detected early. Various abdominal visceral pathology causing bloody dialysate is mentioned in **Table 1**. Bleeding in the peritoneal cavity has been reported with rupture of cysts in kidneys (both acquired and hereditary). Intraperitoneal bleeding secondary to cyst rupture in polycystic kidneys (retroperitoneal organ) is explained by the adhesions formed between the cyst wall and peritoneum [11, 12]. Bloody dialysate has also been noted in hepatic (cysts, malignant lesion,) and splenic (traumatic, splenic infarction, chronic myelogenous leukemia, amyloidosis) rupture. Often these patients present with massive hemoperitoneum and hemodynamic compromise [13, 14]. In some instances, they develop peritonitis (chemical, secondary infection). Similarly, vascular catastrophes like rupture of omental artery aneurysm present with hemoperitoneum and shock [15]. Mesenteric ischemia leading to extensive gut infarction can present with peritonitis and hemoperitoneum. The patient had refractory peritonitis and succumbed to her illness despite all the measures [16]. Hemoperitoneum can happen with misadventures related to intra-abdominal procedures. A case report highlights massive hemoperitoneum requiring blood transfusion following a difficult colonoscopy. Multiple attempts to pass the scope around the splenic flexure lead to splenic avulsion from its attachments from the diaphragm [17].

Uremic coagulopathy and anemia by itself lead to bloody dialysate especially at the time of catheter insertion. In some patients, besides uremia, presence of other factors (thrombocytopenia, warfarin therapy) lead to increased bleeding risk and a bloody dialysate [18].

RBCs are detected during a peritonitis episode but macroscopic blood in the peritoneal dialysate is rare. Peritonitis and hemoperitoneum should lead us to suspect underlying intra-abdominal pathology. A rare case of cytomegalovirus infection induced hemoperitoneum was reported in the literature [19].

Table 1: Causes of Hemoperitoneum

S. No	Causes		
1.	Obstetric		Menstruation
			Ovulation
			Ruptured follicular Cyst
		Hemorrhagic luteal cyst	Pregnancy (Uterine tear, HELLP, Abruptio Placentae)
2.	Catheter related		
3.	Intra-abdominal Pathology	Kidneys	Ruptured Cysts (Acquired, ADPKD, Tuberous sclerosis)
		Spleen	Splenic infarct
			Splenic rupture
		Liver	Ruptured cysts
			Malignancies
4.	Intra-abdominal vascular catastrophes	Aortic aneurysm rupture	
		Gut Infarction secondary to mesenteric ischemia	
5.	Procedure related	Colonoscopy	
		Pericardiocentesis	Radiation
6.	Bleeding diathesis	Thrombocytopenia	
		Anticoagulants	
7.	Infections	Cytomegalovirus infection	
		Peritonitis	
8.	Sclerosing peritonitis		

Hemoperitoneum usually presents early in the course of peritoneal dialysis. However, there are increasing instances of hemoperitoneum occurring years after starting PD. In majority of the cases, the underlying cause is sclerosing peritonitis. Though intestinal obstruction is the major clinical presentation and 8% of these patients develop hemoperitoneum [20]. The blood loss into the peritoneum is believed to be due to the rupture of omental venules of the thickened peritoneum. Prognosis is often poor in these patients [21]. The premise that peritoneal thickening predisposes to hemoperitoneum has also been discussed in a case of hemoperitoneum complicating radiation induced peritoneal membrane injury in a patient on PD [22].

Recurrent Hemoperitoneum

Recurrent hemoperitoneum is defined as two or more episodes of bloody dialysate in the course of CAPD. It is a rare phenomenon and is usually due to:

1. Gynecologic causes (retrograde menstruation).

2. Bleeding diathesis (use of wardfarin, aspirin).

3. Catheter irritation.

4. Ruptured renal/hepatic cysts.

5. Rupture of omental venules in patients with sclerosing peritonitis [23].

Management

A thorough clinical history often gives a clue to the underlying cause. Relation of the bleeding to the menstrual history often leads to the exact gynecologic cause of hemoperitoneum. Possible bleeding diathesis as an underlying cause is ascertained if a positive history of use of anticoagulants is obtained. If the diagnosis is unclear, further abdominal imaging in the form of ultrasound, computed tomography, and/or MRI are performed. Angiography is useful in delineating the site and the source of bleeding in certain cases. In some cases, a diagnostic laparoscopy and even an exploratory laparotomy is required to arrive at the cause of hemoperitoneum. In our case, laparotomy was done which showed the presence of extensive gut infarction [16].

The initial treatment is a rapid exchange with cold dialysate to remove the blood from the peritoneal cavity [24]. Modification of the anticoagulant dose is done if bleeding is because of drugs. Bed rest and intraperitoneal heparin is advised in some cases. Patients with massive bleeding are transfused blood. Intravenous desmopressin, synthetic estrogens, fresh frozen plasma and cryoprecipitates are used to correct uremic bleeding. Further, treatment depends on the results of imaging /laparotomy (catheter removal, catheter repositioning, surgical treatment of ruptured cysts *etc.*) [25]. Tubal ligation has been successful in curing recurrent

hemoperitoneum secondary to retrograde menstruation. The summary of evaluation and management of hemoperitoneum is outlined in **Figure 2**.

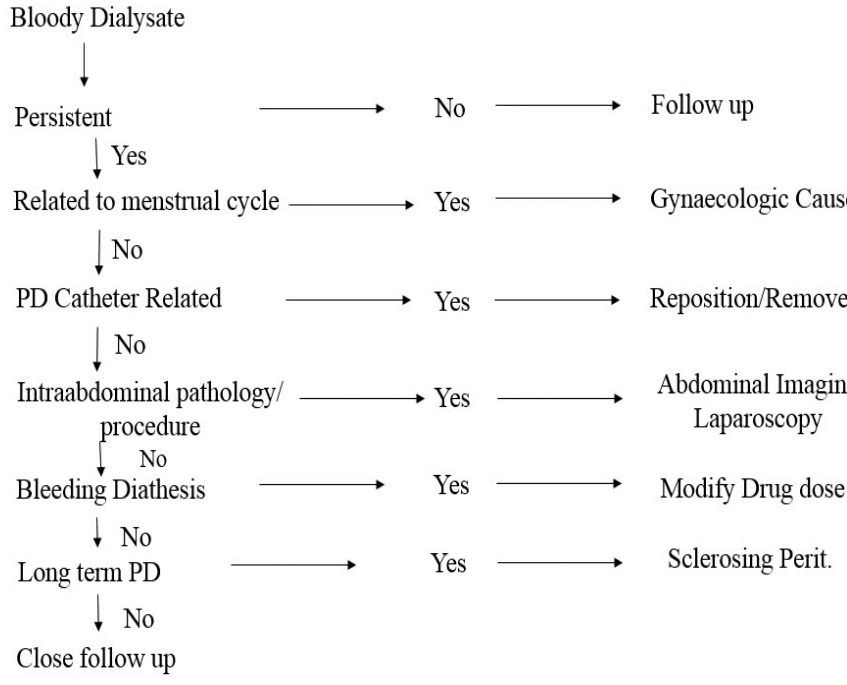

Figure 2: Evaluation and Management of Hemoperitoneum

Complications and Outcomes

Complications are minimal if the bleeding is minor. However, major bleeding may lead to catheter obstruction secondary to blood clots. Procedure failure can happen if the bleeding happens in the dry peritoneal cavity. This can lead to adhesions. Hemoperitoneum does not predispose to peritonitis or ultrafiltration failure [23]. Membrane characteristics also don't change usually because of the hemoperitoneum [26].

Chyloperitoneum

Patient

A 55-year old man with end stage renal disease (ESRD) was initiated on automated PD (APD) with 2.5% Dianealsolution (Baxter India, Haryana, India). The peritoneal effluent was cloudy on starting PD. The patient had no symptoms suggestive of peritonitis. All the cultures were negative. There was no evidence of

solid organ malignancy, pancreatitis or lymphoma. The effluent triglyceride levels were at 540 mg/dl, 610 mg/dl, and 520 mg/dl on 3 consecutive days. The patients was diagnosed with chyloperitoneum (CP). No pathology was observed in Contrast enhanced computed tomography. The effluent was negative for malignant cells. The medications during this phase of cloudy effluent included diltiazem. Diltiazem was stopped and the PD effluent was cleared. The effluent triglyceride levels came down to 100 mg/dl. On restarting diltiazem, the effluent became cloudy once again. This case illustrates a rare cause (drug) of an infrequentn on infectious complication of PD (CP) [27].

CP (**Figure 3**) is a rare complication of PD and is defined as the leakage of lipid rich lymph into the peritoneal cavity [28]. It should be considered in the differential diagnosis of a cloudy peritoneal dialysate. The commonest cause of cloudy dialysate is peritonitis which can be differentiated by the cellular composition of the effluent. Predominant neutrophils are demonstrated in bacterial peritonitis whereas chyloperitoneum is relatively acellular [29]. The incidence of chyloperitoneum is about 0.5% in patients on PD [30]. Very few case reports are published in the literature regarding CP in infants and neonates undergoing PD [31]. Recurrent infections, hyperosmolar dialysate and immunodeficiency states are predisposing factors for CP in patients on PD [32].

Etiology

Chyle in the peritoneal cavity is often because of congenital anomalies, injury, inflammation or obstruction of the lymphatics. It can also be because of increased venous pressure in the abdomen.

The common cause of CP in patients with PD reported in the literature are:

1. Malignancies especially lymphoma [33].
2. Catheter related injury [34].
3. Tuberculous peritonitis [35].
4. Amyloidosis [36].
5. Acute pancreatitis [37].
6. Nephrotic Syndrome: Hypoalbuminemia and subsequent lacteal leakage from the intestinal lymphatics and malabsorption are considered to be probable mechanism for CP in these patients [38].
7. Calcium channel blockers-dihydropyridine [39] and non dihydropyridine [27].
8. Miscellaneous causes like heart failure, cirrhosis, pelvic irradiation, superior vena caval obstruction *etc*. [40].

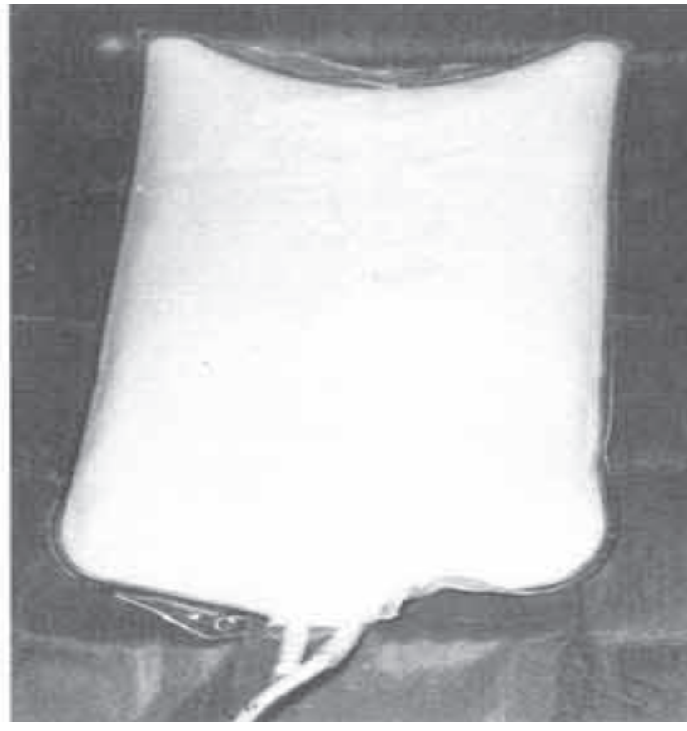

Figure 3: Chyloperitoneum

Evaluation and Management

A diagnosis of CP in a milky white dialysate is made when the PD effluent is relatively acellular and it has:

1. High triglyceride levels of >110 mg/dl.

2. Triglycerides levels higher than that of plasma

3. Cholesterol levels higher than that of plasma.

4. Cholesterol/triglyceride ratio <1.

5. Presence of chylomicrons and lipoproteins [41].

The underlying cause is determined with abdominal imaging (computed tomography, MRI) and delineation of the lymphatic pathology with lymphoscintigraphy and lymphangiography. Often, the search for the definitive cause is unrewarding and patients are put on non specific therapy [34]. Avoidance

of the offending drug and treatment of the underlying malignancy and tuberculosis improve the translucency of the dialysate [27].

Dietary manipulation is the cornerstone of therapy in these patients. A high protein, high carbohydrate, low fat supplemented with medium chain triglycerides (MCT) is often helpful [42]. The long chain triglycerides (LCT) are hydrolysed in the gut and transported with free fatty acids (FFA) through the intestinal lymphatics. Whereas, the MCTs are transported through the portal vein to liver. Hence, diet limited in LCTs, but rich in MCTs reduce chylous effluent. However, it is beneficial in about 43% of the patients. In certain cases, fasting with total parenteral nutrition has been tried [43].

Drug therapy with octreotide has been tried in some patients [44]. Surgical ligation of the thoracic duct is also done but not reported in patients on PD.

Complications and Outcome

Persistent loss of protein lead to malnutrition and recurrent infections due to immunodeficiency state. These patients are volume overloaded and PD results are poor. Because of these complications, some patients are transferred to hemodialysis [41]. The overall patient outcome is usually determined by the underlying cause of CP. Prognosis is often poor for patients with underlying malignancies [33].

Summary

Hemoperitoneum and CP are two rare non-infectious complications of PD. The underlying cause of these complications are PD catheter related injury in a certain subset of patients. In others, often the cause is benign as in a significant percentage of in women patients of the reproductive age group on PD. CP is very rare and the underlying cause, despite investigations, often remain obscure [45]. The outcome of CP in patients on PD depends on the underlying cause of CP. Prognosis is good with infectious and drug related causes of CP. Dietary manipulation with the use of MCTs improves CP in about half of the affected patients.

References

1. McCormick, B. B., and J. M. Bargman, 2007: Non infectious complications of peritoneal dialysis: Implications of patient and technique survival. *J. Am. Soc. Nephrol*., **18,** 3023-3025.

2. Oreopoulos, D. G., R. Khanna, P. Williams, and S. I. Vas, 1982: Continuous ambulatory peritoneal dialysis. *Nephron.*, **30,** 293-303.

3. Bernadini, J., 1996: Peritoneal dialysis catheter complications. *Perit. Dial. Int.,* **16,** 468-471.

4. Greenberg, A., J. Bernadini, B. M. Piriano, J. R. Johnston, and J. A. Perlmutter, 1992: Hemoperitoneum complicating chronic peritoneal dialysis: Single- center experience and literature review. *Am. J. Kid. Dis.* **19,** 252-256.

5. Dimitriadis, C. A., and J. M. Bargman, 2011: Gynecologic issues in peritoneal dialysis. *Adv. In. Perit. Dial.* **27,** 101-105.

6. Camara, O., J. Herrmann, A. Egbe, A. Kavallaris, H. Diebolder, M. Gajda, and I. B. Runnebaum, 2009: Treatment of endometriosis of uterosacral ligament and rectum through the vagina: description of a modified technique. *Hum. Reprod.,* **24,** 1407-1413.

7. Wang, J. Y., F. M. Chen, T. J. Huang, M. F. Hou, C.J. Huang, H. M. Chan, K. I. Cheng, H. C. Cheng, and J. S. Hsieh, 2005: Laparoscopic assisted placement of peritoneal dialysis catheters for selected patients with previous abdominal operation. *J. Invest. Surg.,* **18,** 59-62.

8. Miller, R., R. Denman, D. Saltisi, H. Healy, M. Muller, and S. Fleming, 1996: Erosion of a mesenteric vessel by a Tenckhoff catheter. *Perit. Dial. Int.*, **16,** 528-529.

9. Van der, N. P., J. J. Sennesael, and D. L. Verbeelen, 1994: Massive hemoperitoneum due to spleen injury by a dislocated Tenckhoff catheter. *Perit. Dial. Int.,* **14,** 90-91.

10. Cho, C. Y., I. W. Ting, F. J. Hsieh, and C. N. Lee 2006: Haemoperitoneum in a pregnant woman with peritoneal dialysis. *Nephrol. Dial. Transplant.,* **21,** 1454-1455.

11. Blake, P., and G. Abraham, 1998: .Bloody effluent during CAPD in a patient with polycystic kidneys. *Perit. Dial. Int.*, **8,** 167.

12. Borras, M., J. M. Valdivieslo, R. Egido, V. P. Vincente, J. R. Bordabla, and E. Fernandez 2006: Haemoperitoneum caused by bilateral renal cyst rupture in an ACKD peritoneal dialysis patient. *Nephrol. Dial. Transplant.,* **21,** 789-791.

13. Peng, S. J., and C. S. Yang, 1996: Hemoperitoneum in CAPD patients with Hepatic tumors. *Perit. Dial. Int.*, **16,** 84-86.

14. Kanagasundaram, N. S., I. C. Mcdougal, and J. H. Turney, 1998: Massive hemoperitoneum due to rupture of splenic infarct during CAPD. *Nephrol Dial Transplant.,* **13,** 2380-2381.

15. Park, D. J., K. H. Oh, S. J. Kim, K. W. Joo, J. S. Han, S. Kim, J. S. Lee, and C. Ahn, 2005: True aneurysm rupture of the omental artery leading to hemoperitoneum and shock in a CAPD patient. *Nephrol. Dial. Transplant.,* **20,** 2292.

16. Vishwakarma, K., and U. Anandh, 2015: Mesenteric ischemia masquerading as refractory peritonitis in continuous ambulatory peritoneal dialysis patients. *Ind. J. Nephrol.,* **25,** 380-382.

17. Williams, P. F., and S. Beer, 1985: Hemoperitoneum in a patient with idiopathic thrombocytopenic purpura (ITP) and renal failure. *Perit. Dial. Bull.,* **5,** 258-259.

18. Ohtani, H., H. Imai, A. Komatsuda, H. Wakui, and A. B. Miura, 2000: Hemoperitoneum due to acute cytomegalovirus infection in a patient receiving peritoneal dialysis. *Am. J. kid. Dis.,* **36,** 33.

19. Rigby, R. J., and C. M. Hawley, 1998: Sclerosingperitonitis: the experience in Australia. *Nephrol. Dial. Transplant.* **13,** 154-159.

20. Kittur, D. S., S. W. Korpe, R. E. Raytch, and S. W. Gardener, 1990: Surgical aspects of sclerosing encapsulating peritonitis. *Arch. Surg.* **125,** 1626-1628.

21. Hassel, L. H., J. Moore, and J. J. Conklin 1984: Hemoperitoneum during continuous ambulatory peritoneal dialysis: A possible complication of radiation induced peritoneal injury. *Clin. Nephrol.* **21,** 241-243.

22. Tse, K.C., P. S. Yip, M. F. Lam, F. K. Li, B. Y. Choy, T. M. Chan, and K. N. Lai, 2002: Recurrent hemoperitoneum complicating continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **22,** 488-491.

23. Goodkin, D. A., and M. G. Benning, 1990: An outpatient maneuver to treat bloody effluent during continuous ambulatory peritoneal dialysis (CAPD). *Perit. Dial. Int.,* **10,** 227-229.

24. Maaz, D. E, 2004: Troubleshooting non-infectious peritoneal dialysis issues. *Nephrol. Nurs. J.,* **31,** 521-532.

25. Vazelov, E., 2000: Prolonged periodic intra-abdominal bleeding without serious consequences in a female patient on CAPD. *Perit. Dial. Int.,* **20,** 807.

26. Ram, R., G. Swarnalatha, B. H. S. Pai, C. S. S. Rao, and K. V. Dakshinamurty, 2012: Cloudy peritoneal fluid attributable to non-dihydropyridine calcium channel blocker. *Perit. Dial. Int.*, **32,** 110-111.

27. Cardenas, A., and S. Chopra S, 2002: Chylous Ascites. *Am. J. Gast.*, **97,** 1896-1900.

28. Teitelbaum, I., 2006: Cloudy peritoneal dialysate: it's not always infection. *Peritoneal Dialysis: A clinical Update*, C. Ronco, R. Dell'Aquila, and M. P. Rodighiero, Eds., Karger AG-Basel, Switzerland, **150,** 187-194.

29. Garcia F. T., A. Rodrigues –Carmona, M. P. Fontan, C. R. Fernandez, P. Bouza, I. L. Rodriguez, and F. Valdes, 1994: Complications of permanent catheter implantation for peritoneal dialysis: incidence and risk factors. *Adv. Perit. Dial.*, **10,** 206-209.

30. Melnick, J. Z., C. M. McCarty, M. P. Hunchik, and S. R. Alexander, 1995: Chylous ascites complicating neonatal peritoneal dialysis. *Pediat. Nephrol.,* **9,** 753-755.

31. Cheung, C. K., and A. Khwaja, 2008: Chylous ascites: an unusual complication of peritoneal dialysis. A case report and literature review. *Perit. Dial. Int.,* **28,** 229-231.

32. Bargman, J. M., R. Zent, P. Ellis, M. Auger M, and S. Wilson, 1994: Diagnosis of lymphoma in a continuous ambulatory peritoneal dialysis patient by peritoneal fluid cytology. *Am. J. Kid. Dis.,* **23,** 747-750.

33. Levy, R. I., and R. E. Wenk, 2001: Chyloperitoneum in peritoneal dialysis patients. *Am. J. Kid. Dis.*, **38,** 12.

34. Huang, C. H., H. S. Chen, Y. M. Chen, and T. J. Tsai, 1996: Fibroadhesive form of tuberculous peritonitis: Chyloperitoneum in a patient undergoing automated peritoneal dialysis. *Nephron.*, **72,** 708-711.

35. Colonel, F., and B. Avilles, 2003: Chyloperitoneum in a peritoneal dialysis patient with primary AL amyloidosis. *Perit. Dial. Int.*, **23,** 299-301.

36. Perez, F. M., F. Pombo, A. Soto, F. J. P. Fontan, and A. Rodrguez –Carmona, 1993: Chylous ascites associated with acute pancreatitis in a patient undergoing continuous ambulatory peritoneal dialysis. *Nephron.*, **63,** 458-461.

37. Yoshimato, K., S. Saima, Y. Nakamura, M. Makamaya, H. Kobo, and Y. Kawaguchi, 1998: Dihydropyridine type calcium channel blocker –induced turbid dialysate in patients undergoing peritoneal dialysis. *Clin. Nephrol.,* **50,** 90-93.

38. Poux, J. M., D. Benevent, J, Y. Le Meur, C. Lagarde, and C. leurox-Robert, 1994: Chylous ascites in 12 patients undergoing peritoneal dialysis. *Nephrol.,* **15,** 201-205.

39. Georgieva, I., V. Stamenova, I. Trendafilov, Guiseriev, V. Papazov, D. Terziev, D. Yonova and E. Vazelov, 2012: Chylous peritonitis in patients on continuous ambulatory peritoneal dialysis. *BANTAO J.,* **10,** 84-86.

40. Lanneaux, J., A. Davourie-Salandre, E. Tudorache, I. Stoica, B. Aoun, T. Ulinski, 2013: Chyloperitoneum in pediatric peritoneal dialysis: Rapid remission after introduction of medium –chain triglyceride-based formula. *Perit. Dial. Int.,* **33,** 333-334.

41. Wu, C. H., H. H. Lin, T. N. Tsai, and J. S. Chen, 2007: Chylous ascites in a patient receiving peritoneal dialysis. *J. Med Sci*., **27,** 033-036.

42. Lee, P. H., C. L. Lin, P. C. Lai, and C. W. Yang, 2005: Octreotide therapy for chylous ascites in a chronic dialysis patient. *Nephrol.,* **10,** 344-347.

43. Roodhoft, A. M., K. J. van Acker, and M. E. de Broe 1987: Chylous peritonitis: An infrequent complication of peritoneal dialysis. *Perit. Dial. Bull.,* **7,** 195-196.

Chapter 42

Nutrition Management in Peritoneal Dialysis

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Nutrition Management in Peritoneal Dialysis

The patients with an End Stage Renal Disease (ESRD) require an alternate method of treatment for improving life span. Currently, there are three replacement modalities available; hemodialysis (HD), continuous peritoneal dialysis (CAPD) and renal transplantation. Peritoneal dialysis (PD) appears to be the most beneficial and effective in adding years to an individual's life with better quality of life (QoL) compared to HD; however, there are constraints with either of the methods.

The outcomes of CAPD are impacted by various comorbid conditions, the quality of dialysis, socio economic background, education and awareness of treatment modality, mental and physical health of an individual, nutritional status and care, compliance and medical management, family support etc.

Nutrition counselling is the most crucial and challenging task aimed to improve the overall health of the patients. The approach must be aggressive, extremely convincing and result oriented. This chapter will help us understand practically the nutritional management for individuals on PD with an Indian perspective. The discussion will also bring to notice certain special foods which impact (positively and negatively) the nutritional status of individuals on CAPD.

The following nutritional parameters are the most commonly impacted when an individual is on PD. We shall understand the need for each of the nutrient, recommended dietary allowance of various nutrients, practical usage and care in preservation of palatability, acceptance of certain foods, and various sources of these nutrients which are essential for patients on CAPD.

1. Protein
2. Energy - Carbohydrates,
3. Fats / Lipids
4. Sodium
5. Potassium
6. Phosphorous and Calcium
7. Vitamins, minerals and fibre
8. Water /fluid balance

Protein

To sustain good muscle mass and bone strength, a normal induvial requires high-quality protein diet which boosts immune system and prevent infections in the body. In case of individuals undergoing CAPD, protein loss occurs in the form of peptides with each dialysis (exchange) as albumin and globulin etc are lost during

S. Suguna

treatment. Total amount of protein loss per day varies between 5-15g. The amount doubles considering peritonitis attack.

Several studies have examined nitrogen balances in patients on CAPD consuming various levels of dietary protein. These studies indicate that DPIs of 1.2 g/kg/d or greater are almost always associated with neutral or positive nitrogen balance [1]. Several studies show a relationship between DPI and such nutritional parameters as serum albumin, total body protein and nitrogen balance in patients undergoing CAPD. Based on these considerations, it is recommended that a safe DPI that will maintain protein balance in almost all clinically stable patients on CAPD is at least 1.2 g protein/kg body weight/d.

A DPI of 1.3 g/kg/d probably increases the likelihood that an adequate protein nutrition will be maintained in almost all clinically stable individuals. At least 50% of the protein should be of high biological value. The nPNA for a 70 kg man ingesting 1.2 g and 1.3 g protein/kg body weight/d, based on the Bergstrom and Blumenkrantz data, is estimated to be 1.02 and 1.14 g protein/kg/d [2, 3]. It is recognised that some patients on CAPD will maintain good protein nutritional status with somewhat lower dietary protein intakes. The current guidelines recommend to provide assurance that almost all the clinically stable patients on CAPD will have good protein nutrition.

Dietary Protein Recommendation

Recommended daily dietary intake of protein for individuals undergoing CAPD is 1.2-1.5g/ kg bodyweight. Type of Protein: Irrespective of the source 50% pf the protein consumed should be of high biological value (BV) [1]. BV: Percent of N (Nitrogen) absorbed from the diet consumed and excreted. High the N absorbed, greater is BV.

Sources of Proteins

Plant Proteins: All cereals are good sources of protein while pulses, nuts and legumes are rich sources of protein.

Nuts and Seeds: Though these foods are high in calories, these are packed with filling protein and healthy fat that can help keep your weight in check. Snacking on nuts like almonds, walnuts, and groundnuts is a healthy option, because these foods contain high level of polyunsaturated fatty acids improves the body's sensitivity to insulin, and regulate glucose absorption.

Legumes: Beans, lentils and other dals /pulses provide blood sugar-stabilizing fibre and are a great source of protein and other nutrients, including potassium making them a good substitute for meat. Vegetarian diet can be made protein rich by fortifying regular cereal foods with pulses and nuts especially in dosa batter and wheat flour upma mixes etc.

Liberal use of soy products like soy granules, flakes and nuggets/meal maker in vegetables and as snack foods, however soy foods must be used with caution as some individuals might be allergic to soy and are not recommended in case of thyroid imbalance.

However, many resist the use of plant proteins in light phytates, uric acid, and some amount of sodium, potassium presently in dals/lentils /pulses. This can be eliminated by adopting simple changes in our cooking methods.

Indians traditional practice of cooking dals still holds good. Dals were always soaked in water for few hours prior to cooking to cook faster as soaked dals melt faster and taste better when cooked on a low flame. This preserves the nutrients and drains off the waste materials in the process of soaking and rinsing. Dals are also sundried; so we can assume that these dals are Vitamin D fortified and while cooking a little of turmeric powder, grated ginger and oil are added to make them germfree and enhance the taste, palatability, prevent bloating and gases.

Hence, it's ideal to cook plant proteins by soaking in water for 1-2 hours, rinsing it with fresh water before cooking. More and more research is promoting use of plant proteins /dals as these are best foods for diabetes, weight loss, and general wellbeing. In case of CAPD as well, plant proteins are ideal with some supporting animal foods like dairy products and eggs.

Animal proteins are richest sources of protein namely, fish, eggs, poultry. These are better options compared to red meat and other large animal meat sources as they are rich in protein and low on fat. Fatty fish also contains omega-3 fatty acids, which is heart healthy and cuts down the risk of cardiovascular problems.

Avoid: Red meat and chicken. Why?

1. Red meats and chicken are heavy foods to digest and stay longer in the gut leading to petrification of these foods and invite unwanted microbes in the gut. These microbes increase acid in your abdomen, leading to constipation, acidity and gastritis.

Patients on CAPD are prone to infections due to poor immunity, metabolic acidosis and constipation. In such conditions, a plant based protein rich diet is more helpful compared to animal protein.

2. We are not aware of the kind of feeds animals are fed and grown, place where they are butchered and health of the animal. This can lead to several hormonal imbalances, weight gain, etc.

3. All these impact the gut and hormonal balance in the body inviting many metabolic and endocrine disorders.

Dairy and Poultry: Milk and milk products like yoghurt, cottage cheese etc can be consumed compared to red meat. The cheapest and complete source of protein is

egg and two eggs per day in any form must be included in the diet of patients on CAPD. **Table 1** gives a list of animal and plant proteins.

For many, this might come as a surprise to note that the BV of certain plant foods is higher compared to animal foods like BV of fish and rice is same. The BV of meat and Bengal gram is similar. Hence, even if the patients are on vegetarian plant based proteins and few animal proteins like milk; these can help them get the best quality protein, provided the quantities are slightly above normal.

Table 1: Percent Biological Value of Protein in Food.

Animal Protein	
Egg	96
Milk	90
Meat	74
Fish	80
Plant Protein	
Rice	80
Wheat	66
Maize	50
Bengal gram	74
Red gram	72
Groundnut	55

Another important aspect in terms of Indian diets especially the south Indian food is that it is not very high on protein, however the key cereal rice has a high BV protein. We can as well continue the patients on rice and pulse combination diets with same amount of protein rich foods in case of vegetarians. It's ideal to add liberal amounts of dals in diets of patients on CAPD since dals are diluted to various consistencies across the country. Ideal way is to use your fist, eat three fist full of dals (raw weight) everyday apart from cereals like rice, wheat, jowar, ragi, maize.

Ideally based on your body weight and your amount of protein loss in urine, you need to consume minimum of 1.2 gm of protein per kg body weight when on CAPD. It means that if you weigh 50 kg; you would consume 50 x 1.2 gm= 60 gm of protein per day. The simplest way is take two fist full of dal (uncooked) every

day in cooked form in your diet and rest will come from a small amount of 10 gm of sprout, nuts and cereals like rice and roti.

However, we practically do not meet the recommended protein on a day to day basis; hence, fortifying foods with protein dense plant and animal foods on a regular basis apart from fixed amounts of protein rich foods will support optimum consumption of protein as per the recommendations.

Carbohydrates: The main source of energy - glucose - produced in the body is from carbohydrates which is one of the essential nutrients. PD fluids/dialysate (dextrose/sugar) used by patients on PD provide extra calories in carbohydrate (sugar) form. To prevent excessive calorie intake, patients on PD need to take into consideration the calories (sugar) from the dialysate. Glucose absorption from dialysate may contribute to excess caloric intake, weight gain, and the metabolic syndrome [3].

Glucose absorbed from dialysate can be estimated using the following equation: – Glucose absorbed (g/day) = 0.89x (g/day) -43 – x = the total amount of dialysate glucose instilled each day [4].

In patients on CAPD with normal peritoneal transport capacity, about 60% of the daily dialysate glucose load is absorbed: about 100-200 grams/24 hours.

The patients on CAPD with diabetes need to be extra cautious in terms of medication, timely food and consuming controlled portions of carbohydrate dense foods. Bloating, constipation and weight gain needs to be closely monitored and treated timely to improve QoL of these patients.

Recommended Dietary Intake of Energy:

The number of calories required per individual on CAPD as per K/DOQI guidelines is 35 kcal/kg/day for patients younger than 65 years and 30-35 kcal/kg/day for patients older than 65 years.

Ideally, 35-30 Kcal /kg /body weight is recommended for patients on PD [1]. It implies that for a body weight 50 kgs, 50x30= 1500 Kcal of diet is recommended.

When we practically consider these many number of calories consumed, it comes close to 1200 to 1300 calories on an average in Indian patients based on hands on practical diet recalls with patients on CAPD. Majority of the patients complain of bloating, poor appetite, constipation which prevents them from consuming required amounts of calories. This is one of the leading cause of poor nutrition among these patients.

The protein foods usually recommended have high satiety levels and prevent individuals from eating more frequently. This is ideal since the dialysate provides additional glucose to the body. However, due to a lack of appetite, many times

patients tend to consume low amounts of foods irrespective of protein or carbohydrate dense leading to Protein Energy Malnutrition (PEM).

Sources of Energy foods: Foods made with whole grains, whole-wheat flour roti / phulka / chapati / broken wheat upma, porridge, boiled rice and brown rice, are healthy sources of carbohydrates and at the same time help in slow absorption in the body leading to lesser hunger pangs. Millets like ragi, jowar, maize and bajra are other great sources of energy and minerals. Inclusion of at least two cereals and one millet in everyday diet can help in adding good number of carbohydratess, proteins and minerals like Calcium and Iron. Hence, various cereal foods are a must in the daily diet. The best way is to consume complex carbohydrates is to mix rice with plenty of vegetable curries and dals.

The high levels of phosphates in cereal foods and protein rich foods is a matter of concern; however, ideally these patients are advised to take phosphate binders with each meal to prevent excess phosphates in the diet. In anuric patients, maintaining normal phosphorous levels will be difficult with the recommended dietary protein intake.[6]

Recommendation

Focus on a variety of dishes, spare few minutes discussing new recipes and encourage the patient to take a variety of foods made at home. These include traditional recipes like pongal, daliya, paysam with sago or vermicelli or suji, chalividi (rice cake with jaggery)

Protein energy Malnutrition (PEM)

How common is protein-energy wasting in patients on dialysis?

Estimates of protein-energy wasting among patients on dialysis vary. The average estimate of PEM in patients on dialysis is about 40%. Most patients have mild to moderate protein-energy wasting and 6-8% have severe protein-energy wasting [7]. Dialysis is a hyper catabolic state and apparently well-dialysed patients consume approximately 80% or less of their recommended energy intake. Inadequate nutrient intake may have a variety of causes and some of the most common ones are listed below

- Frequent inflammation, infections.
- Uremic symptoms
- Acidosis
- Anorexia
- Intercurrent comorbid physical illness
- Loss of amino acids
- Anaemia
- Mental Illness (Depression, Psychiatric illness) and

- Certain Socio-economic factors (treatment/food affordability, compliance, family support *etc*)

Metabolic acidosis is a stimulus for net protein catabolism. It elicits the transcription of genes for proteolytic enzymes in muscle. The patients on CAPD with metabolic acidosis are more malnourished compared to those without acidosis. Correction of acidosis may lead to an improvement in protein turnover with decreased protein degradation. Treatment with oral bicarbonate resulted in improved nutritional status among individuals [5].

Evaluating for reversible causes of malnutrition like inadequate dialysis is done by dialysis adequacy assessment. If dialysis dose is inadequate, modify prescription. Consider modality switch to HD, if protein energy wasting is severe and it is difficult to increase the dose of PD. In case of metabolic acidosis, add sodium bicarbonate as a part of the treatment plan.

Evaluate for reversible causes of malnutrition. For example, in case of psychiatric conditions like depression and consider prescribing an anti-depressant. For socioeconomic factors like poverty or inability to buy nutritious food/inability to prepare nutritious foods; look for voluntary organisations to adopt such patients for financial support. In case of medical condition like gastroparesis/malabsorption/ early satiety/inflammation/infection; consider prompt correction with an appropriate line of therapy/treatment.

As per the K/DOQI Guidelines for nutritional support, if oral nutrition, including nutritional supplements, is inadequate, tube feeding should be offered if medically appropriate. If the combination of oral intake and tube feeding does not meet protein and energy requirements, daily total or partial parenteral nutrition should be considered [8].

PEM in Indian context has an additional reason that of low protein diet with onset of diabetic nephropathy. Several patients with diabetes are detected with diabetic nephropathy. They are counselled thoroughly for low protein diet, low calorie diet. Given the background especially in the south of India, the quality of protein in diet is minimal and not very dense despite one being a non-vegetarian. Unlike in western countries, where an individual eats non-vegetarian food alteast twice in the day, not all non -vegetarians in India can afford to eat non-vegetarian food on all days. So, the definition of non-vegetarian or vegetarian does not simply matter since either diet are poor in terms of protein. When a person is diagnosed with diabetic nephropathy, the foundation of PEM is set. The challenge during ESRD is making these patients understand and unlearn the low protein and low calorie diet and switching to high protein and optimum calories. It is extremely important to understand the individual patient's pathophysiology while counselling for diet and ensure that the person is not consuming suboptimal levels of protein and calories in fear of further worsening of the condition leading to PEM, much before the ESRD.

PEM is one of the most critical issue in stage 4 and 5 of ESRD. The patients on CAPD need to be dealt with care and caution as multiple areas are associated leading to PEM. Nutrition counselling should be intensive initially and provided every 1 or 2 months thereafter. If nutrient intake appears inadequate, malnutrition is apparent, or adverse events or illnesses threaten nutritional status, counselling should be increased. A coordinated effort between nephrologists and paramedics (PD educators, laboratory technicians, nursing staff, nutritionists, medico social workers, clinical psychologist, physiotherapist etc)

Fats and Oils

Fat are essential source of energy, and help in several metabolic activities in the body and effective brain functioning. We cannot function normally if we are deprived of fat in food. However, the amount required for the body is very small, excess amounts leads to dyslipidaemia, and patients on CAPD are at the greatest risk for the development of coronary artery disease, worsened heart related disorders, diabetes, hypertension and obesity.

Elevation of serum triglycerides, low density lipoproteins (LDL) cholesterol and very low density lipoprotein (VLDL) cholesterol and lowering of high-density lipoprotein (HDL) cholesterol is very common in patients with ESRD. Initial dietary guidance should concentrate on restricted intake of simple sugars and visible fats in the diet when patient is on CAPD. These patients should follow a diet low in saturated fat and cholesterol.

Sources of Fats and Oils

It's smart to avoid saturated fats and trans fats (found in meat, butter and full-fat cheese and vanaspati /dalda, margarine, heavy creams, fast food/deep fried junk foods), which raise LDL levels.

Switching to heart-friendly options of vegetable oils (few are rich in mono and few are rich in poly unsaturated fatty acids), to maintain a balance of both fatty acids is suggested. It is ideal to mix one or two oils together or keep changing different oils.

Gingelly, groundnut, sunflower, safflower oils are common oils mix or use oils in rotation. Despite having a good amount of saturated fat, Ghee / clarified butter is rich in mono unsaturated fatty acids and has fair amounts of poly unsaturated fatty acids apart from vitamin A and trace amounts of potassium and protein. Traditionally, ghee has been widely used in Indian cooking specially to make sweets and savouries and based on affordability, it’s still the best option compared to other saturated fats.

Limit the foods rich in refined sugars, fats cream, butter, deep fried foods, salty fried snacks etc. These also increase the thirst quotient leading to more water consumption. Hence, appropriate amounts of fats and oils are essential for overall wellness and nourishment. It is important to consider the lipid analysis on a

bimonthly basis to ensure the cholesterol levels are not too low which can lead to comorbidity.

It is ideal to maintain choleterol between 170 to 200 mg anything beyond 200 mg calls for interventions in terms of nutrition, however raised cholesterols due to sugars from exchange bags can lead to raised lipids and weight gain. This needs to be addressed with an effective nutrition counselling with an experienced renal nutrition counsellor and change in the exchanges.

Recommended Dietary Fat Intake: Since there are no specific quantity of fat mentioned as standards; considering the type of Indian diets, it's ideal to limit usage of fats. Consume 500 ml of oil /adult /month or ideally 15 ml or 3 table spoon per day. Of the total energy that one consumes, only 20 to 25 % should be from oils and fats. Opt for seaming and toasting vegetables in oil instead of deep frying and shallow frying vegetables and making gravies with loads of oil.

Old is gold and so is our good old ghee (clarified). It makes our brains sharp, lubricates our gut and bones, delays gastric emptying by up-regulating the response of a gut hormone GLP-1. Basically, this means that it lowers the glycemic index and helps regulate the blood sugar response. Hence, adding ghee to food, in this case adding it to rice, roti, dosa, idly, lowers the glycemic index of these carbohydrate dense foods which on its own is high on the GI. A little of ghee will certainly add zing and make the food palatable. Remember, all baby foods taste so good why? Since, we add oodles of ghee in these foods while serving. However, here the requirements are of different kind but let us not deny thepatients on dialysis of this comfort food. It would be appropriate to put ghee as an emotional bonder, since irrespective of the region Indians like to eat ghee but unfortunately with everyday new theories on fats have kept this great food in dark for a long time. Ideally, one teaspoon of ghee with your cereal foods twice a day will bring in more beneficial effects. Cow ghee or homemade ghee would be a better option since we are assured of the quality and source of the ghee.

Sodium

Human body does not require high amounts of sodium for general wellbeing. Sodium is an essential mineral. In the body, sodium is the most predominant ion in the extracellular fluid and is subject to a tight regulation. Sodium consort with potassium (the main cation within the cells) to maintain a proper body water distribution and blood pressure. This means, the body needs a small amount of sodium to regulate blood volume and blood pressure to regulate acid/base balance, to maintain a normal function of muscles and nerves. Since Sodium balances the acid in the body, when kidneys function poorly, and sodium levels are high, it may lead to excess thirst, leading to a greater consumption of liquids, further leading to water retention –oedema and increased blood pressure and few other symptoms like feeling thirsty, swelling of hands or feet, eyebags, facial puffiness, breathing

problems. Make sure that theprescribed diet is followed to help prevent these symptoms.

Hence, one needs to adopt to salt free cooking and avoid all snack foods and preserved tinned, canned fruits and pickles which are high on salt. High amounts of salt present in spicy, salty snacks and oily deep fried snacks etc increases the thirst quotient leading to more water consumption, leading to water retention. It is ideal to reduce consumption of such foods

Recommended Dietary Intake of Sodium is 5-6 gm/day, thus, ideally try salt free cooking since all foods contain sodium [1]. Avoid additional table salt while eating the meal.

Sources of Sodium: Sodium is naturally occurring electrolyte present in almost all the foods. We add salt to enhance the taste of the food hence do not go overboard especially if you want healthy weight. However, it is essential and should not be avoided totally. Avoid salted deep fried snacks, especially bought from market as these are high on salt and quality of oil used is difficult to know.

Do not opt for low sodium salt, since these are only food label gimmicks as these will be high in some other electrolyte or chemical like potassium, and excess potassium in case of dialysed patients is equally harmful. Traditionally, Indians prepare a long list of preserved foods rich in salt and hence these foods might be avoided considering low sodium diet recommendations.

1. Salty foods:
2. Papads (fried crispies) /perugu mirchi (sun dried curd chillies)/Masala Mirchi (spice stuffed chillies)
3. Karam podi / Kamma podi (preserved spicy powders)
4. Sun dried Salty sea food
5. Potato wafers, chunks, French fries, Popcorns
6. Pickles and preserved Chutneys,soy sauce, ketchup
7. Pani puri, pakora/ bhaji (deep fried Indian savouries)
8. Puffed rice, readymade snack mixtures
9. Soft drinks, preserved fruit juices,
10. Bakery snacks, Yeast products like breads and buns
11. Ready to eat Noodles and Indian curries
12. Sodium content is high in 4 commonly used spices especially in south of India (Fenugreek, Coriander seeds, Red chillies and Cumin)

Potassium

Potassium regulates heart beats and contraction of the muscles. High potassium leads to weak heart, irregular heartbeats, heart attacks, breathing difficulty and extreme cases lead to death. Potassium is naturally present in almost all the foods. Peritoneal dialysis helps to remove the extra potassium.

Dietary recommendation of Potassium is 2000 to 2500-2730 mg /day, ideally 40 meq of potassium is recommended for patients on dialysis. Usually patients on CAPD have normal levels of potassium, however it's important to ensure that the potassium levels are within the ranges and potassium restriction is required only in hyperkalaemia.

Sources of Potassium Rich fruits: Sweet lime, mango (challenge in summers!), pomegranate, melon (musk and water), peaches, plums (albukhara) and sapota (chikoo).

However, there is always a surprise when we ask patients to eat banana apart from apple, if we consider the Sodium and Potassium content of apple (28mg and 75mg in 100gms of edible fruit) and banana (36.6mg and 88 mgin 100 gms of edible fruit); its only Sodium (8mg) and Potassium (13 mg) which are more in banana. It will not cause any alarming effects unless 3 bananas are consumed per day continuously for a weeklong duration! Doctors and nursing staff fear of easy availability of banana and overconsumption by the patients and hence restrict this otherwise equally healthy fruit option even for patients on CAPD.

Fruits with zero amounts of Sodium and Potassium are highly recommended and these are seasonal fruits of Indian origin which are ignored by many of the patients due to poor awareness.

Safest fruits as these are Sodium and Potassium free [9]:

Wood apple (Kavath / (Velaga pandu),

Zizyphus (Beaer/ Regi pandu)

Custard Apple (Seethapahal),

Jack fruit (Phanasa pandu) and

Fresh Dates

In the order of lowest levels of Potassium and Sodium

Grapes, orange, apple, banana, pineapple, papaya, guava

How much of fruit to be consumed?

At least one fruit serving / day is recommended. Eating fruit during day time prior to breakfast and midday is ideal than eating later in the night since the bodies' basal metabolic rate is higher in the morning and nutrients from fruits are better absorbed compared to night times when BMR is low.

Fresh Dates 3-4, papaya 2/3 slices, guava 1 medium sized, apple1, banana 1, grapes green 100 gms, pineapple 3 slices and orange 1

Amount of Na / K (mg) in commonly used vegetables, per 100gms of each of these vegetables.

Onion 4.0/127, Brinjal 1.8/87, Cucumber 10.2/50, Tomato (Ripe) 12.9/146, Tomato (Raw) 45.8/114

Onion, brinjal, cucumber and tomatoes form an integral part of several Indian dishes and many times the patients are denied these foods due to potassium content. Using one or two of these vegetables in 500 gm of other vegetables is safe.

From the start of early stage of ESRD, patients are restricted on choice of vegetables due to potassium levels and advised to leach the vegetables. Strangely, this leaching of vegetables is followed so religiously that they land up making a pasty curry.

The right method of leaching of vegetables with high potassium.

Cut vegetables and put in hot water for 10 to 15 min. Drain the water, rinse again in normal water and let the water drain by leaving the vegetable in a strainer for 10-15 minutees. This leached vegetable is now ready to be tossed in tampering and can be steamed or sautéed as per the choice of individuals.

We also come across patients with naturopathy or herbal treatments for certain ailments. Like for instance, a diabetic patient using fenugreek to bring down blood sugar while he is not aware of his diabetic nephropathy condition. By the time things are investigated, we find high levels of Potassium, and the cause is daily consumption of fenugreek and cumin seeds (50gms each) three times a day!

The following spices mg/100gms of edible seeds) must be used with a word of caution, namely.

Fenugreek 530mg, Coriander seeds 990mg, Cumin seeds 980 mg, Red chillies powder /chillies 530mg as these are extremely high on potassium ranging

These four spices are used regularly in several Indian dishes (curries, rasam, sambar, dals, chole, rajmha, etc) and hence the amounts need to be reduced or ideally an alternate spice need to be replaced as these are very high in potassium and regular use might raise the potassium levels.

Phosphorus and Calcium

Phosphorus is a mineral found in almost all the foods. However, it is best to avoid high phosphorus foods, since when phosphorus build up in the body, it causes calcium to build up. Phosphate is a mineral that combines with calcium to form the hard structure of bones and teeth. High levels of phosphorus leads to weak, painful, brittle bone, itchy skin, red eyes and calcium deposits or crystals.

Sources of Phosphorous and Calcium: Milk, yoghurt, cheese, meat (especially liver and other organ meats), fish (canned and fish products), dried beans and peas,

millets, whole grains or cereals, cocoa/chocolate, cola/beer. Moreover, all fruits and vegetables have varying levels of phosphorous and calcium. It is ideal to take more plant based foods and few animal foods like eggs and fish to reduce the phosphorous concentrations in the body. PD does not efficiently remove phosphorus from the blood. Patients may need medicine (phosphate binders) to carry phosphorus out of the body. Binders are effective only when it is taken along with the meal as it works by preventing phosphorous to be absorbed in the blood steam after the food is being digested. The time of ingestionof binders is very important for its efficacy [1].Calcium is the most abundant mineral in the body. Almost all the calcium found in body is within the bones and teeth, where it is responsible for their strength and stability. Beside this, a small quantity of calcium is always in the bloodstream and has many important functions like formation of bones and teeth, coagulation of blood contraction of muscles (including heart), transfer of chemical messages from the cell membrane into the cell.

Unfortunately, good calcium sources are high in phosphate and protein. By limiting the dietary protein intake in the pre-dialysis stages, also leads to cutting down important calcium sources. However, the intake of calcium must be guaranteed – otherwise bones become fragile or very painful (like in osteoporosis). Ideally, an additional calcium supplement is recommended in certain patients will low calcium levels [10, 11].

The patients on dialysis might need high doses of calcium-containing phosphate binders. Thus, calcium intake may become too heavy. In these cases, it is reasonable to reduce the intake of calcium. The best natural sources for calcium are: milk and milk products, cheese, eggs, fish, green leafy vegetables, peas, beans, lentils, potatoes, Cereals and drinking water

Recommended Dietary intake of Phosphorus and Calcium [10, 11].

Phosphorous: If the levels of parathyroid hormone are elevated, recommended dose is between 800 to 1.000 mg/day. Calcium: < 2,000 mg/day (including calcium from phosphate binders)

Maintaining Serum phosphorous and calcium levels > 65. (This precaution will prevent the patients from developing bone diseases). Ideally a normal plant based diet with a combination of eggs and fish will be more helpful in patients on PD.

Vitamins Minerals and Fibre

Vitamin A, D, E are fat soluble vitamins and required for healthy vision, skin, bones, and fertility etc. Vitamin B complex vitamins are Vitamin B1 (thiamine), Vitamin B2 (riboflavin),Vitamin B3 (niacin or niacin amide), Vitamin B5 (pantothenic acid), Vitamin B6 (pyridoxine), Vitamin B7 (biotin), Vitamin B9 (folic acid) Vitamin B12 (cyanocobalamin) and Vitamin C are water soluble vitamins and are essentially required for various physiological functions of the body. All the systems of the body require vitamins for proper functioning and deficiency of any

specific vitamin leads to disorders which can be cured by supplementary supply of this vitamin or mineral to the body. Important minerals are calcium, iron, phosphorus, potassium, sodium, Zinc, manganese. And, there are several other trace minerals which are required in very small quantities.

All seasonal fruits are sweet treats and a must have every day 2-3 times a day. They do contain sugar, in fructose form, but the rate at which it enters the bloodstream is slowed by fibre. Fruits with an orange, red, blue or purple hue might be particularly beneficial, because these are loaded with pigments like anthocyanin, lycopene, carotene, and xanthophyll are rich in antioxidants, which boost immune system and help fight the body with seasonal changes and infections.

In a study by Martín-del-Campo, Fabiola *et al*, "Dietary Micronutrient Intake in Peritoneal Dialysis Patients: Relationship with Nutrition and Inflammation Status." [10]. The patients on PD had inadequate dietary intakes of iron, zinc, calcium, and vitamins A, B6, C, niacin, and folic acid. Low nutrient intake was associated with malnutrition and inflammation, but not with renal or dialysis clearance. Patients with inflammation had lower intakes of sodium, calcium, vitamin B2, and especially vitamin A.

Micronutrient intake and supplementation must be investigated in various populations so that adequate supplementation can be tailored and deficiencies avoided per need. In populations, such as ours, multivitamin and mineral supplements (including at least zinc, folic acid, niacin, and vitamins A, B6, and C) could be advised; alternatively, zinc and folic acid supplementation might be prioritized to improve anorexia and appetite, in the hope of subsequently increasing dietary intake of other micronutrients.

In patients on CAPD, about 6 mg/kg of oral iron is recommended instead of 2 mg/kg/day. Intravenous iron may be given at a dose of 1500 mg/year. Zinc supplementation may be needed. Other minerals are given in the usual recommended doses.

Green leafy vegetables owing to it their potassium levels are barred; however, leaching will help remove excess electrolytes and can be safely use including spinach, amaranth, methi, coriander, mint and curry leaves and other local varieties available apart from cabbage, leaves of radish, and turnips. They have high fibre, mineral and vitamins like calcium, iron, sodium, potassium (can be leached), vitamin C, A and B complex vitamins and water content. They are also an important source of magnesium, which improves the body's ability to turn glucose into energy and keeps up metabolism.

Diets abundant in fresh vegetables, lentils, whole grains and fruits prevent constipation among patients on CAPD and keep the gut healthy. Its only matter of careful choice of fruits and vegetables and avoiding those rich in Sodium and Potassium.

Fluids and Water consumption

Human body constitutes more than 50 % of water (57%) in a normal healthy adult. With increased body weight or obesity, the water level gradually comes down. Water is the key ingredient in the body and maintaining a good fluid balance in our body is very important. Hence, drinking water every time we are thirsty and sipping water regularly especially when we work in air conditioned environment is mandated as this causes severe dehydration. There is no fixed amount of water one needs to consume, however in our current life styles, its ideal to take 8- 10 glasses of water and never deprive the body of thirst and nature calls. Kidneys also need good amount of water to flush our toxins from the body. Good water balance can prevent dehydration, constipation, keep skin hydrated, and prevent renal stones if someone is predisposed. However, in case of renal disease like ESRD and on dialysis, kidneys will not be able to flush out the desired amount of fluids. Ideal way is to limit the water consumption as follows in case of CKD or ESRD (CPD/HD).

Water consumed = amount of urine output + 500 ml of water

We do consume 500 to 1000 ml of water

1. Since the kidneys have a reduced ability to produce urine, it is necessary that fluid intake is limited. Excess fluid build-up with in the body can be hard on the heart and lungs and cause fluid build-up in bodily tissues known as oedema.
2. Fluid intake is calculated as – amount of urine excreted + 500 ml and 500 ml accounting for fluid loss through the skin and lungs. This implies that one should not consume more than 1500ml of fluid in the entire day. Since some amount of water (500 ml water), is also consumed in the cooked foods, hence remember not to have to many fluids in the meal, like rasam, sambar, lassi, thin dals, soups, buttermilk, liquid /gravy curries etc.
3. Patients should not be encouraged to take more fluids especially liquids like soft drinks, soups, fruit juices, sugar cane juice, frooti and tender coconut water, milk with malted chocolate, cocoa, horlicks and complan. Beverages such as tea, coffee should be limited to 1/ 2 cups /day.

Nutritional Assessment and Monitoring

Nutrition education and counselling is effective only when we understand and make correct assessment and regularly monitor certain parameters to assess the progress of the individuals on CAPD. The following are the assessment and Monitoring measures as per National Kidney Foundation and K/DOQI (Table 2).

As per the Indian context, most of the above listed measurements are possible and must be monitored as recommended to help patients get the best of the CAPD modality. It is economically more viable in a country like India since the cost of HD varies between 1000-3000 rupees with an additional cost of erythropoietin being 5000 rupees /month. Cost of CAPD using “Y” set with three exchanges/week is ~

25000/month [13]. Hence, ideally a holistic approach to treatment and care must be considered and help the patients by providing enhanced QoL with CAPD.

Table 2: NKF/K/DOQI Assessment and Monitoring Recommendations [1, 12]

Measure	**Minimum Frequency of Measurement**
Serum albumin	Monthly
Percent of usual post-drain body weight	Monthly
Percent of standard (NHANES II) body weight	Monthly
Subjective Global Assessment	Monthly
Dietary interview and/or diary	Every 6 months
nPNA	Every 6 months
Anthropometrics	As needed
DEXA	As needed

It is important to remember and counsel patients that diet alone will not help in improving the general health and one can improve the QoL by adapting to a regimen involving simple breathing exercises yoga and meditation which can bring out the best effect of nutrition. As we say every coin has two facets, same is the case with nutrition management.

The counselling is incomplete if the individual is not involved in any form of physical activity involving at least 150 hours a week or on an average meaning 20 minutes per day. Time and again, it has been proved that improved physical activity helps improve QoL of individuals. Thepatients on PD are fortunate since this modality provides individuals to have a better QoL compared to HD.

Summary of recommended foods for PD patients in India

What to change in your food purchase?

1. Consume sesame, safflower and sunflower oils apart from groundnut oil in rotation to or mix two oils and use to get the best possible MUFA PUFA fats from oils. 1 kg /2 people /month.
2. Do purchase cow ghee or homemade ghee about 1000 gms for 2 people/month.
3. Use sesame, ragi and flax (Avise ginjalu) seed powders and whole roasted seeds I tsp in the curries or vegetable salads or chutneys.
4. Try sweet recipes using milk and fresh fruits and vegetables (carrot halwa, lauki /Sorakaya halwa).
5. Refined sugar 1 kg for 2 people /month.
6. Buy separate atas/ flours of different grains mix and use whole grain mix ata/ flour.
7. The dal must have some vegetable or green leafy vegetables about 1 bunch in the food every day.
8. Cook the vegetables by adding little water instead of making oil fried shallow fried form of curries.
9. Do not overcook vegetables in spices.

Foods That You Can Forget:

1. All forms of soft drinks, alcoholic beverages, fruit juices and tetra packed fruit juices.
2. All forms of bakery foods, pizza, burgers and deep fried pakoras, chips, Apapads spicy chillies, preserved chutneys etc.
3. High protein foods like soya, tofu, paneer, cheese, meat, chicken.
4. Preserved, tinned canned fruits and vegetables.
5. Thokku, pachhadi, avakai, and all forms of preserved pickles with high salt chilly and oil content.
6. Sweets made of refined flours and milk sweets and sweets cooked in sugar concentrate.
7. Do not try any Ayurveda or other forms of alternate drugs in the form of additives to food as these react with the corticosteroids and other drugs that you have been using. Seek doctor's advice before going for any alternative therapies.
8. Food at hotels should not be consumed more than once in a month one meal – if you are serious about getting well.
9. Do not buy snacks from swagruha foods claiming these are home-made, it's very important that you avoid oily deep fried snacks and sweets to the best possible effect.
10. All forms of panipuri, chats and road side snack foods are best to be avoided as patients on dialysis are more prone to infections than normal people.

References

1. NKF KDOQI Guidelines, 2000:

fhttp://www2.kidney.org/professionals/KDOQI/guidelines_nutrition/nutaref.html

2. Bergstrom, J., P. Furst, A. Alvestrand, and B. Lindholm, 1993: Protein and energy intake, nitrogen balance and nitrogen losses in patients treated with continuous ambulatory peritoneal dialysis. *Kid. Int.,* **44,** 1048-1057.

3. Blumenkrantz, M. J., J. D. Kopple, J. K. Moran, and J. W. Coburn, 1982: Metabolic balance studies and dietary protein requirements in patients undergoing continuous ambulatory peritoneal dialysis. *Kid. Int.,* **21,** 849-861.

4. Nephrol Dial Transplant; 20 [Suppl 9]:28-33, 2005.

5. Szeto, C. C., T. Y. Wong, K. M. Chow, C. B. Leung, and P. K. Li, 2003: Oral sodium bicarbonate for the treatment of metabolic acidosis in peritoneal dialysis patients: a randomized placebo-control trial. *J. Am. Soc. Nephrol*., **14,** 2119-2126.

6. Uribarri, J., 2001: DOQI guidelines for nutrition in long-term peritoneal dialysis patients: a dissenting view. American journal of kidney diseases. **37,** 1313-1318.

7. Mehrotra, R., and J. D. Kopple, 2001: Nutritional management of maintenance dialysis patients: why aren't we doing better? *Annu. Rev. Nutr.,* **21,** 343-347.

8. Am J Kidney Dis; 35 (6) Suppl 2: S17-S104, 2000.

9. Dietary Guidelines for Indians, National Institue of Nutrtion Second Edition 2011 http://ninindia.org/dietaryguidelinesforninwebsite.pdf

10. Martín-del-Campo, F., C. Batis–Ruvalcaba, L. González–Espinoza, E. Rojas–Campos, J. R. Ángel, N. Ruiz, J. González, L. Pazarín, and A. M. Cueto–Manzano, 2012: Dietary micronutrient intake in peritoneal dialysis patients: relationship with nutrition and inflammation status. *Perit. Dial. Int.,* **32,** 183-191.

11. NKF K/DOQI, 2003: Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. *Am. J. Kid. Dis.,* **42,** 1-202.

12. Fouque, D., M. Vennegoor, P. ter Wee, C. Wanner, A. Basci, B. Canaud, P. Haage, K. Konner, J. Kooman, A. Martin-Malo, and L. Pedrini, 2007: EBPG Guideline on Nutrition. *Nephrol. Dial. Transplant.,* **22,** 45–87.

13. Agarwal, S. K., 2005: Chronic Kidney Disease and its prevention in India. *Kid. Int.,* **98,** 41-45.

14. Suguna, N., 2008: PhD Thesis, Assessment of Quality of Life Measures Using SF 36 in HD, CAPD and Transplant patients, Nizam's Institute of Medical Sciences Hyd, India.

Chapter 43

Protein Energy Malnutrition during Peritoneal Dialysis

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Protein Energy Malnutrition during Peritoneal Dialysis

Introduction

Patients with chronic kidney disease (CKD) especially those undergoing dialysis, are prone to the development of nutritional disturbances, termed as the protein-energy wasting (PEW) syndrome or other mal-nutritional states like obesity, dyslipidemia or malnutrition inflammation Atherosclerosis syndrome (MIA syndrome). This nomenclature has been suggested by an expert panel of the international society of renal nutrition and metabolism.

The prevalence of protein calorie/energy wasting (PEW) ranges from 18 to 80% in patients on dialysis depending on the characteristics of the population studied (*i.e.*, CKD Stage, dialysis modality, presence of comorbidities and ethnicity) and on the method applied for diagnosis of PEW. In case of PD, it has been described to range between 18-51% [1].

PEW is associated with increased rates of morbidity and mortality; it is one of the strongest risk factors for adverse outcomes [2]. The cause for PEW in patients on dialysis is multifactorial involving factors leading to decreased appetite and factors leading to an increased protein catabolism (**Table 1**). Due to its multifactorial pathophysiology, the treatment of this condition requires a multifaceted approach, combining clinical, nutritional and pharmacological strategies [3].

Factors Affecting Nutrition on Peritoneal Dialysis

The causes of malnutrition in patients on dialysis can be multifactorial including biochemical, gastrointestinal, low socio-economic status as well as miscellaneous factors such as depression, multiple medications, recurrent hospitalizations and underlying illness (**Figure 1**) [4].

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Table 1: Recommended criteria for the clinical diagnosis of PEW proposed by the International Society of Renal Nutrition and Metabolism (ISRNM) (Fouque *et al.*, 2008a) and by the European Best Practice Guideline (EBPG) in Nutrition (Fouque *et al.*, 2007)

Reference (year)	Study design	Subject Characteristics	Favour CAPD	Details
Hiroshige *et al.* (1996)	6-month prospective	Prevalent 8 NIPD, 5 CCPD, 5 CAPD	Yes	Rate of change of RRF in -0.29 (NIPD) versus -0.34 (CCPD) versus +0.01(CAPD) ml/min/month
Rodriguez *et al.* (1998)	3-year prospective	Prevalent 25 CAPD, 20 APD	No	
Hufnagel *et al.* (1999)	18-month prospective	Incident 6 NIPD, 12 CCPD, 18 CAPD	Yes	Rate of change of RRF in -0.26 (APD) versus -0.13 (CAPD) ml/min/month
Bro *et al.* (1999)	6-month randomised controlled trial	Prevalent 13 CAPD, 12 APD	No	
Moist *et al.* (2000)	3-year retrospective	Incident 722 CAPD, 310 APD	No	
De Fijter *et al.* (2000)	2-year RCT	Incident 13 CCPD, 11 CAPD	No	
Gallar *et al.* (2000)	1-year prospective	Incident 11 CAPD, 9 APD	No	
Singhal *et al.* (2000)	4-year prospective	Incident 211 CAPD, 31 APD	No	
Holley *et al.* (2001)	9-year retrospective	Incident 11 CAPD, 9 APD	No	
Jansen *et al.* (2002)	1-year prospective	Incident 243 PD subjects	No	
Hidaka *et al.* (2003)	6-year prospective	Incident 27 CAPD, 7 APD	Yes	Approximate time to decrease 50%of RRF in CAPD is 15 months versus APD 4 months, P<0.001
Johnson *et al.* (2003)	6-year prospective	Incident 134 CAPD, 12 APD	No	
Rodriguez-Carmona (2004)	1-year prospective	Incident 53 CAPD, 51 APD	Yes	Hazardratio of APD versus CAPD= -1.2(-2.25 to -0.15, P=0.02)
Rabindranath (2007)/Liao (2009)	Systemic review of 3 RCT 10-year retrospective	49 PD subjects Incident 188 CAPD, 82 APD	No	
Su *et al.*	9-year	Prevalent 140	No	

(2010)	retrospective	CAPD, 32 APD		
Cnossen *et al.* (2010)	7-year retrospective	Incident 179 CAPD, 441 APD	No	
Balasub ramanion *et al.* (2011)	5-year retrospective	Incident 178 CAPD, 13 APD	No	
Micheis *et al.* (2011)	3-year retrospective	Incident 505 CAPD, 7 APD	Yes	Higher risk of loss of RRF in APD compared to CAPD in first year of treatment (a adjusted hazard ration 2.66, CI 1.66-4.44)

In fact, there are many factors unique to peritoneal dialysis (PD) that may contribute to the overall malnutrition. For instance, patients on PD maintain lower serum albumin for their, age and weight controlled patients on hemodialysis (HD) with loss of albumin through PD fluid ranging from 5.5 – 11.8 gm/day, while low flux dialyzers in HD account for protein losses of 5.6-7.1 gm/day in patients on HD [5, 6]. Other causes responsible for hypoalbuminemia in patients on PD include older age, transport status and chronic inflammation. Anorexia can result from distension due to fluid in the abdomen. Episodes of peritonitis can cause protein losses up to 15 gm per day [7]. Over hydration and early satiety due to absorption of glucose from PD fluid can also be a cause of malnutrition on PD [8].

Even though malnutrition is very common and strongly predicts outcome, it is not thought to directly cause death, rather a combination of malnutrition, inflammation and cardiovascular disease may be interrelated on dialysis related mortality [9, 10].

Malnutrition has been categorized into type 1 and 2 [11]. Type 1 malnutrition is related to the uremic syndrome *per se* and can be corrected by adequate dialysis. It is characterized by a normal / low serum albumin, absence of inflammation or comorbidity, low food intake and decreased protein catabolism. Type 2 malnutrition is thought to be "Cytologie driven" and is clinically more severe, characterized by hypoalbuminemia, inflammation, presence of comorbidity and increased protein catabolism.

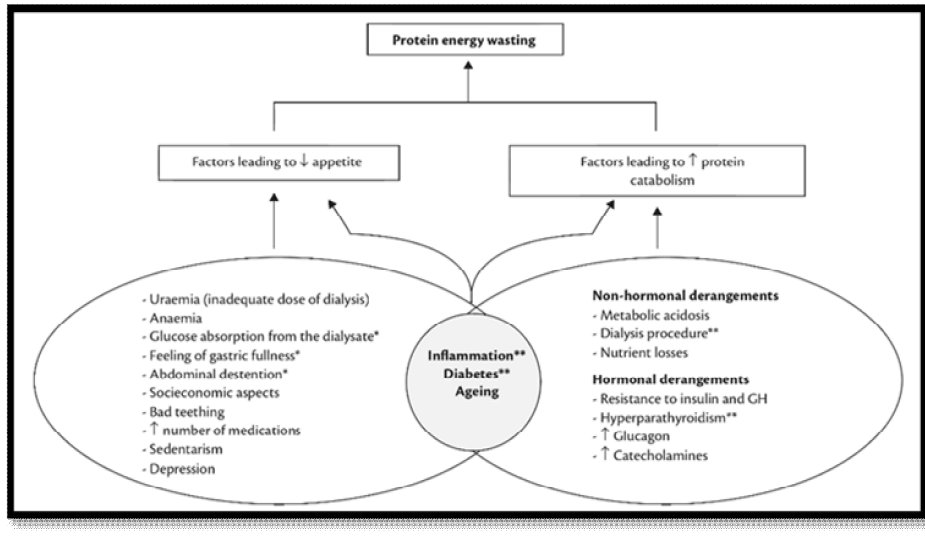

Figure 1: Causes of Protein Energy Wasting in Dialysed Patients.

GH = growth hormone; PTH = parathyroid hormone. * For patients on peritoneal dialysis. ** Factors associated with increased resting energy expenditure.

Nutritional assessment of dialysis patients

Ideally, a nutritional marker should not only predict outcome, but also identify patients at a nutritional risk, be sensible enough to evaluate the impact of a nutritional intervention, and detect longitudinal changes.

The assessment of nutritional status of dialysed patients should include a detailed history, clinical examination along with a combination of methods that evaluate body composition, laboratory parameters, food intake, and composite indices of nutritional status in order to guarantee a precise nutritional diagnosis in a given patient [12].

Body composition assessment

Monitoring body composition is an important tool for nutritional screening. The method of choice depends on the body compartment to be measured, for example, water (total, intra and extracellular), fat (total and regional fat stores), bone or lean body mass or muscle and on the reason why nutritional assessment is performed (research or clinical practice).

Methods for assessing body composition can be classified by their applicability. Methods with high applicability such as anthropometry, bioelectrical impedance analysis (BIA) and near infrared interaction have relatively low precision.

On the other hand, a more precise assessment is available with computed tomography, nuclear magnetic resonance, hydro densitometry, neuron activation analysis, isotopic dilution, and total potassium counting. Dual energy X-ray absorptiometry (DEXA) has been considered as a method of intermediate applicability and is largely used for research purposes [13].

Anthropometry

Anthropometric measurements include body weight, height, skinfold thickness (triceps, biceps, subscapular, supra iliac) and circumferences (arm, waist). The equipment used for such measurements (weight scale balance, skinfold caliper, and non-stretchable metric tape) are simple, have low cost and could be applied bedside. With these measurements it is possible to monitor somatic protein stores, body fat (total, abdominal) and a rough assessment of body water.

For patients on HD these measurements should be performed after the dialysis session and for those on PD, it is desirable to perform these measurements with an empty abdominal cavity, in particular when assessing body weight and waist circumference. To diminish intra-observer variation, the same observer should perform longitudinal measurements.

Bioelectrical impedance

BIA works by measuring body resistance (opposition offered by the body to the flow of an alternating electrical current) and reactance (capacitance properties of the cell membrane depending on its integrity, function and composition). BIA provides measurements of body water (total, extra and intra cellular), lean body mass and body fat. The BIA alters with hydration status, hence should be performed approximately 30 minutes after the dialysis session, or for patients on PD with a dry abdominal cavity.

Dual energy X-ray absorptiometry

DEXA has been used widely in clinical research as a means of quantifying body composition. With DEXA bone mineral, fat mass (FM) and lean body mass (LBM) distribution are estimated directly, without making assumptions about the two-compartment model. However the assessment of LBM by DEXA is subject to flaws, because it assumes that 72% of the LBM compartment is water [14]. As patients on PD can exhibit abnormal hydration status, DEXA might not be a very precise method for assessing LBM in dialyzed patients.

Handgrip strength

Decreased muscle mass is an important criterion for the presence of PEW. Handgrip strength (HGS) with measurement of the maximal voluntary force of the hand and arm assessed by a dynamometer is a useful tool to assess muscle function [15].

Many studies have assessed HGS in dialyzed patients and results show a high association between values coming from HGS and those from lean body mass assessed by DEXA, as well with results obtained by composite methods to assess nutritional status, such as the subjective global assessment (SGA) and the malnutrition inflammation index (MIS) [15-17].

Biochemical parameters

Serum albumin

Albumin constitutes 60% of human plasma protein and has a relatively long half-life (14 -20 days). The amount of circulating serum albumin is determined by its synthesis, breakdown, and volume of distribution serum albumin concentration on CKD is influenced by factors such as over hydration, proteinuria, losses into the dialysate and presence of inflammation [18]. For these reasons, the utility of serum albumin as a marker of malnutrition in dialysis patients has been questioned [19].

In spite of these limitations, measurement of serum albumin is simple, readily available and remains an outcome marker in PEW syndrome and also reflects the severity of the disease. In addition, its routine availability and responsiveness to nutritional interventions makes it a relevant index. There is a strong association between hypoalbuminemia (and albumin losses) and morbidity and mortality in patients with CKD. It is therefore recommended to evaluate temporal trends and to always combine Serum albumin measurements with additional complementary markers of malnutrition in patient monitoring.

Pre-albumin

Pre albumin (also known as transthyretin) a transporter of thyroxin and retinol, is mainly synthesized in the liver, and a reduced protein intake is associated with a decline in its serum concentrations, which can be rapidly restored by re-feeding due to its lower concentration and shorter half-life (2-3 days) [20]. Normal values of pre-albumin ranges between 15 to 36 mg/dL.

Two recent studies showed that the change in serum transthyretin over time is associated with changes in survival in patients on dialysis [21, 22]. Even if baseline serum transthyretin may not be superior to albumin in predicting mortality in patients on HD, transthyretin concentrations <20 mg/dl are associated with death risk even in normoalbuminuric patients, and a fall in serum transthyretin over 6 months is independently associated with increased death risk [22].

Creatinine Kinetics

The primary source of serum creatinine is skeletal muscle, and concentrations are elevated in individuals with greater muscle mass, independent of rental function [23]. Creatinine kinetics is based on the principle that creatinine production is proportional to lean body mass, and the sum of creatinine excretion (urinary and dialytic) and metabolic degradation represents a simple and reliable tool for the

assessment of protein nutritional status and muscle mass. Indices derived from Creatinine kinetics are strongly associated with the patient's nutritional status and are prognostic markers of mortality in HD patients [24].

Assessment of energy and nutrient intake

The methods applied to assess energy and nutrient intake include 24 hour food recalls, 3 to 7day food records, and food questionnaires. The assessment of energy and protein intake by these methods has been shown to predict outcome [25].

In addition, particularly for the assessment of protein intake, the protein equivalent of nitrogen appearance (PNA) can also be used in dialysed patients. It relies on the principle that during steady-state conditions, nitrogen intake is equal to or slightly greater than total nitrogen appearance [26]. Therefore, on the clinically stable patient, PNA can be used to estimate protein intake. Because protein intake is usually prescribed according to edema – free body weight, PNA is commonly normalised by body weight and is known as normalised PNA (nPNA).

Composite indices of nutritional status

The seven point subjective global assessment (SGA) and the malnutrition inflammation score (MIS) are the most frequent composite methods used to assess PEW in dialysed patients. Both combine assessments of the medical history as well as functional capacity, dietary history, and physical examination.

MIS includes three objective components (BMI, serum albumin, and total iron bonding capacity) or transferrin. Some researchers consider MIS as a more complete method to assess PEW, because it includes the measurement of laboratory parameters that can predict outcome [27].

Nutritional intervention

Energy

The recommended energy intake for dialysed patients according to the NkF – KDOQI nutrition guidelines is 35kcal/kg/day for patients aged <60yrs and 30-35kcal/kg/day for those aged >60yrs. However, it is important to individualise the energy recommendations, in patients with sedentary lifestyle [28]. According to the EBPG in nutrition, this individualisation is done by estimating the resting energy or Schofield equation and then multiplying this by a factor of physical ctivity. Particularly for obese patients on PD, it is appropriate to discount the energy contributed by glucose absorption from the dialysate.

Protein and Phosphorous intake

The suggested recommended protein intake for dialysed patients by the NkF-KDOQI guidelines is 1.2gm/kg/day in patients on HD and 1.3gm/kg/day in patients on PD. One important issue while planning and counselling the protein intake is to

control phosphorous intake as well, since the many food sources of protein are also food sources of phosphate. According to the EBPG on nutrition, a daily intake of 1.1gm/kg/day of protein and up to 800-1000mg of dietary phosphate is recommended [12]. To reach this goal, it is important to develop nutritional educational programmes that teach the patient about the choice of food sources of protein with low phosphate content.

Common Problems during CAPD

1. Nausea

2. The last thing the patient may want to think about is food.

3. Weight loss may occur during this time.

4. Suggestions to help him feel better and to keep up daily good nutrition:

i. Have small, frequent meals.

ii. Avoid liquids at mealtime. They should be taken 1 hour before or 1 hour after meals.

iii. Eat a cracker or piece of dry toast after resting, but before getting up.

iv. Avoid fried or fatty foods.

v. Rest following meals.

vi. Avoid cooking odors; they may increase your nausea.

vii. Suck on hard candy

These foods may be easier to eat when you feel nauseated

1. Custard

2. Dry toast

3. Jelly

4. Mashed potatoes

5. Kheer

6. Ice Cream

7. Cold milk *Diabetic patients should add sugar free to the desserts.*

Constipation

- A regular lifestyle helps have more regular bowel habits.

- Avoid keeping irregular hours
- Daily physical activity
- Raw (unrefined) bran can be added to food
- Art of the fluid allowance can be used as a warm beverage first thing in the morning or before going to bed in the evening. Warm water, tea, or coffee work well
- Eat fiber rich foods like whole cereals and pulses, sprouts, vegetables and fruits like papaya.
- Patients should always respond to their urges, no matter busy they are
- Check with the doctor about a laxative

Feeling of fullness

- 1. The dialysis solution may give the patient a sense of fullness in the stomach.
  - Eating smaller meals 5-6 times a day.
- 2. Loss of appetite
  - Get help from the dietitian for an individualised diet chart
  - Try nutritional supplements after consulting the doctor
  - Increase variety in the food
  - One can follow a 3 meal and 2 snack pattern.

Nutritional support – Route of administration

According to the European society for parenteral and enteral nutrition guidelines, nutritional support should be considered for patients with signs of PEW, such as BMI < 20 kg/m^2, body weight loss >10% over 6 months, serum albumin <35 g/L and serum transthyretin <300 mg/L [29].

Oral nutritional support should be the first option for treating PEW. It can provide approximately an additional 7-10 kcal/kg/day of energy and 0.3-0.4 kg/day of protein [2]. To reach this level of oral supplementation, the supplement should be given 3-4 times daily on small doses after the meal, and should never replace a meal.

If adequate intake cannot be achieved by oral supplementation and nutritional status continues to deteriorate, enteral nutrition with tube feeding should be considered [30]. For both interventions, oral or enteral supplementation formulas specifically designed for dialyzed patients are preferred as they have higher energy density (and

therefore reduced volume) and protein content, but reduced potassium and phosphate concentration.

The use of intra dialytic parenteral nutrition (IDPN) is an additional option for treating PEW, but its effectiveness is not clear. Its main advantage is easy administration through pre-existing vascular access, control of nutritional content, and prevention of net loss of amino acids and water solute vitamins. However during IDPN, nutrients are rapidly removed from blood, and it can be seen as a non-physiologic circumvention of the normal nutrient-gut interactions.

Intra peritoneal amino acids

Intra peritoneal amino acids have been used in CAPD patients using 1.1% amino acid dialysate solutions (Nutrineal) to replace one to two of the usual daily glucose exchanges and it may show some improvement in nutritional status, especially in those with PEW. Limitation are that, it is expensive, only leads to a small improvement in nutrition, and the exchange must be done at the same time as a meal to enhance amino acid uptake.

Conclusion

The nutritional management of dialysed patients requires a multifaceted team approach, including assessment of the nutritional status and prescription of appropriate diet together with periodic follow-up, so that early changes in nutritional status can be diagnosed and treated accordingly. The whole team should be aware of the nutritional derangements that these patients are prone to and every patient should ideally have periodic consultation with a renal dietician.

References

1. Bergstrom, J., and B. Lindholm, 1993: Nutrition and adequacy of dialysis: how do hemodialysis and CAPD compare? *Kid. Int.,* **43,** 39-50.

2. Kalantar-Zadeh, K., N. J. Cano, K. Budde, C. Chazot, C. P. Kovesdy, R. H. Mak, R. Mehrotra, D. S. Raj, A. R. Sehgal, P. Stenvinkel, and T. A. Ikizler, 2011: Diets and enteral supplements for improving outcomes in chronic kidney disease. *Nat. Rev. Nephrol.,* **7,** 369-384.

3. .Mak, R. H., A. T. Ikizler, C. P. Kovesdy, D. S. Raj, P. Stenvinkel, and K. Kalantar-Zadeh, 2011: Wasting in chronic kidney disease. Journal of cachexia, sarcopenia and muscle. **2,** 9-25.

4. Hakim, R., and N. Levin, 1993: Malnutrition in hemodialysis patients. *Am. J. Kid. Dis.,* **21,** 125-137.

5. Blumenkartz, M. J., J. D. Koppale, and J. W. Coburn, 1982: Metabolic balance studies and dietary protein requirements in patients undergoing continuous ambulatory peritoneal dialysis. *Kid. Int.,* **21,** 849-861.

6. Ikizler, T. A., P. J. Flakoll, R. A. Parker, and R. M. Hakim, 1994: Amino acid and albumin losses during hemodialysis. *Kid. Int.,* **46,** 830-837.

7. Bannister, D. K., S. R. Acchiardo, L. W. Moore, and A. P. Kraus Jr., 1987: Nutritional effects of peritonitis in CAPD patients. *J. Am. Diet. Assoc.,* **87,** 53-56.

8. Sezer, S., E. Tutal, Z. Arat, A. Akçay, H. Çelik, F. N. Özdemir, and M. Haberal, 2005: Peritoneal transport status influence on atherosclerosis/inflammation in CAPD patients. *J. Renal Nutrit,* **15,** 427-434.

9. Bergstrom, J., and B. Lindholm, 1998: Malnutrition, cardiac disease and mortality – an integrated point of view. *Am. J. Kid. Dis.,* **32,** 1-10.

10. Stenvinkel, P., O. Heimburger, B. Lindholm, G. A. Kaysen, and J. Bergström, 2000: Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrol. Dial. Transplant.,* **15,** 953-960.

11. Wang, T., O. Heimburger, J. Bergstrom, and B. Lindholm, 1999: Nutritional problems in peritoneal dialysis: an overview. *Petit. Dial. Int.,* **19,** 297-303.

12. Fouque, D., M. Vennegoor, P. Ter Wee, C. Wanner, A. Basci, B. Canaud, P. Haage, K. Konner, J. Kooman, A. Martin-Malo, and L. Pedrini, 2007: EBPG guideline on nutrition. *Nephrol. Dial. Transplant.,* **22,** 45–87.

13. Ellis, K. J., 2000: Human body composition: *in vivo* methods. *Physiol. Rev.,* **80,** 649–680.

14. Abrahamsen, B. O., T. B. Hansen, I. M. Høgsberg, F. B. Pedersen, and H. Beck-Nielsen, 1996: Impact of hemodialysis on dual X-ray absorptiometry, bioelectrical impedance measurements, and anthropometry. *Am. J. Clin. Nutr.,* **63,** 80–86.

15. Silva, L. F., C. M. Matos, G. B. Lopes, M. T. Martins, M. S. Martins, L. U. Arias, R. L. Pisoni, and A. A. Lopes, 2011: Handgrip strength as a simple indicator of possible malnutrition and inflammation in men and women on maintenance hemodialysis. *J. Ren. Nutr.,* **21,** 235–245.

16. Heimburger, O., A. R. Qureshi, W. S. Blaner, L. Berglund, and P. Stenvinkel, 2000: Hand-grip muscle strength, lean body mass, and plasma proteins as markers of nutritional status in patients with chronic renal failure close to start of dialysis therapy. *Am. J. Kid. Dis.,* **36,** 1213–1225.

17. Carrero, J. J., M. Chmielewski, J. Axelsson, S Snaedal, O. Heimbürger, P. Bárány, M. E. Suliman, B. Lindholm, P. Stenvinkel, and A. R. Qureshi, 2008: Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. *Clin. Nutr.,* **27,** 557–564.

18. Klein, S., 1990: The myth of serum albumin as a measure of nutritional status. *Gastroenterol.,* **99,** 1845–1846.

19. Mak, R. H. and W. Cheung, 2006: Energy homeostasis and cachexia in chronic kidney disease. *Pediatr. Nephrol.,* **21,** 1807–1814.

20. Chertow, G. M., K. Ackert, N. L. Lew, J. M. Lazarus, and E. C. Lowrie, 2000: Prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients. *Kid. Int.,* **58,** 2512–2517.

21. Cano, N. J., D. Fouque, H. Roth, M. Aparicio, R. Azar, B. Canaud, P. Chauveau, C. Combe, M. Laville, and X. M. Leverve, 2007: Intradialytic parenteral nutrition does not improve survival in malnourished hemodialysis patients: a 2-year multicenter, prospective, randomized study. *J. Am. Soc. Nephrol.,* **18,** 2583–2591.

22. Rambod, M., C. P. Kovesdy, R. Bross, J. D. Kopple, and K. Kalantar-Zadeh, 2008: Association of serum prealbumin and its changes over time with clinical outcomes and survival in patients receiving hemodialysis. *Am. J. Clin. Nutr.,* **88,** 1485–1494.

23. Macdonald, J. H., S. M. Marcora, M. J. Kumwenda, M. Jibani, G. Roberts, R. Glover, J. Barron, and A. B. Lemmey, 2006: The relationship between estimated glomerular filtration rate, demographic and anthropometric variables is mediated by muscle mass in non-diabetic patients with chronic kidney disease. *Nephrol. Dial. Transplant.,* **21,** 3488–3494.

24. Keshaviah, P. R., K. D. Nolph, H. L. Moore, B. Prowant, P. F. Emerson, M. Meyer, Z. J. Twardowski, R. Khanna, L. Ponferrada, and A. Collins, 1994: Lean body mass estimation by creatinine kinetics. *J. Am. Soc. Nephrol.,* **4,** 1475–1485.

25. Kovesdy, C. P., C. S. Shinaberger, and K. Kalantar-Zadeh, 2010: Epidemiology of dietary nutrient intake in ESRD. *Semin. Dial.,* **23,** 353–358.

26. National Kidney Foundation, 2000: Clinical practice guidelines for nutrition in chronic renal failure. K/DOQI, National Kidney Foundation. *Am. J. Kid. Dis.,* **35,** 1–140.

27. Kalantar-Zadeh, K., J. D. Kopple, G. Block, and M. H. Humphreys, 2001: A malnutrition inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am. J. Kid. Dis.,* **38,** 1251–1263.

28. Baria, F., M. A. Kamimura, C. M. Avesani, B. Lindholm, P. Stenvinkel, S. A. Draibe, and L. Cuppari, 2011: Activity-related energy expenditure of patients undergoing hemodialysis. *J. Ren. Nutr.* **21,** 226–234.

29. Cano, N., E. Fiaccadori, P. Tesinsky, G. Toigo, W. Druml, M. Kuhlmann, H. Mann, and W. H. Hörl, 2006: ESPEN guidelines on enteral nutrition: adult renal failure. *Clin. Nutr.,* **25,** 295–310.

30. Oxford handbook of dialysis. Edition 2; **6,** 556.

Chapter 44

Peritoneal Dialysis and Renal Osteodystrophy

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Peritoneal Dialysis and Renal Osteodystrophy

Introduction

There is an increasing prevalence of mineral bone disease in patients on peritoneal dialysis (PD). This has coincided with a decrease in the prevalence of aluminum associated bone disease. Comparing the 1980s to the 1990s, the prevalence of Brazilian patients with hyperparathyroid bone disease increased from 32.3% to 44.0%, while aluminium overload decreased from 61.3% to 42.4% [1]. Renal osteodystrophy seems to progress slowly for patients on CAPD [2].

Renal osteodystrophy can present with a wide spectrum of bone disease pathologies, ranging from high bone turnover state to low bone turnover state **(Table 1)**. Various medications like phosphate binders, calcium supplements and calcimimetics, patient profiles (diabetics and elderly) and dialysis vintage influences the bone lesions. There is a greater prevalence of low turnover state namely adynamic forms of renal osteodystrophy in patients on PD. It has been noted that patients with adynamic bone disease (AMD) have more difficulties in handling and buffering calcium loads and consequently have a higher risk of extra osseous calcifications [3].

On comparing bone histology in 259 chronic dialysis patients, a different pattern of bone lesions was seen in PD as compared with HD, with low turnover disorders comprising 66% of the lesions seen in PD and high turnover lesions accounting for 62% of the bone histologic findings in HD. The levels of parathyroid hormone (PTH) are higher up to 2.5 times in patients on PD as compared to patients on HD [4].

M. Parikh, A. M. Konnur

Table 1: Characteristics of High and Low Turnover Bone Disease

High Turnover Bone Disease	Low Turnover Bone Disease

• Increased bone resorption
• Increased osteoblastic activity
• Markedly increased osteoclastic activity
• Endosteal and peritrabecular fibrosis
• High Parathormone levels
• Normal bone mineralization
• Osteoclasts increase in size and nuclei number and tunnel through the trabecular bone leading to large cavities and bone surface resorption. The bone appears as woven bone
	• Osteomalacia and rickets
	• Deficiency of active Vitamin D
	  o Defective bone mineralization
	  o Increased osteoid /unmineralised bone matrix
	• In aluminum toxicity, deposition at the interface of mineralized bone and unmineralised osteoid
	• Adynamic bone disease
	  o Low bone formation
	  o Defective bone mineralization
	  o Normal/decreased osteoid thickness
	  o Decreased osteoclastic activity

Pathogenesis and clinical features

Renal osteodystrophy and PD

Renal osteodystrophy, worsens the quality of life and contributes to the morbidity in patients on continuous ambulatory peritoneal dialysis.A form of the bone disease, the osteomalacic dialysis osteodystrophy was earlier attributed to be due to aluminum toxicity from untreated or softened water used in HD. In patients undergoing PD, aluminum toxicity may be due to the use of aluminum-containing phosphate binders since the process of preparation of PD fluid reduces most of the trace metals [5]. With decreasing use of aluminium containing binders, this lesion has slowly become rare. **Figure 1** represents classification of patients based on turnover state.

Adynamic bone disease in PD

A newer form of bone lesion characterized by a marked decrease in bone turnover without osteoid accumulation. AMD was initially demonstrated in 1984 in the laboratory. It was thought that this was related to aluminum-containing phosphate binders but since then despite the use of calcium salts, AMD incidence has not decreased. Factors associated with the occurrence of AMD include:

1. Aluminum accumulation which is currently found in 60% of the patients on chronic maintenance dialysis undergoing biopsies.

2. Increasing age of the patients on dialysis.

3. Diabetes.

4. Chronic ambulatory peritoneal dialysis (CAPD).

Older age, higher prevalence of diabetes and a shorter duration of dialysis may contribute to the increased prevalence of AMD in patients on PD. Higher calcium levels in patients on PD may lead to suppression of PTH secretion and promote presence of this lesion in patients on PD. As this condition is associated with hypercalcemia, stunted bone remodeling leading to ageing of bone is observed. This is possibly due to an impaired bone repair of physiologic micro damages, and accumulation of micro fractures leading to mechanical failure and ultimately an increased risk of fractures [7]. (**Figure 2**)

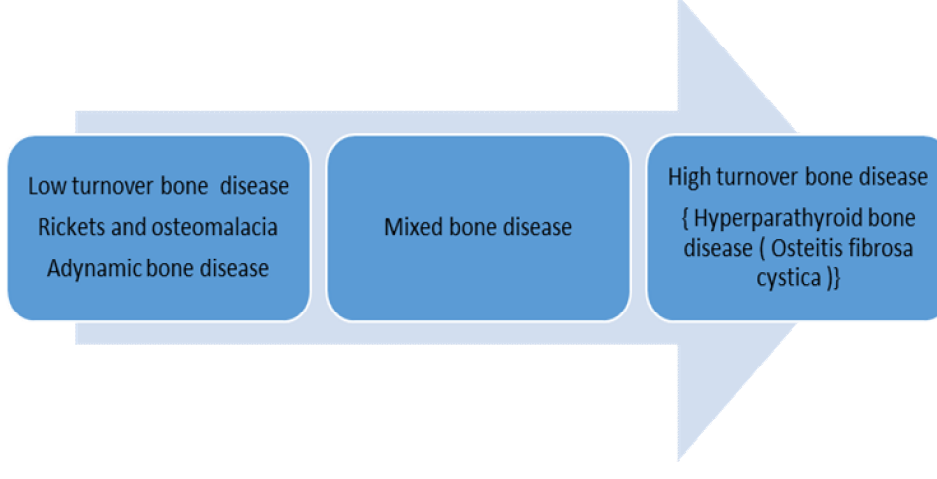
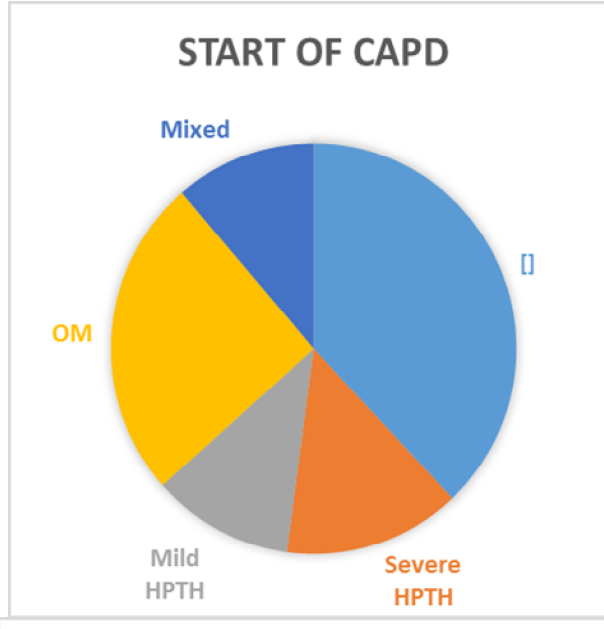
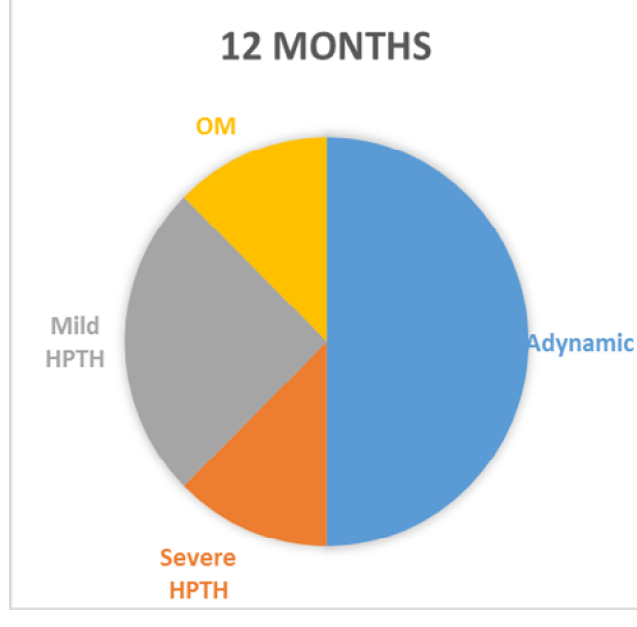
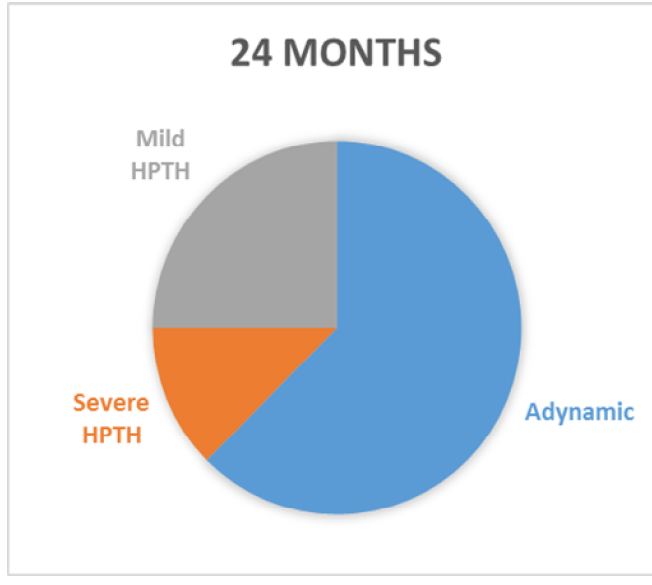


Figure 1: Classification of Patients Based on Turnover State


START OF CAPD
Mixed
[]
OM
Mild
HPTH
Severe
HPTH


12 MONTHS
OM
Mild
HPTH
Adynamic
Severe
HPTH



(OM: osteomalacia, HPTH: hyperparathyroidism)

Figure 2: Progression of Patients on CAPD

At present, sparse data is available on the effects of CAPD on renal osteodystrophy. Twelve patients on CAPD were studied for one year, in order to evaluate the progress of renal osteodystrophy. There was a downward trend of plasma calcium, a good control of phosphatemia, a significant increase of alkaline phosphatase and PTH. A significant decrease of plasma vitamin D metabolites 25(OH)D and 1,25-$(OH)_2D_3$ and bone mineral content was noted. Bone biopsies done showed a general worsening of both secondary hyperparathyroidism and osteomalacia. The conclusion of this study was that an adequate CAPD alone is not able to control the evolution of renal osteodystrophy [8].

In another case series by Buccianti G *et al,* [8], 10 cases of asymptomatic AMD were noted among a group of 32 continuous patients on ambulatory PD, most of whom had never been exposed to aluminum-containing phosphate binders. Compared to the remaining 22 patients, they were older (Mean age: 54 +/- 11.4 *vs.* 42 +/- 11.8 years; $p< 0.05$), a longer pre-dialysis duration of renal failure (10.9 *vs.* 7.1 years), higher mean ionized calcium (1.30 +/- 0.04 *vs.* 1.15 +/- 0.02 mmol/l; $p< 0.01$), and a lower mean intact PTH (31.5 *vs.* 200.3 pg/ml; $p< 0.001$). The bone density was not different between the two groups, but 9 of the 10 adynamic patients had significant vascular calcification seen on plain radiology as compared with only 7 of 20 in the comparison group ($p< 0.05$). Follow-up of the adynamic patients showed a close association with serum intact PTH and ionized calcium levels. With one exception, a dynamic bone did not appear to be associated with lower bone density than other types of osteodystrophy [9].

In the present scenario, ABD is increasingly being associated with oral calcium carbonate use, vitamin D supplements, or supraphysiological dialysate calcium. In a study to assess the effect of lowering dialysate calcium on episodes of hypercalcemia, serum PTH levels as well as bone turnover, 51patients treated with PD and biopsy-proven AMD were randomised to treatment with control calcium, 1.62 mM, or low calcium, 1.0 mM, dialysate calcium over a 16-month period. In the low dialysate calcium group, 14 patients completed the study. This group experienced a decrease in serum total and ionized calcium levels, and an 89% reduction in episodes of hypercalcemia, resulting in a 300% increase in serum PTH values, from 6.0+/-1.6 to 24.9+/-3.6 pM ($P<0.0001$). Bone formation rates, all initially suppressed, at 18.1+/-5.6 $microm^2/mm^2$/day rose to 159+/-59.4 $microm^2/mm^2$/day ($P<0.05$), into the normal range (>108 $microm^2/mm^2$/day). In the control group, nine patients completed the study. Their PTH levels did not increase significantly, from 7.3+/-1.6 to 9.4+/-1.5 pM and bone formation rates did not change significantly either, from 13.3+/-7.1 to 40.9+/-11.9 $microm^2/mm^2$/day. Lowering of peritoneal dialysate calcium reduces serum calcium levels and hypercalcemic episodes, which results in increased PTH levels and normalization of bone turnover in patients with AMD [10].

Another interesting corollary is whether recurrent episodes of peritonitis can contribute to an increased incidence of AMD. It has been noted that peritoneal macrophages stimulated by infection can metabolize 25(OH)D to the active vitamin D3 metabolite, $1,25(OH)_2D_3$. The subsequent hypercalcemia may promote AMD [11].

The prevalence of low-turnover lesions in patients undergoing PD is high. In a study of 57 patients studied by bone biopsy, AMD was found in 63.2%, and 36.8% showed high-turnover bone disease.

Patients with AMD when compared with the high turnover bone disease have [12].

1. Higher prevalence of diabetes.
2. Older age.
3. Higher calcium salt intake.
4. Lower calcitriol doses.
5. Low osteocalcin level.
6. Lower ultrafiltration.
7. Low levels of PTH.
8. PTH secretion capacity is maintained.
9. Hyper responsive parathyroid gland to hypocalcemia.
10. Increased aluminum levels despite low exposure [13].

Cardiovascular Outcomes in Patients on Peritoneal Dialysis *[14]*

ROCK-PD study by Galleini *et al*. showed cardiovascular calcification. The prevalence increased from 77% of patients at baseline (*N*=369) to 90% of patients over 3 years, progressing in 73% of the patients. There were 42 deaths (11%).

Analyses showed a marked correlation between baseline P levels and the presence of left ventricular hypertrophy. However, there was no consistent correlations between serum calcium or phosphorous with mortality or morbidity.

Clinical and radiological features are not different in patients with renal osteodystrophy on hemodialysis or PD:

Skeletal

1. Bone tenderness.
2. Arthralgia.
3. Spontaneous fracture.
4. Growth retardation.

Extra skeletal

1. Uremic conjunctivitis: Red eye syndrome.
2. Myopathy.
3. Myositis ossificans.
4. Calciphylaxis.
5. Medial vascular calcification: Monckebergs calcification.

Radiological manifestations

1. Tip erosion of terminal phalanges, radial surfaces of middle phalanges, distal end of clavicles.
2. Pepper pot skull.
3. Thinning of cortex of axial bones.
4. Rugger jersey spine: osteopenic vertebrae with sclerotic upper and lower surfaces.
5. Vascular calcification.
6. Looser's zone: pubic bones or femur.

Special cases

Patients on PD with Diabetes:

In a database assessment of 256 patients (45% on HDand 55% on PD), who were prospectively studied in 3 Toronto dialysis centers between October of 1987 and 1989 involving a series of investigations that included the deferoxamine test, measurement of intact 1-84 PTH levels, and an iliac crest bone biopsy; it was noted that they had decreased dialysis vintage (2.4 +/- 0.3 *vs.* 4.7 +/- 0.3 years; P< 0.0002),used calcium carbonate as the only phosphate binder more frequently (40 *vs.* 25%; P< 0.007), and had lower levels of PTH (12 +/- 1.4 *vs.* 24 +/- 2.3 pmol/liter; P< 0.002). High-turnover bone disorders (that is, osteitis fibrosa and mixed disorder) were distinctly uncommon (8% *vs.* 33%; P< 0.01 by Fisher's exact test), while the mild (19% *vs.* 9%; P = NS) and the aplastic disorders (with mean stainable bone surface aluminum of 6.5 +/- 0.7%) (46% *vs.* 31%; P = NS) tended to be more common in patients with diabetes [15].

Elderly Patients on PD

Elderly patients on PD differ from younger patients on HD in the following ways: [16]

1. Poor nutritional intake and resultant low calcium and phosphate levels and involutional changes in bone turnover makes dialysis related hypercalcemia, hyperphosphatemia and hyperparathyroidism easily preventable.
2. The prevalence of AMD is higher.
3. The risk of fracture is higher in the elderly and in women. The incidence of hip fractures in dialysis patients is 4 – 5 times higher than in the general population and rises to 9 times after 4 years of dialysis. Risk varies between 0.5 - 1.5%/year and overall fracture incidence between 1.2 -4.5%/ year.
4. Vertebral fractures are also common. Elderly patients are at a particular risk of hip fractures with rates of 3.3 – 4.7%/ year.
5. Fracture rates have fallen since 2004. Mortality rates in excess of 50% are seen among elderly patients in the first year after a fracture. Fracture incidence in HD is 1.3 – 1.5 times higher than PD either due to a higher fall rates associated with postural hypotension after HD, better preserved bone microarchitecture in PD, or higher bone mass density (BMD).
6. Protein malnutrition is higher in the elderly contributing to decreased bone mass and increased fracture risk.
7. The risk of vitamin D deficiency is higher not only due to increased loss of vitamin D in the dialysate but also depleted Vitamin D in patients on PD with preserved residual renal function and in the presence of nephrotic syndrome, vitamin D reserves will be depleted. The management of Renal Osteodystrophy in CAPD is shown in **Figure 3**.

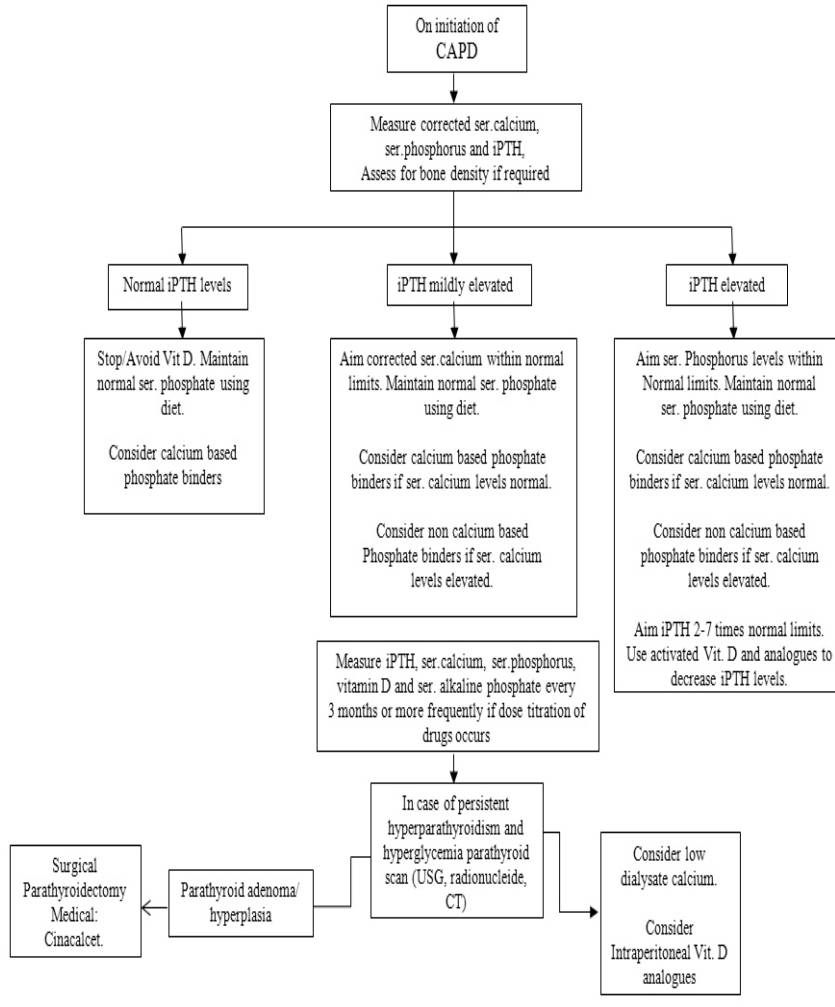
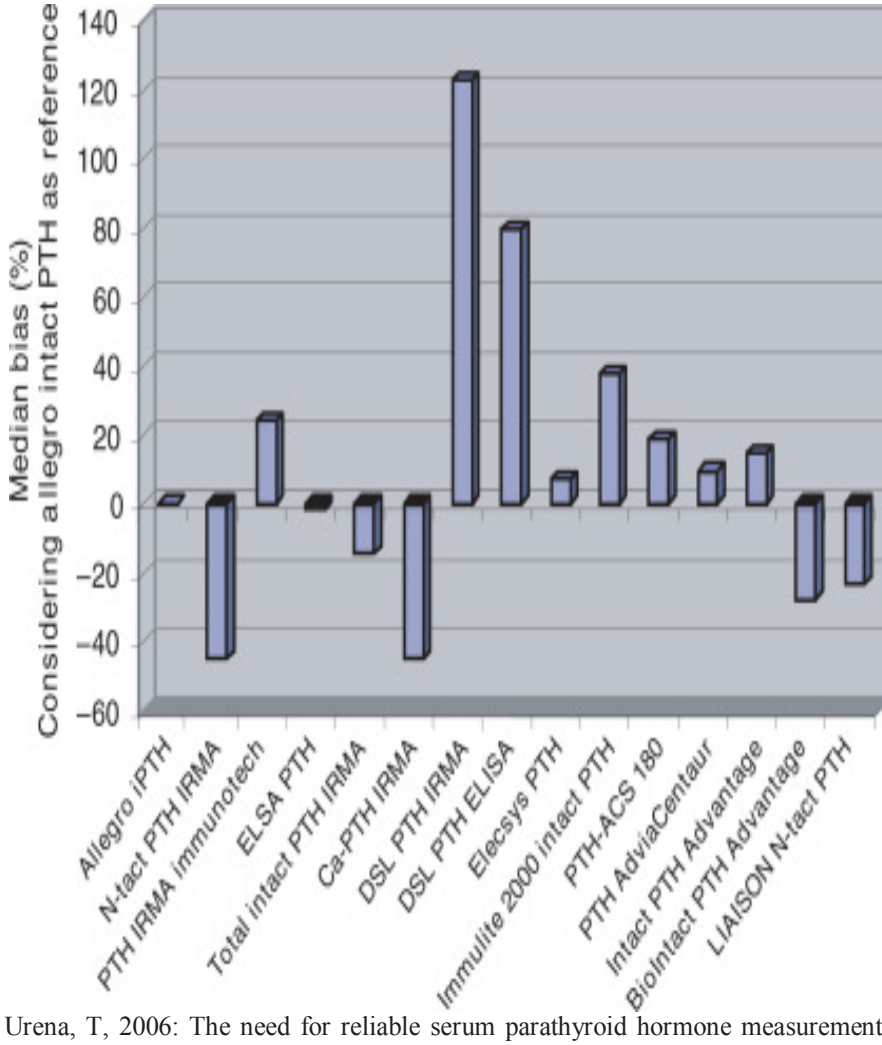


Figure 3: Management of Renal Osteodystrophy in CAPD

Investigations

Serum PTH levels: Variability in the PTH measurement has led to a difficulty in taking important decisions like scheduling parathyroidectomy, starting calcimemitics or titrating the dose of phosphate binders. Bone response to circulating PTH concentration in uremic patients is very variable as it depends on

the quantity of PTH receptor expression and function and also on the existence of a specific C-terminal PTH receptor (**Figure 4**).



Urena, T, 2006: The need for reliable serum parathyroid hormone measurements. *Kid. Int.*, **70,** 240–243.

Figure 4: Factors Affecting Levels of Serum PTH.

Combining PTH measurements with specific biochemical markers of bone formation rate — such as bone-specific alkaline phosphatase — and of bone resorption rate — such as collagen type I breakdown cross-linked peptides (cross-laps) —might improve the prediction of the type of ROD. This kind of study is yet to be performed.

The National Kidney Foundation/Kidney-Dialysis Outcome Quality Initiative guidelines recommend to maintain the serum intact PTH concentration between 150 and 300 ng/l in patients with stage 5 chronic kidney disease (CKD). As is evident in the Figure 4, a fair amount of bias is observed in the commercially available PTH assays and these limits of 150 and 300 ng/l in patients with CKD were derived from studies that used the Allegro intact PTH assay. The unfortunate consequence is that opposite therapeutic decisions may be reached in a single patient depending on the PTH assay used. Hence, it may be clinically advantageous to use the same kind of assay serially in ESRD patient to monitor PTH levels [17].

Treatment

Renal osteodystrophy treatment is broadly the same depending on the clinical presentation. In case of high turnover bone disease, the thrust is on normalizing serum phosphorus levels using dietary modifications, drugs like phosphate binders (depending on the serum calcium levels using calcium containing or non-calcium containing phosphate binders) and dialysis. In case of hyperparathyroidism, use of activated vitamin D and vitamin D analogues which normalize the serum calcium levels and suppress the PTH secretion are used. A down side is that this can increase serum phosphorus levels. PD offers a few modifications in the treatment of renal osteodystrophy.

Initially used peritoneal dialysate solutions with high-calcium concentrations (1.75 mmol/L) have been now replaced by solutions with a lower, more physiological calcium content [18]. But, there is still a debate as to how far the dialysate calcium should be lowered (1.25 mmol/L or less) and what the long term outcomes are. The CMS study by Weinrich *et al*, concluded that in patients on CAPD proposed that low-calcium dialysate solutions can be used successfully over prolonged periods of time with stable control of serum calcium. The risk of hypercalcemia resulting from calcium-containing phosphate binders and the need is markedly diminished. However, there is a certain risk that severe secondary hyperparathyroidism with long-term low concentration of dialysate calcium (1.0 mmol/L) therapy will develop, even if normocalcemia is maintained. Thus, low dialysate calcium dialysis requires close and continuous monitoring of PTH and bone metabolism [18].

Intraperitoneal calcitriol instillation $1,25(OH)_2D_3$ during PD may be a simple and effective means to suppress secondary hyperparathyroidism in patients undergoing CAPD. In a study of 11 patients with hyperparathyroidism, it was noted that increasing calcium mass transfer using a 4.0 mEq/liter Ca dialysate leads to a small reduction in PTH concentrations. On the other hand, intraperitoneal $1,25(OH)_2D_3$ is well absorbed into the systemic circulation, raises ionized calcium levels, and leads to a marked suppression of PTH. This can be an interesting option for treating hyperparathyroidism in patients on CAPD [19].

Oral pulse calcitriol administered at a dose of 5 micrograms given twice per week in patients on CAPD with dialysate calcium concentration of 1.75 mmol/L (3.5

mEq/L) has been shown to decrease PTH levels rapidly, and, after 4 to 6 weeks of therapy, with values reaching 60% lower than pretreatment values. Interestingly, mean values for serum calcium did not change significantly (2.29 +/- 0.12 mmol/L [9.6 +/- 0.5 mg/dL] before treatment compared with 2.32 +/- 0.08 mmol/L [9.7 +/- 0.25 mg/dL] after therapy) as also serum phosphorus was also unchanged. This can be another effective option to treat high turnover bone disease in patients on CAPD [20].

Unfortunately, the treatment of AMD has very few evidence based treatment available. The usual strategy is to prevent hypercalcemia either due to inappropriate use of high calcium dialysate, omitting the use aluminum based phosphate binders or vitamin D or its analogues. Usually, the bone disease responds but very slowly. It is unclear whether use of bisphosphonate therapy or low calcium dialysate as a preemptive modality in at risk population like in elderly diabetic patients with ESRD on CAPD will prevent the incidence of this bone lesion. Future studies are required to clarify this situation.

At our institution**,** Muljibhai Patel Urological Hospital**,** we retrospectively studied mineral bone disease parameters of 64 patients who were initiated on CAPD from 2009 to 2016. .

Mean follow up duration was 10.3 months**.** Of the 56 patients, prevalence of low bone turn over disease at initiation was 58.9% (n=33) and high bone turn over prevalence was 40% (n=23). Despite poor follow up, out of 8 patients whose reports of PTH at 2 years were available 5 had AMD with 2 having mild hyper PTH and 1 having moderate hyper PTH. None of the patient had severe hyper PTH (**Figures 5 and 6**).

Mean corrected serum calcium levels at the initiation were 8.9mg/dl, at 6 months 9.60mg/dl, at 12 months 9.643mg/dl and at 24 months were 10.129mg/dl. Thus, it is evident that serucalcium levels slowly improved and increased over follow up of 3 years to 10.175mg/dl (**Figure 3, 4**).

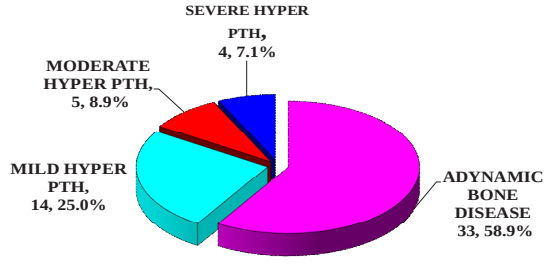


Figure 5: Levels of PTH at the initiation.

Mean Serum albumin levels at initiation were 3.39 mg/dl and improved over 3 years to 3.50 mg/dl suggesting improvement in overall nutritional status of the patient while on CAPD. (**Figure 7, 8**).

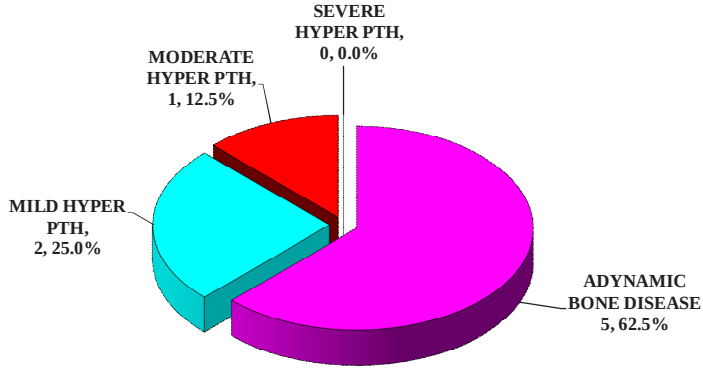
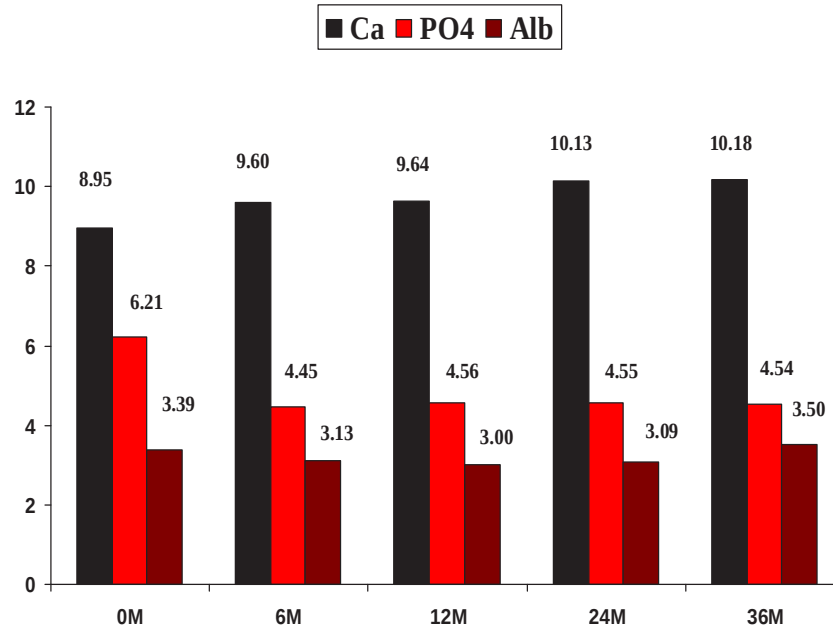
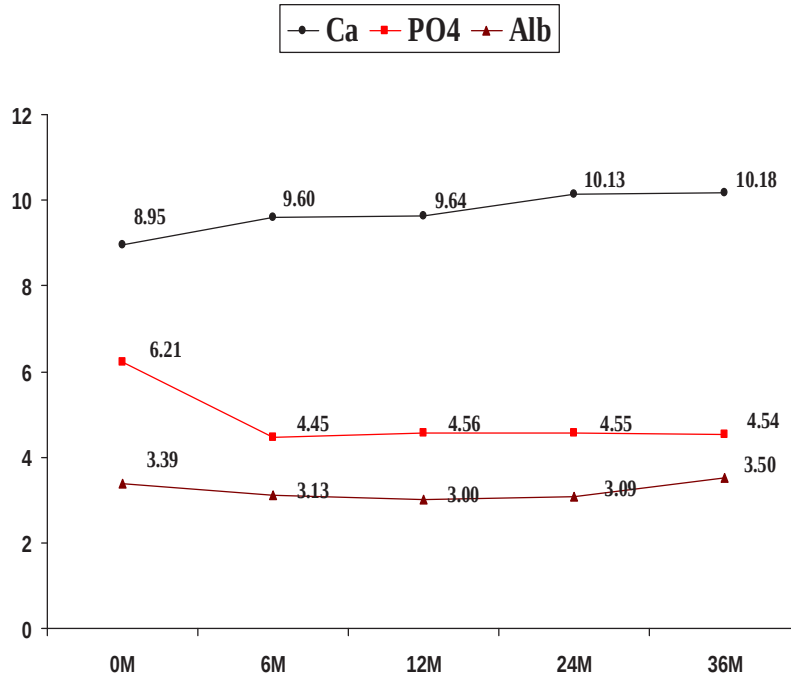


Figure 6: Levels of PTH after 2 years of Follow up



CALCIUM, PHOPSPHORUS AND ALBUMIN LEVELS ON SERIAL FOLLOW UP

Figure 7: Levels of Calcium, Phosphorous and Albumin on Serial Follow up



CALCIUM, PHOPSPHORUS AND ALBUMIN LEVELS ON SERIAL FOLLOW UP

Figure 8: Trend in the Levels of Calcium, Phosphorous and Albumin on Serial Follow up

References

1. Araújo, S. M., P. Ambrosoni, and R. R. Lobão, 2003: The renal osteodystrophy pattern in Brazil and Uruguay: an overview. *Kid. Suppl.*, **85,** 54-56.

2. Dombros, N. V., G. E. Digenis, and E. V. Balaskas EV, 1993: Long-term continuous ambulatory peritoneal dialysis. *Clin. Nephrol*., **39,** 70-74.

3. Cannata, A. J. B, 2000: Adynamic bone and chronic renal failure: an overview. *Am. J. Med. Sci*., **320,** 81-84.

4. Sherrard, D. J., G. Hercz, and Y. Pei, 1993: The spectrum of bone disease in end-stage renal failure: an evolving disorder; *Kid. Int.,* **43,** 436-442.

5. Gokal R., M. Jose, and A. R. Hewett, 1983: Histological renal osteodystrophy, and 25 hydroxycholecalciferol and aluminum levels in patients on continuous ambulatory peritoneal dialysis. *Kid. Int.,* **23,** 15–21.

6. Hutchison, A. J., A. J. Were, H. F. Boulton, E. B. Mawer, I. Laing and R. Gokal, 1996: Hypercalcemia, hypermagnesemia in CAPD : improvement in serum biochemistry by reduction in dialysate calcium and magnesium concentration. *Nephron.*, **72,** 52-58.

7. Malluche, H. H., and M. C. Monier-Faugere, 1992: Risk of adynamic bone disease in dialyzed patients. *Kid. Int. Suppl.,* **38,** 62-67.

8. Buccianti, G., M. L. Bianchi, and G. Valenti, 1984: Progress of renal osteodystrophy during continuous ambulatory peritoneal dialysis. *Clin. Nephrol.,* **22,** 279-283.

9. Hutchison, A. J., R. W. Whitehouse, and A. J. Freemont, 1994: Histological, radiological, and biochemical features of the adynamic bone lesion in continuous ambulatory peritoneal dialysis patients. *Am. J. Nephrol*., **14,** 19-29.

10. Haris, A., D. J. Sherrard, and G. Hercz, 2006: Reversal of adynamic bone disease by lowering of dialysate calcium. *Kid. Int.,* **70,** 931-937.

11. Hayes, M. E., D. J. O'Donoghue, and F. W. Ballardie, 1987: Feb Letters: Peritonitis induces the synthesis of 1α,25-dihydroxyvitamin D_3 in macrophages from CAPD patients. **220,** 307-310.

12. Sánchez, M. C., M. AuxiliadoraBajo, and R. Selgas, 2000: Parathormone secretion in peritoneal dialysis patients with adynamic bone disease. *Am. J. Kid. Dis*., **36,** 953-961.

13. Couttenye, M. M., P. C. D'Haese, and J. T. Deng, 1997: High prevalence of adynamic bone disease diagnosed by biochemical markers in a wide sample of the European CAPD population. *Nephrol. Dial. Transplant.,* **12,** 2144-2150.

14. Gallienic M., F. Caputo, and A. Filippini, 2012: For the ROCK-PD Study Investigators- Prevalence and progression of cardiovascular calcifications in peritoneal dialysis patients: A prospective study. *Bone*, **51,** 332–337.

15. Pei, Y., G. Hercz, C. Greenwood, and G. Segre, 1993: Renal osteodystrophy in diabetic patients. *Kid. Int.,* **44,** 159-164.

16. Heaf. J. G., 2015: Chronic Kidney Disease-Mineral Bone Disorder in the Elderly Peritoneal Dialysis Patient. *Perit. Dial. Int.*, **35,** 640-644.

17. Souberbielle, J. C., A. Boutten, M. C. Carlier, 2006: Inter-method variability in PTH measurement: implication for the care of CKD patients. *Kid. Int.,* **70,** 345-350.

18. Weinreich, T., E. Ritz, J. Passlick-Deetjen, 1996: Long-term dialysis with low-calcium solution (1.0 mmol/L) in CAPD: effects on bone mineral metabolism. *Collaborators of the Multicenter Study Group. Perit. Dial. Int.,* **3,** 260-268.

19. Delmez, J. A., C. S. Dougan, and B. K. Gearing, 1987: The effects of intraperitoneal calcitriol on calcium and parathyroid hormone, *Kid. Int.*, **31,** 795-799.

20. Martin, K. J., H. S. Ballal, and D. T. Domoto, 1992: Pulse oral calcitriol for the treatment of hyperparathyroidism in patients on continuous ambulatory peritoneal dialysis: preliminary observations. *Am. J. Kid. Dis.,* **19,** 540-545.

Chapter 45

Peritoneal Dialysis in Elderly

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Peritoneal Dialysis in Elderly

WHO Definition: Most developed world countries have accepted the chronological age of 65 years as a definition of 'elderly' or older person, but like many westernized concepts, this does not adapt well to the situation in Africa/Asia. While this definition is somewhat arbitrary, it is many times associated with the age at which one can begin to receive pension benefits.

Chronic kidney disease (CKD) is becoming a major public health problem worldwide and majority of the patients diagnosed with CKD are elderly. In a systematic review conducted by Qiu-Li Zhang and Dietrich Rothenbocher to study CKD burden in various populations, median prevalence of CKD was found to be 7.2% in persons 30 years and older, whereas in persons aged 65 years or older, the prevalence varied from 23.4% to 35.8% [1]. The exact disease burden of CKD in India is not clear in the absence of regular national registry data. The approximate prevalence of CKD is 800 per million population (pmp) and incidence of end stage renal disease (ESRD) is 150-200pmp [2]. Further, with an increasing life expectancy, magnitude of elderly patients with CKD is going to increase in future. Chronic kidney failure disproportionately burdens the elderly. The median age of new dialysis patients now is 65 years, and the fastest growing age group is >75 years. Thus, kidney disease in elderly patients is an important focus for public health and clinical care [3].

Dialysis for older patients with ESRD is a significant challenge for the healthcare providers. These individuals are often referred to the nephrologists during the later stages of the disease. Moreover, these patients tend to have more comorbidities such as cardiovascular diseases, malnutrition, and hearing and visual impairments [4, 5]**.** All of these factors are problematic for any dialysis modality. The prevalence of elderly patients requiring renal replacement therapy (RRT) has also increased in the recent years. Genestier, reported that 15% of the PD population was elderly and projected that this proportion would increase to 40-41% in the future [6]**.**

As the proportion of the older population increases, the number of older PD patients will also increase. Mortality rates in elderly PD patients are not favorable. In one study, the mean survival time was 38.9 months, and the mean survival rates were 78.8%, 66.8%, and 50.9% at 1, 2, and 3 years, respectively. Mortality rates in that study was higher than observed in a previous study that evaluated all of their PD patients between 2001 and 2010 [7]. Different results are observed in other centers and other countries. One of the reasons for some of the discrepancies in the reports is the lack of a standard definition of “elderly patient.” Some authors consider patients over 65 years of age as elderly, but heterogeneity regarding this definition exists between studies.

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The issue of whether and how to implement peritoneal dialysis (PD) in elderly patients is increasingly important given the rapid growth of this dialysis population. PD has some particular advantages and disadvantages in the elderly. Furthermore, these advantages and disadvantages are not always fully understood by medical providers. Not only is a better understanding of PD in elderly patients relevant for patient autonomy, medical outcome, and comfort, but there are systemic implications for cost and education as well.

In the United States, PD is used less frequently in elderly patients than in younger patients, and the rate is declining. In recent USRDS data, 12% of patients ages 20 to 55 were on PD, whereas only 4% of dialysis patients >75 yr of age used this modality [8]. In France, PD is dominant in the elderly patients, with more than one half of all PD patients being >70 year old. In Hong Kong, 80% of all dialysis patients are on PD, with a median age of 62 years. The United Kingdom and Canada are intermediate, with 17% and 12% of incident elderly dialysis patients treated with PD [9].

The cost of PD is generally less than that of hemodialysis (HD) [10]. Because elderly patients are the fastest-growing segment of the dialysis population, their relatively infrequent use of PD has financial implications. The reasons for the wide variation in use of PD in the elderly patients are multifactorial, including financial, resource availability, and cultural issues. However, a particular concern is that unfamiliarity of providers with the use of PD in elderly patients leads to a self-perpetuating cycle of underuse. This is especially of note because, given the opportunity, many elderly would elect PD. It is not always an option; in one study, it was considered contraindicated for medical or social reasons in about one half of patients older than 65 year. However, if there was not a contraindication, one third of elderly patients would elect to start PD rather than HD [11]. Jager *et al*, believe that many elderly would select PD if they were fully informed about this modality well in advance [11]. Furthermore, an increasing use of the less expensive PD has clear financial advantages, because elderly patients constitute the faster growing segment of dialysis population. Benain *et al*, showed that PD saved money for the French Health Care Insurance, even with the additional cost of paid visiting nurses to assist PD [12].Elderly patients on PD can do quite well: The 2- and 5-yr survival of patients over 65 years of age in Hong Kong was reported to be 88 and 56%, respectively [13]. In comparing PD and HD, one should keep in mind that data quality is limited by the inability to randomise patients. The larger prospective cohort studies such as the North Thames Dialysis Study (NTDS) have subject numbers in the hundreds, whereas registry studies are larger but presumably are confounded by selection bias. Furthermore, all comparisons are complicated by varying definitions of what age constitutes “elderly.” Most use >65 years as a cut-off, whereas others use 70 years or higher.

The fundamental physiology of PD is not age dependent; a rich capillary plexus brings blood into the peritoneum and filtrate flows across the peritoneal membrane into the dialysate. However, there are several physiologic considerations unique to

elderly patients that may affect clinical outcomes. Emerging data suggest that peritoneal mesothelial cells change during the aging process and may be more prone to inflammation. Whether this observed pro inflammatory profile in elderly patients actually has a clinical significance remains untested at this point.

In addition to possible age-related changes in the peritoneal membrane, elderly patients have a higher incidence of intestinal pathology, including diverticulosis, bowel perforation, and constipation. All of these can affect the underlying physiology of the membrane, as well as the functionality of the peritoneal catheter. In addition, many elderly patients have undergone previous abdominal surgeries, which will increase the risk of adhesions and potential abdominal wall leaks. Overall, PD represents a continuous and stable therapy, that is free of the rapid changes in hemodynamic and fluid status associated with HD that often are poorly tolerated by older patients. An important advantage of PD therapy over HD is that it can be performed at home, although it requires some degree of mobility, adequate vision, and the ability to learn in order to achieve an independent application. Otherwise, PD may require assistance. A recent study from Hong Kong has demonstrated that in patients older than 65 years who are capable of performing their own exchanges, self-care PD provides an independent life away from hospital [14]. Thus, a high percentage of elderly PD patients become autonomous, although they require a slightly longer training time, as was expected.

A French study described the experience of PD as their first and exclusive dialysis therapy in 213 patients over 75 years old, for a mean period of 21±20 months (cumulative time of 4551 patient months) [14]. Thirty patients had an effective autonomous life in which they carried on normal activities, 26 patients lived in institutions and 187 lived at home. One hundred and two patients (102) were cared for by a private nurse at home, and 46 were cared by a family member. Most (152) patients were treated with three exchanges per day and used a non-disconnect system (175 patients). The rate of peritonitis was one episode per 16.8 patient-months. Patient survival was 74%, 59%, 45%, and 19% at one, two, three, and five years, respectively. The causes of death varied with a higher frequency of cardiovascular causes (48.3% of the 116 deaths). Thirty-three patients died in less than six months including 18 patients who died in less than three months. The high mortality was due chiefly to age and poor general status. These authors concluded that elderly patients with ESKD can be treated with long-term PD with relatively good results. The availability of private visiting home nurses is very important and frequently is a prerequisite to maintaining these elderly patients at home. Furthermore, the higher failure rate of AV-fistulae, may also explain why elderly patients are more frequently treated by PD when assisted PD is available. Finally, assisted PD at home (aPD) was associated with a good quality of life.

There have been conflicting data, with studies showing both higher and lower peritonitis rates, as well as showing both a negative and a neutral effect of having visiting assistance. Overall, the data do not show a consistent difference. For example, a recent study found that, in comparing incident patients over 65 years

versus under 65 years, all of whom were performing their own care, there was no difference in the probability of being peritonitis free for 12 months (76.6 *versus* 76.5%) [15]. When peritonitis does occur, several studies have found different proportions of causative organisms than are seen in the younger patients. However, these studies are not consistent in their findings, and there is no recommendation for different empiric treatment on this basis. Interestingly, there is evidence that exit site and tunnel infections are less common in elderly patients, perhaps because of less vigorous activity [16]. In younger patients, PD is often associated with a better quality- of-life rating than HD, although this is likely in part because of self-selection. There are limited data specifically in older patients, but overall, elderly patients report the same quality of life whether on HD or PD [17]. Of course, PD may be particularly appropriate for individual patients who place a high value on independence or who would prefer to dialyze at night.

In general, elderly patients on any kind of dialysis have poor nutritional status. The data comparing PD to HD are scant, but there is no clear evidence that nutritional status is poorer in the elderly PD patients despite potential protein losses in the effluent.

There is a lack of Indian data on PD in elderly. At our centre, we had two cases above 60 years of age. Contrary to the general assumption, there is no dramatic difference in clinical outcomes in elderly patients who are on PD *versus* those on HD. Furthermore, quality of life seems to be at least as good. Although, the available information may be affected by selection bias, these conclusions remain even in cohorts that have a high use of PD, indicating that they may nevertheless be generalizable. Nevertheless, rates of PD in the elderly are very low in the United States, implying underuse. The elderly already tend to have less pre-dialysis care and a greater need for urgent dialysis starts, both factors that tend to increase the initial use of HD over PD. It is important for the nephrologists to recognize this disparity and guard against assumptions on the basis of age that would prevent advocating for PD. Particularly for patients valuing the PD lifestyle, PD should be offered to the elderly among their dialysis options.

References

1. Zhang, Q. L., and D. Rothenbacher, 2008: Prevalence of chronic kidney disease in population based studies: systematic review. *BMC Public Health*, **8,** 117-129.
2. Agarwal, S. K., and R. K. Srivastava, 2009: Chronic kidney disease in India; challenges and solutions. *Nephron. Clin. Prac*., **111,** 197-203.
3. Stevens, L. A., J. Coresh, and A. S. Levey, 2008: CKD in the elderly-old questions and new challenges: World Kidney Day 2008. *Am. J. Kid. Dis.,* **51,** 353-357.
4. Valderraban, F., R. Jofre, and J. M. Lopez-Gomez, 2001: Quality of life in end stage renal disease patients. *Am. J. Kid. Dis.,* **8,** 443–464.
5. Joly, D., D. Anglicheau, C. Alberti, A. T. Nguyen, M. Touam, J. P. Grünfeld, and P. Jungers, 2003: Octogenarians reaching end stage renal disease- cohort study of decision making and clinical outcomes. *J. Am. Soc. Nephrol.,* **14,** 1012–1021.
6. Genestier, S., N. Meyer, F. Chantrel, F. Alenabi, P. Brignon, M. Maaz, S. Muller, and B. Fuller, 2009: Prognostic survival factors in elderly renal failure patients treated with peritoneal dialysis- a nine year retrospective study. *Perit. Dial. Int.,* **30,** 218–226.
7. Unsal, A., Y. Koc, T. Basturk, T. Sakaci, E. Ahbap, A. Sinangil, S. K. Budak, M. Sevinc, E. Kara, and B. Doner, 2013: Clinical outcomes and mortality in peritoneal dialysis patients- a 10-year retrospective analysis in a single center. *Clin. Nephrol.,* **80,** 270–279.
8. Finkelstein, F. O., B. Afolalu, D. Wuerth, and S. H. Finkelstein, 2008: The elderly patient on CAPD: helping patients cope with peritoneal dialysis. *Perit. Dial. Int.,* **28,** 449–451.
9. Brown, E. A. 2008: Should older patients be offered peritoneal dialysis? *Perit. Dial. Int.,* **28,** 444–448.
10. Shih, Y. C., A. Guo, P. M. Just, and S. Mujais, 2005: Impact of initial dialysis modality and modality switches on Medicare expenditures of end-stage renal disease patients. *Kid. Int.,* **68,** 319–329.
11. Jager, K. J., J. C. Korevaar, F. W. Dekker, R. T. Krediet, and E. W. Boeschoten, 2004: Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) Study Group: The effect of contraindications and patient preference on dialysis modality selection in ESRD patients in The Netherlands. *Am. J. Kid. Dis.,* **43,** 891–899.
12. Benain, J. P., B. Faller, and G. Duru, 2007: Cost of dialysis in France. *Nephrol. Ther.,* **3,** 96-106.
13. Li, P. K., M. C. Law, K. M. Chow, C. B. Leung, B. C. Kwan, K. Y. Chung, and C. C. Szeto, 2007: Good patient and technique survival in elderly patients on continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **27,** 196–201.
14. Issad, B., D. Benevent, M. Allouache, P. Y. Durand, D. Aguilera, R. Milongo, P. Dubot, S. Lavaud, and J. Gary, 1996: 213 elderly uremic patients over 75 years of age treated with long-term peritoneal dialysis: A French multicenter study. *Perit. Dial. Int.,* **16,** 414-418.

15. Szeto, C. C., B. C. Kwan, and K. M. Chow, 2008: Peritonitis risk for older patients on peritoneal dialysis. *Perit. Dial. Int.,* **28,** 457–460.
16. Dimkovic, N., and D. G. Oreopoulos, 2002: Chronic peritoneal dialysis in the elderly. *Semin. Dial.,* **15,** 94–97.
17. Harris, S. A., D. L. Lamping, E. A. Brown, and N. Constantinovici, 2002: North Thames Dialysis Study (NTDS) Group: Clinical outcomes and quality of life in elderly patients on peritoneal dialysis versus hemodialysis. *Perit. Dial. Int.,* **22,** 463–470.

Chapter 46

Peritoneal Dialysis in Children

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Peritoneal Dialysis in Children

Burden of Pediatric ESRD

The average incidence and prevalence of end stage renal disease (ESRD) in children is 9 and 65 pmp (per million age related population), respectively [1]. According to the NAPRTCS database, hypoplasia/aplasia/dysplasia, obstructive uropathy and focal segmental glomerulosclerosis are the most common causes of chronic kidney disease (CKD) in children undergoing renal transplantation [2]. The CKD study also showed a similar etiological profile of CKD in children [3].

Chronic Peritoneal dialysis (PD):

PD as a Choice of Dialysis in Children- The Global Scene

There are striking disparities in the practices, modalities and outcomes of PD in children, across the globe [4]. Economic wealth has a major impact on these disparities. While preemptive transplantation and prioritized organ allocation have taken over cumulative dialysis times in the developed nations limiting PD use to 50-70%; in the developing world, dialysis programmes are rapidly expanding as transplantation is not an easy option [5].

Two important registries reflect on PD practices and outcomes. The NAPRTCS registry confirms that 92% of PD is undertaken in infants [5]. The IPPN registry reflects 92% of data on PD from the high economy countries [6]. A brief report from eastern India, in a reasonably good number of children revealed PD to be a successful bridge to transplantation [7]. Our center's data (unpublished) is presented at the end of this chapter.

PD indications specific to children

An estimated GFR <10 ml/min/1.73m^2 is generally accepted as the cut off value to initiate dialysis [8]. Indications unique to children include [9, 10]

- Neonates and infants.
- At higher eGFR, in the presence of uremia or growth failure.
- In toddlers and older children with vascular access limitations.
- To facilitate school attendance and have lesser dietary restrictions.
- In situations when anticoagulation is contraindicated.

Contra-indications unique to children include:

- Conditions like exstrophy, omphalocoele, diaphragmatic hernia, and gastroschisis.
- Peritoneal membrane failure.

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The presence of gastrostomy, colostomy and ureterostomy are not contra-indications for chronic PD.

The PD procedure:

Pediatric PD Catheters

Pediatric catheter sizes (from the cuff to tip) are 42 cm and 37 cm in length. For infants, a shorter (31 cm cuff to tip) catheter is available. According to the NAPRTCS database report 2011 [5], the most common type of catheter used in children were the Tenckhoff catheters (88%) with curled catheters in 62.1% and straight catheters in 25.9%. The ISPD guidelines recommend the use of double cuff catheters, preferably curled, double cuffed (except in young infants) with downward (preferable) or lateral facing exit site [9].

Techniques of dialysis

Though automated PD is the most common and recommended modality of PD in children, as it allows the child to be active and go to school; in the developing countries, CAPD continues to be the most common modality as the PD machine is not easily available and adds to the cost of dialysis.

Techniques of Catheter Insertion

Prior to catheter insertion, the exit site should be marked on the abdomen. The exit site should be placed as far as possible from diaper lines and ostomies as possible. Partial omentectomy is preferred prior to catheter insertion. The catheter may be inserted by a mini-lapartotomy, laparoscopic technique or percutaneously depending on the experience of the surgical team placing the catheter.

PD Fluids

The various PD fluids with their compositions are mentioned in **Table 1** [10]. Dextrose based fluids are most commonly used in children. Bicarbonate based fluids are more biocompatible and recommended in children. Studies in children have shown that bicarbonate based fluids are more biocompatible, have better CA-125 levels, better preservation of residual renal function and better correction of acidosis [11].

Table 1: Constitution of various PD fluids

Contents	Dianeal	Physioneal	Extraneal	Nutrineal
Sodium(meq/L)	132	132	133	132
Calcium(mmol/L)	1.25	1.25	1.75	1.25
Magnesium (mmol/L)	0.25	0.25	0.25	0.25
Lactate (mmol/L)	40	15	40	40
Bicarbonate (mmol/L)	0	25	0	0
pH	5.5	7.4	5.5	6.7
Osmotic agent	Glucose	Glucose	Icodextrin	Amino acid
Strength (osmolality in mosm/L)	1.36% (344) 2.27(395) 3.86 (483)	1.36% (344) 2.27(395) 3.86 (483)	7.5% (284)	87mmol/L (365)

Icodextrin has been shown in children to provide sustained ultrafiltration, good solute clearance and sodium removal [12]. Amino acid based solutions are more biocompatible when compared to dextrose based solutions but are more expensive and not recommended as a source of nutrition.

The calcium content of dialysate should be decided based on the mineral bone disease status of the child with ESRD [13].

Standard Prescription

PD prescription should be tailored to the child's age, body size, residual renal function (RRF), nutritional intake and transporter status of the peritoneal membrane.

Fill volume: Though the fill volume was based on the body weight of the child (30-50 ml/kg) in the past, the ideal way to calculate the fill volume is based on body surface area. The scaling to body surface area allows optimal volume and prevents rapid equilibration of solutes across the peritoneum. In children younger than 2 years of age, the fill volume can be at a maximum of 800 ml/m^2; whereas in the older children, the fill volume can be increased to a maximum of 1200-1400 ml/m^2 [14].

Dwell time: The dwell time is decided based on the peritoneal membrane characteristics. Shorter dwells favour removal of small molecular weight solutes and fluid and longer dwells favour the removal of middle molecules. A practical way to determine the ideal dwell time is to look at the APEX time on the peritoneal equilibration test (PET). The APEX time corresponds to the time point at which the D/P urea and D/D0 glucose curves intersect [13].

Number of exchanges: The number of exchanges are decided based on the age, residual renal function, peritoneal membrane characteristics and dwell time.

Complications

Non Infectious Complications [10]:

- Inflow or outflow failure may be seen in the presence of constipation, absence of omentectomy at the time of catheter insertion and rarely due to blood or fibrin clots.

- Catheter migration is seen in children with habitual constipation or in those with neurogenic bladder.

- Leaks may be common in young infants, children with large abdominal mass (large polycystic kidneys), abdominal wall defects (Prune belly syndrome) or in early use of PD catheter without a break in period.

- Cuff extrusion may be seen in infants, malnourished children and children with abdominal wall defects.

- Abdominal hernias, incisional hernias are more common in infants, children with multiple abdominal surgeries

- Encapsulating peritoneal sclerosis – usually seen in children on dialysis for a long duration, use of bio-incompatible fluids. This results in membrane failure and usually requires a switch to hemodialysis.

Infections

- Peritonitis: The NAPRTCS database of 2010 shows that the annualized peritonitis rate is around 0.68 in children, suggesting one episode in 17.8 months. The incidence of peritonitis was highest in the younger age group.

Though gram positive organisms were more commonly associated with peritonitis, with change in exit site orientation, screening for nasal carriage, Gram negative organisms have been found to be the most common cause in recent reports of the NAPRTCS and IPPN. The IPPN reported a high rate of culture negative peritonitis – around 31% worldwide with significant regional variations.

The NAPRTCS data showed that the presence of two cuffs, swan neck configuration and downward facing exit site are associated with longer time to first

episode of peritonitis. The novel risk factors for peritonitis in children are younger age, single-cuff catheter, shorter duration of training, presence of gastrostomy, ureterostomy [15].

The treatment strategy is no different in children with peritonitis. The initial empiric therapy should include a gram positive and gram negative cover and this is subsequently changed based on the Gram stain and the culture report [9].

Peritonitis is the most common reason for technique failure in children on PD. Majority of the children (about 90%) with peritonitis had complete recovery. Mortality was seen in 1% following acute peritonitis.

- Exit site and tunnel infections: Exit site and tunnel infections are most commonly caused by *Staphylococcus aureus* or *Pseudomonas aeruginosa*. Both these are most often associated with peritonitis and result in catheter removal. Studies have found that the regular use of mupirocin and sodium hypochlorite to the exit site resulted in a significant reduction in number of infections.

Monitoring/ Adequacy

Monitoring a child on peritoneal dialysis:

- Evaluation of the peritoneal membrane characteristics: (PET has been found to be useful in characterizing the membrane characteristics at the onset of PD. A fill volume of 1100 ml/m^2 of 2.5% glucose containing fluid is used with patient in the supine position. It is also a sensitive marker of change in the membrane characteristics and has shown to correlate with PD outcome. A study has shown that the short PET correlates well with the standard PET protocol and can be used in children. High transporter status in children has been associated with poor growth and hypoalbuminemia. Repeated episodes of peritonitis and prolonged use of PD (>2 years) have been associated with high transporter status [16].

- PD adequacy: The minimum adequacy measured by Kt/V_{urea} is similar for children and adults. The adult guidelines are followed for the timing of PD adequacy and the minimum adequacy limits. In younger children, there may be a discrepancy between the urea clearance and the creatinine clearance due to the higher ratio of body surface area to weight in these children. The clinical parameters like growth, improvement of appetite, control of hypertension are considered important parameters in assessing adequacy of PD [17].

Comorbidities

In general, there seems to be a contrasting difference in the comorbidities associated with an increased risk for poor outcomes in adult ESKD patients versus those seen in children. While diabetes mellitus, chronic obstructive lung disease, peripheral vascular disease, and cerebrovascular disease are common in the adult patients, these are strikingly not seen in children who present with other comorbidities, such

as neurocognitive impairment and heart disease that may independently influence outcomes. The IPPN revealed the presence of comorbidities to be more likely in children with CAKUT as the cause of their ESKD [18].

Growth

As per the KDOQI guidelines, the recommended energy intake for children with CKD is 100% of the estimated energy requirement for their chronological age. The recommended protein intake is 100–140% of the dietary reference intake depending on the CKD stage, with an allowance for dialytic protein losses [19]. In addition to the non modifiable factors of abnormal birth history or congential anomalies, modifiable factors like calorie and protein intake, metabolic acidosis and inflammation have a great impact on nutritional status. Comparing the growth in children on dialysis *versus* renal transplantation, dialyzed children had reduced median z scores for height and weight. In comparison with HD, children on a PD programme had improved z scores for height, particularly those who were younger than 6 years old at the commencement of dialysis [5].

Cardiovascular morbidity and Mineral Bone Disease

Children on dialysis die from cardiovascular disease (CVD), which accounts for ~30% of all deaths [20]. The calcification in the vessel wall has been identified to be markedly increased in patients on dialysis and strongly correlates with time on dialysis and mean circulating calcium phosphate levels [21]. Though, hypertension is an important independent predictor of LVH in children with early stages of CKD, fluid overload, anemia, and hyperparathyroidism are associated with increased prevalence of LVH and myocardial dysfunction in patients on dialysis. Dyslipidemia is also thought to be a non uremic contributor to cardiovascular morbidity [22].

Children are unique with respect to the skeletal growth that demands more calcium compared to adults. The deficiencies in mineralization was observed in >90% of children on dialysis, compared to only 3% of adult patients on dialysis. Reduced bone mineral density is associated with risk of subsequent fracture and children with CKD have a 2–3 fold higher fracture risk compared to their healthy peers [23].

Anemia

Similar to adults, in children, a higher risk of mortality is found to be associated with a mean achieved Hb <11 g/dl. An important finding of high ESA dose has a significant association between mortality and anemia in the children on PD. The other significant observations in anemia management include, preferential dosing of ESA by the body surface area, the apparent relative safety of Hb levels near or within the normal range, the potential confounding roles of fluid overload, severe hyperparathyroidism and male puberty in the management and the adverse patient outcomes associated with weekly ESA doses >6000 IU/m^2 [24].

Access revision

A recent study by the IPPN registry on access revision in children on chronic PD revealed a significant association with younger age, diagnosis of congenital anomalies of the kidney and urinary tract, coexisting ostomies, presence of swan neck tunnel with curled intraperitoneal portion and high gross national income. Need for access revision increased the risk of peritoneal dialysis technique failure or death [25].

Quality of life (QoL)

Studies on QoL in children with CKD and on renal replacement therapy (RRT) conclude that the parent or caregiver proxy QoL scores were not equivalent to child self QoL scores. This emphasizes the need to evaluate both the parent and the child to obtain valid results. Comparing children with CKD to healthy children, there were obvious findings of lower QoL scores in the CKD group. However, it is interesting to observe that children on dialysis scored equal to or higher than the transplant recipient children in all the domains. Comorbidities including cardiovascular, gastrointestinal, endocrinologic, hematologic and neurologic disorders have been shown to have a bearing on the QoL in children with ESRD [26].

Mortality

It is important to note that mortality in children on dialysis is not necessarily due to renal dysfunction but secondary to other risk factors like sepsis and cardiac disease. The mortality rate has been reported to be10% for younger children during dialysis and 17% during their entire follow-up period. The relative risk of death was seen to be 2.7 times higher than that of the older dialysed children [27].

Special situations

PD in infants*:* There are several medical, ethical and technical issues in initiating chronic dialysis in an infant.

- PD is the modality of choice in infants with CKD because it is technically easy, more physiological and does not involve a vascular access.

- PD also provides a better lifestyle and promotes better growth.

- A double cuffed catheter should ideally be used, however due to small size of the infant, single cuff catheters are often used. There is a higher risk of catheter loss and leak following catheter insertion due to thinness of the abdominal wall.

- If a gastrostomy tube is required in an infant on PD, an open gastrostomy must be done to avoid risk of fungal peritonitis. The maximum exchange volume should be 800 ml/m^2 and adjusted frequently as the infant grows.

• Growth was better in infants on PD when compared to those on hemodialysis. However, infants on PD are at a higher risk for peritonitis, technique failure and mortality when compared to older children [28].

• PD in children with abdominal wall defects: As CAKUT and obstructive uropathy account for a large proportion of CKD in children, they may require ureterostomy, colostomy *etc*. Gastrostomy is also a recommended modality of providing adequate nutrition in children with CKD. In such children, special care needs to be taken during the insertion of a PD catheter. The catheter exit site must be placed as far away from the ostomy as possible to reduce the risk of peritonitis and exit site infection. If a gastrostomy is required, a percutaneous gastrostomy may be performed prior to the insertion of a PD catheter. If the gastrostomy is required in a child who has a PD catheter *in situ*, an open procedure is required to reduce the risk of fungal peritonitis. Children with prune belly syndrome have a thin abdominal wall resulting in increased risk of leaks.

• PD for isolated ultrafiltration in edema*:* PD is regularly used in the post operative care following cardiac surgery in children to prevent/treat fluid overload. Though, there are few case reports on the use of PD in non-cardiac indications, we have in our practice found that a short duration of PD is extremely beneficial in children with refractory edema or those requiring isolated ultrafiltration.

Challenges of Pediatric Chronic PD in Developing Nations Including India

A systematic review of the dialysis outcomes in adults and children reveals the burden of poor affordability and accessibility to dialytic therapies resulting in 36% pediatric deaths and 19% children moving ahead with transplantation in the sub Saharan Africa [29].

A successful pediatric chronic PD programme demands a highly skilled team of nephrologists, PD nurse, nutritionist, social worker and a counselor. To establish such a multidisciplinary care is a challenge in most centers of India.

Some of the key concerns pertinent to chronic PD programmes in India include:

• Lack of sustainability to continue PD, in view of high cost that is usually borne by families, with lack of an adequate insurance support.

• Difficulty in procuring child specific consumables in India like infant size PD catheter, 1litre PD fluid bags, low calcium, amino acid based and bicarbonate based fluids, specific nutritional supplements and formulations applicable to children (Ex: Inj EPO containing 1000 units or 500 units and syrup based phosphate binders.

• Managing comorbidities in children on PD is challenging especially due to late initiation of RRT or unaffordability to undergo evaluation and treatment of comorbidities.

- Major dependence on manual PD and limitations in using ideal modalities like automated PD.

- As dialysis is just a bridge to transplantation in children, it is critical to have access to an active transplant programme.

- Children on PD have an advantage of attending school. However, this modality could restrict the lower middle and lower socioeconomic strata of patients from attending school due to heavy financial burden of sustaining dialysis.

- With regard to adolescents on PD waiting for transplantation, it is crucial to have a structured and smooth system of transition from the pediatric care to adult nephrology care.

Our data

We report our data that represents a cohort from a tertiary care referral hospital in South India (unpublished). About 70-80 new cases of CKD are seen in our unit every year. Of these, 10-15 are newly diagnosed as ESRD. Of the 40% who opt for RRT, around 20% of patients in ESRD opt for PD as a modality of dialysis and 10% undergo renal transplantation.

Clinical Profile of children on CPD (n=35)

Our cohort of children on CPD consists of 35 children; of these 30 are on active follow up. The median age is 84 [34, 123] months and the majority (66%) are boys. Around 60% of the cohort had non glomerular disease as an etiology for CKD.

The median duration of PD is 16 (5.7, 30) months. The median weight at initiation was 13.7 (10.9, 19) kg. The average break in period was 13 days. Only 2 (6%) used automated PD. At initiation, PET (25 children) showed that 10 children (40%) were low transporters, 7 (28%) were low average, 4 (14.2%) each were high average and high transporters. The mean Kt/V_{urea} (n=14) was 1.33 (0.7SD).

The peritonitis rate is 0.47 per patient per dialysis year. Overall, 46% of the patients with peritonitis had more than one episode. Access revision was required in 2 (6%) and mechanical complications were seen in 2 (6%) patients. The co-morbidities were highly prevalent in our cohort. The median height z score was 3.45 (-2.22, -4.47). Anemia was seen in 72%, Vitamin D deficiency in 80%, hypertension in 86% and left ventricular hypertrophy in 60%. PD was done by the mother in 26 (86.6%) children. Only 20% of children were attending school. More than 90% of the children belonged to the middle class and about 80% of families were self-funding the expenses of ESRD care. **Table 2** provides comparison between PD in children: CKD versus AKI.

Table 2: Comparing peritoneal dialysis in CKD and AKI

	CKD	AKI
Indications	GFR <10ml/min/1.73m^2	Stage III AKI or
	Uremic symptoms	Uremic symptoms
	Poor growth	Fluid overload
	Fluid overload	Refractory hyperkalemia
	Refractory hyperkalemia	Refractory metabolic acidosis
		To create space to provide nutrition/ blood products
		Hyperammonemia
		GFR – actual value per se may not be an indication
Modality	CAPD/ automated PD	Intermittent PD
Catheter	Double cuff Tenckhoff , Swan neck catheter, straight/curled	Rigid catheter/ Single cuff Tenckhoff catheter
Catheter insertion	Laparotomy/laparoscopic/ percutaneous	Usually percutaneous insertion
	Omentectomy- preferred	No omentectomy
Break in period	2 weeks if feasible	No break in period
Complications	Mechanical,	Mechanical, peritonitis
	Peritonitis	
Duration	Prolonged, usually continued till renal transplantation	2-3 weeks (soft catheter)
		Up to 72 hours (rigid catheter)
Long term complications	Peritoneal sclerosis, membrane failure	None

Type of CPD: Automated PD is the recommended modality as it provides a better lifestyle for the child and allows the child to go to school.

PD catheter: The size of the catheter should be based on the size of the child. Single cuff catheters may be used in small infants. Care must be taken to insert the catheter away from the ostomy sites.

Prescription: Children have a larger peritoneal surface area per kg body weight. Hence PD fluid fill volume should be titrated to body surface area. The fill volume can be increased to a maximum of 800 ml and 1400 ml/m^2 in infants and children, respectively.

Transporter status: Children, especially young infants are usually high transporters and require shorter dwell times

PD adequacy: Growth is an important parameter to assess adequacy in a child on PD.

Peritonitis: Children, especially young infants are at a higher risk of peritonitis when compared to adults.

References

1. Harambat, J., K. J. Van Stralen, J. J. Kim, and E. J. Tizard, 2012: Epidemiology of chronic kidney disease in children. *Pediat. Nephrol*., **27,** 363–373.

2. Emmes Corporation. cited 2014: Collaborative Studies NAPRTCS 2014 Annual Transplant Report. [Available from: https://web.emmes.com/study/ped/annlrept/annualrept2014.pdf].

3. Copelovitch, L., B. A. Warady, and S. L. Furth, 2011: Insights from the chronic kidney disease in children (CKiD) study. *Clin. J. Am. Soc. Nephrol.,* **6,** 2047–53.

4. Schaefer, F., D. Borzych-Duzalka, M. Azocar, R. L. Munarriz, L. Sever, N. Aksu, L. S. Barbosa, Y. S. Galan, H. Xu, P. A. Coccia, A. Szabo, W. Wong, R. Salim, E. Vidal, S. Pottoore, and B. A. Warady, 2012: Impact of global economic disparities on practices and outcomes of chronic peritoneal dialysis in children: Insights from the international pediatric peritoneal dialysis network registry. *Perit. Dial. Int.,* **32,** 399–409.

5. NAPRTCS. 2011: Dialysis report. Natl Institutes Heal Natl Inst Diabetes Dig Kidney Dis., 1–26.

6. Van Stralen, K. J., E. J. Tizard, E. Verrina, F. Schaefer, and K. J. Jager, 2007: Demographics of paediatric renal replacement therapy in Europe: 2007 annual report of the ESPN/ERA-EDTA registry. *Pediat. Nephrol.,* **25,** 1379–1382.

7.Rajiv Sinha, S. S., 2015: Continuous Ambulatory Peritoneal Dialysis in Children – Experience from Eastern India. **5,** 6–7.

8. White, C. T., M. Gowrishankar, J. Feber, and V. Yiu, 2006: Clinical practice guidelines for pediatric peritoneal dialysis. *Pediat. Nephrol.,* **21,** 1059–1066.

9. Warady, B. A., S. Bakkaloglu, J. Newland, M. Cantwell M, E. Verrina, A. Neu, V. Chadha, H. K. Yap, and F. Schaefer, 2012: Consensus guidelines for the prevention and treatment of catheter-related infections and peritonitis in pediatric patients receiving peritoneal dialysis: 2012 update. *Perit. Dial. Int.* **32,** 32-86.

10. Fraser, N., F. K. Hussain, and R. S. M. Connell, 2001: Chronic peritoneal dialysis in children. *Nephrol. Dial.,* **2015,** 125–37.

11. Canepa, A., E. Verrina, and F. Perfumo, 2008: Use of new peritoneal dialysis solutions in children. *Kid. Int. Suppl.,* **73,** 137-144.

12. Cho, Y., D. W. Johnson, J. C. Craig, G. F. M. Strippoli, S. V. Badve, and K. J. Wiggins, Biocompatible dialysis fluids for peritoneal dialysis. Cochrane Database *Syst. Rev*., **2014.**

13. Verrina, E., V. Cappelli, and F. Perfumo, 2009: Selection of modalities, prescription, and technical issues in children on peritoneal dialysis. *Pediat.*

Nephrol., **24,** 1453–1464.

14. Fischbach, M., and B. A. Warady, 2009: Peritoneal dialysis prescription in children: Bedside principles for optimal practice. *Pediat. Nephrol.,* **24,** 1633–1642.

15. Chadha, V., F. S. Schaefer, and B. A. Warady, 2010: Dialysis-associated peritonitis in children. *Pediat. Nephrol.,* **25,** 425–440.

16. Schaefer, F., 2007: The petiatrics of peritoneal solute transport: Is short also good for the young ones? *Perit. Dial. Int.,* **27,** 413–414.

17. Fischbach, M., C. J. Stefanidis, and A. R. Watson, 2002: Guidelines by an ad hoc European committee on adequacy of the paediatric peritoneal dialysis prescription. *Nephrol. Dial. Transplant.,* **17,** 380–385.

18. Neu, A. M., A. Sander, D. Borzych-Duzalka, A. R. Watson, P. G. Vallés, I. S. Ha, H. Patel, D..Askenazi, I. Balasz-Chmielewska, J. Lauronen, J. W. Groothoff, J. Feber, F. Schaefer, and B. A. Warady, 2012: Comorbidities in chronic pediatric peritoneal dialysis patients: a report of the International Pediatric Peritoneal Dialysis Network. *Perit. Dial. Int.,* **32,** 410–418.

19. National Kidney Foundation. 2009: Clinical Practice guideline for nutrition in children with CKD. *Am. J. Kid. Dis.*, **53,** 1–124.

20. Institutes N, Health of, Diseases K. Data report. 2011.

21. Shroff, R., D. A. Long, and C. Shanahan, 2013: Mechanistic insights into vascular calcification in CKD. *J. Am. Soc. Nephrol.,* **24,** 179–189.

22. Brady, T. M., M. F. Schneider, J. T. Flynn, C. Cox, J. Samuels, J. Saland, 2012: Carotid intima-media thickness in children with CKD: results from the CKiD study. *Clin. J. Am. Soc. Nephrol.,* **12,** 1930–1937.

23. Bertram, J. F., S. L. Goldstein, L. Pape, F. Schaefer, R. C. Shroff, and B. A. Warady, 2016: Kidney disease in children: Latest advances and remaining challenges. *Nat. Rev. Nephrol.,* **12,** 182–191.

24. Borzych-Duzalka, D., Y. Bilginer, I. S. Ha, M. Bak, L. Rees, F. Cano, R. L. Munarriz, A. Chua, S. Pesle, S. Emre, A. Urzykowska, L. Quiroz, J. D. Ruscasso, C. White, L. Pape, V. Ramela, N. Printza, A. Vogel, D. Kuzmanovska, E. Simkova, D. E. Müller-Wiefel, A. Sander, B. A. Warady, and F. Schaefer, 2013: Management of anemia in children receiving chronic peritoneal dialysis. *J. Am. Soc. Nephrol.*, **24,** 665–676.

25. Borzych-duzalka, D., T. F. Aki, M. Azocar, C. White, E. Harvey, S. Mir, M. Adragna, E. Serdaroglu, R. Sinha, C. Samaille, J. J. Vanegas, J. Kari, L. Barbosa, A. Bagga, M. Galanti, O. Yavascan, G. Leozappa, M. Szczepanska, K. Vondrak, K. C. Tse, F. Schaefer, and B. A. Warady, 2016: Article Peritoneal Dialysis Access

Revision in Children : Causes, Interventions , and Outcomes. *Clin. J. Am. Soc. Nephrol.,* **12,** 105–112.

26.Mckenna, A. M., L. E. Keating, A. Vigneux, S. Stevens, A. Williams, and D. F. Geary, 2006: Quality of life in children with chronic kidney disease — patient and caregiver assessments. *Nephrol. Dial. Transpl.,* **21,** 1899–1905.

27.Shroff, R., L. Rees, R. Trompeter, C. Hutchinson, and S. Ledermann, 2006: Long-term outcome of chronic dialysis in children. *Pediat. Nephrol.,* **21,** 257–264.

28.Zaritsky, J., and B. A. Warady, 2011: Peritoneal Dialysis in Infants and Young Children. *Semin. Nephrol.*. **31,** 213–24.

29.Ashuntantang, G., C. Osafo, W. A. Olowu, F. Arogundade, A. Niang, J. Porter, S. Naicker, and V. A. Luyckx, 2017: Outcomes in adults and children with end-stage kidney disease requiring dialysis in sub-Saharan Africa: a systematic review. *Lancet Glob. Heal.,* **17,** 408-417.

Chapter 47

Peritoneal Dialysis in Neonates and Infants

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Peritoneal Dialysis in Neonates and Infants

Introduction

Peritoneal dialysis (PD) is considered as the easy, safe and flexible renal replacement therapy (RRT) that can be adopted for a comparable lifestyle in all pediatric patients. This was proved by the seminal work of Moncrief and Popvich**.** [1] Maintenance of hemodynamic stability through the slow removal of solutes and fluid makes PD an ideal therapy in neonates and infants [2]. It is an ideal therapy both in acute and chronic kidney disease (CKD) patient population.

Prevalence of ESRD in Children

Of the total end stage renal disease (ESRD) population, infants and neonates constitute a fraction. In children requiring RRT, more than 50% have congenital or hereditary disorder and the other half acquired renal disease [3]

Indications and Contraindications

Automated cycling device have been utilized as the modality in infants. The absolute indications are small infants < 5 Kg, lack of vascular access and contraindication for anticoagulation. Contraindications: Contraindications which are unique to this population include ompholocele, gastrochisis, bladder exostrophy, diaphragmatic hernia, obliterated peritoneal cavity and peritoneal membrane failure [4].

Special PD Catheter for Neonates

The smooth silicone polymer of methyl silicate has been used to fabricate the soft silastic in straight and curved forms for neonates. PD catheter can be introduced directly into the abdominal wall without the tunneling.Placing the PD catheter in the exit site, outside the diaper area would prevent the contamination and infections.

Leakage of the PD fluids along the tunnel can be cumbersome and a source of infection. The approaches to address this problem are decreasing the PD fill volume, replacing the PD catheter and discontinuation of the PD [5-7].

Peritoneal Membrane Function and Dynamics

There are unique factors which can influence the membrane functions as compared to the adults in this group. Prescription of the therapy needs acquaintance of the transport dynamics of peritoneal membrane.The PET remains the mode of characterizing the solute transport across the peritoneal membrane.

In children the BSA standardized PET exchange volumes of 1000-1100 ml/m^2 body surface area are recommended, based on the relationship between BSA and

peritoneal surface area. The Pediatric Peritoneal Dialysis Study Consortium (PPDSC) and the Mid European Pediatric Peritoneal Dialysis study group have established reference curves for children. Another approach to study peritoneal membrane is by the three pore model of peritoneal mass transport, by Rippe *et al*. Glucose equilibration in infants using volumes scaled to BSA is comparable to children and adults.

Type I ultra filtration failure was more common due to the use of relatively smaller exchange volume; calorie consumption is predominantly by liquids in this group. Hence, this may be of concern. By using exchange volume scaled to BSA and utilizing APD and nocturnal short dwells of 40-60 minutes, ultra filtration can be maximized by recruiting the maximum peritoneal membrane. Tidal PD can also be used as a rescue therapy in infants with poor functioning [8]. Prescription of the PD Volume: In infants, though the maximum volume is customised to the patient tolerance, an initial volume of 600-800 ml/m^2 must be prescribed.

Peritoneal Dialysis Adequacy Assessment: Total solute clearance (peritoneal and renal must be equal to the delivered solute clearance) of Kt/v 1.8 is recommended in children/infants. This can be estimated by using the sex specific nomograms.

Though Kt/vurea and weekly creatinine clearance are markers of peritoneal dialysis clearance, both dialysis and urine Kt/vurea are presently recommended due to their simplicity of calculation. Ideally, measurement of Kt/V should be done within the first month of the inception, and whenever recurrent peritonitis impacts the dialysis performance.

Complications Specific to the Age Group

Hyponatremia: Hyponatremia is observed in this age group due to the high ultra filtration scaled to BSA, obligate sodium losses, inadequate ultra filtration, in addition, low sodium content of the infant formulas also contribute.

Hypophosphatemia: Hypophosphatemia occurrence is due to the use of alternate infant formulae with low phosphate content as low as 6-8 mmol/litre. This may necessitate supplementation of phosphate to these infants.

Peritonitis: Peritonitis and catheter exit site/ tunnel infections are the most important complications which can profoundly influence the morbidity and mortality in this young group.

The NAPRTCS 2011 annual report have shown an immense relationship between age and infection rate. The youngest < 1 year display an infection ratio 0.79 as compared to adults who show a rate of 0.57. Addressing the risk factors like proper hand hygiene, prophylaxis and early treatment of exit site/tunnel infection, using long catheters with two cuffs ensures a decreasing peritonitis risk. The characteristics of the micro organisms causing peritonitis have shown a change due

to the advances in decreasing the exposure to Staphylococcus and Gram negative peritonitis is becoming an important complication [9].

Diagnosis and Management: Infants with peritonitis may present with the abdominal pain, fever, irritability, feeding intolerance or merely with cloudy peritoneal fluid. Cloudy fluid with more than 100 leucocytes/mm^3 with >50% of polymorphs can make presumptive diagnosis of peritonitis. By performing PD fluid cell count, differential count, gram stain and culture, the diagnosis can be confirmed. Combining the cephalosporinis or vancomycin with third generation cephalosporinis or aminoglycoside as the empirical therapy has been recommended [10].

Exit Site and Tunnel Infection

They constitute the most important causes of peritonitis and catheter failure in the infantile group, employing routine use of mupirocin and sodium hydrochloride for prophylaxis of exit site infection ensures a reduced rate of infections and catheter survival. *Treatment:* Guidelines on the treatment of peritonitis in children are provided by the ISPD Advisory Committee on peritonitis management. Intraperitoneal treatment has been advocated for neonates with peritonitis. Loading dose of intraperitoneal antibiotics and heparin to clear the fibrin are advocated. During this period, exchanges with long dwell are maintained. Once the PD Fluid clouding resolves and leukocyte count normalizes, the initial prescription may be resumed.

Management of the Young Infant: The development of the chronic peritoneal dialysis techniques suitable for use in very small infants has changed the topography of the Pediatric CKD Care. Care of the ESRD infants includes ensuring adequate nutritional support to prevent uremia and mineral bone disorders and delay the need for RRT and rhGH. Optimal nutritional care is of paramount importance in achieving the growth potential. Linear Growth in the early 2 years is both by the energy provided and by the growth/ somototrophic hormonal influences during this period. Uremia with the associated inflammation and anorexia may severely impair the growth in children with CKD.

Young infants whose growth is dependent on calories in the early formative period are the most affected population, as they are easily susceptible to anorexia and inflammation with resultant linear growth failure. Usage of enteral feeding or the percutaneous gastrostomy can ameliorate the effects and promote the catch-up growth [11]. Inflammation observed in uremia causes resistance to the growth hormone signaling with simultaneous up regulation of growth hormones cytokine signaling suppression. Uremia induces growth hormone resistance and overcoming this resistance by the usage of recombinant growth hormone therapy has shown less response in infants on CPD as compared to the early CKD population.

Immunisation

Although the infants and neonates on CPD show varied responses to the immunization they should be immunized, and receive all the immunizations as per the recommendations [12].

Anemia

Anemia in an infant with CKD may be a factor contributing to the poor growth observed in them. Utilizing erythropoietin and ESA would help in improving the quality of life, and improving the brain stem evoked responses, this enables the children to study and play with their peer group. The EPO is recommended at higher doses in infants and young children, approximately 200 units per kg per week, preferably by the subcutaneous route [13].

Transplantation

Ideally to the infants on CPD, transplantation is recommended, as the transplantation contributes to the growth in the post transplant period, infants are maintained on CPD till they achieve optimal size approximately 10 kgs for a favorable outcome. The patient and graft survival are comparable with the older children survival rates especially with the living renal transplantation [14].

Conclusions

PD is the most simple, easy and flexible means of RRT in children of both acute and CKD population. PD over the decades has markedly improved and provides an excellent avenue of survival for infants with renal failure.

CAPD in neonates and infants – Highlights

- 50 % have congenital or hereditary disorder. In the placement of exit site, avoiding diaper area is pivotal.

- The recommended exchange volume in this age group is 1000-1100 ml/m^2 BSA though an initial volume of 600-800 ml/m^2 is usually practiced.

- Type 1 UFF is more common.

- Hyponatremia and hypophosphatemia are more common than their adult counterparts.

- A special emphasis on growth velocity is a key element of the comprehensive care.

References

1. Cole, W., and J. Montgomery, 1929: Intraperitoneal blood transfusion. *Am. J. Dis. Child,* **37,** 497-510.

2. Rath, B., S. Gopalan, and S. Gupta, 1994: Simpler tools for peritoneal dialysis of term newborns and young infants. *Indian Pediatr.,* **31,** 1131-1132.

3. North American Pediatric Renal Trials and Collaborative Studies. NAPRTCS 2011 Annual Dialysis Report [online]

4. Warady, B.A., F. Schaefer, S. R. Alexander, C. Firanek, and S. Mujais, 2004: In Care of the pediatric patient on peritoneal dialysis: clinical process for optimal outcomes (brochure). (Baxter Healthcare Corporation, McGaw Park, 2004)

5. Vidal, E. et al. on behalf of Italian Registry of Paediatric Chronic Dialysis. Peritoneal Dialysis in infants: the experience of the Italian Registry of Paediatric Chronic Dialysis. Nephrol. Dial. Transplant

6. Gokal, R., S. Alexander, and S. Ash, 1998: Peritoneal catheters and exit-site practices toward optimum peritoneal access: 1998 update. Official report from the International Society for Peritoneal Dialysis. *Perit Dial Int.,* **18,** 11–33.

7. Rodrigues, A., A. Cabrita, and C. Nogueira, 2004: Techniques of peritoneal catheter insertion. *Contrib. Nephrol.,* **142,** 402– 409.

8. Kohaut, E.C., F. B. Waldo, and M. R. Benfield, 1994: The effect of changes in dialysate volume on glucose and urea equilibration. *Perit. Dial. Int.*, **14,** 236-239.

9. Poyrazoglu, H. M., R. Dusunsel, T. Patiroglu, Z. Gunduz, C. Utas, and T. Gunes, 2002: Humoral immunity and frequency of peritonitis in chronic peritoneal dialysis patients. *Pediatr. Nephrol.,* **17,** 85–90.

10. Warady, B. A., F. Schaefer, and M. Holloway, 2000: Consensus guidelines for the treatment of peritonitis in pediatric patients receiving peritoneal dialysis. *Perit. Dial. Int.,* **20,** 610 – 624.

11. Ledermann, S. E., L. Spitz, J. Moloney, L. Rees, and R. S. Trompeter, 2002: Gastrostomy feeding in infants and children on peritoneal dialysis. *Pediatr. Nephrol.*, **17,** 246-250.

12. Fivush, B., and A. Neu, 1998: Immunization guidelines for pediatric renal disease. *Semin. Nephrol.,* **18,** 256-263.

13. Warady, B., R. Sabath, and C. Smith, 1991: Recombinant human erythropoietin in pediatric patients receiving long-term peritoneal dialysis. *Pediatr. Nephrol.,* **5,** 718-723.

14. Sarwal, M. M., J. M. Cecka, M. T. Millan, and O. Salvatierra, 2000: Adult-size kidneys without acute tubular necrosis provide exceedingly superior long-term graft outcomes for infants and small children: a single center and UNOS analysis. United Network for Organ Sharing. *Transplant.,* **70,** 1728 –1736.

Chapter 48

Peritoneal Dialysis in Acute Renal Failure

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Peritoneal Dialysis in Acute Renal Failure

Introduction

Acute Kidney injury (AKI) is a common medical problem accounting for around 5% of hospital inpatients [1].While majority of such patients get admitted with AKI (community acquired), several develop AKI following hospitalisation (hospital acquired) [2]. Despite advances in knowledge on the pathogenetic factors responsible for developing AKI and newer modalities of renal replacement therapies, mortality remains high. Recognising the need for avoiding preventable deaths from AKI, a goal of 0 by 25 was set, aiming to reduce the number of preventable deaths in AKI to zero by 2025 [3]. Considering the fact that AKI accounts for 1.7 million preventable deaths per year worldwide [3], and most occur in the developing countries where resources may limit the options of renal replacement therapies [4, 5], it may be worthwhile to consider whether peritoneal dialysis (PD) has a place in the management of AKI in the present times.

Modalities of Dialysis in AKI

Various modalities of dialysis are available for the management of AKI (**Figure 1**). The choice of dialysis is influenced by several factors like infrastructure, hemodynamic and coagulation status, stage of AKI and associated complications (**Figure 2**).

J. George

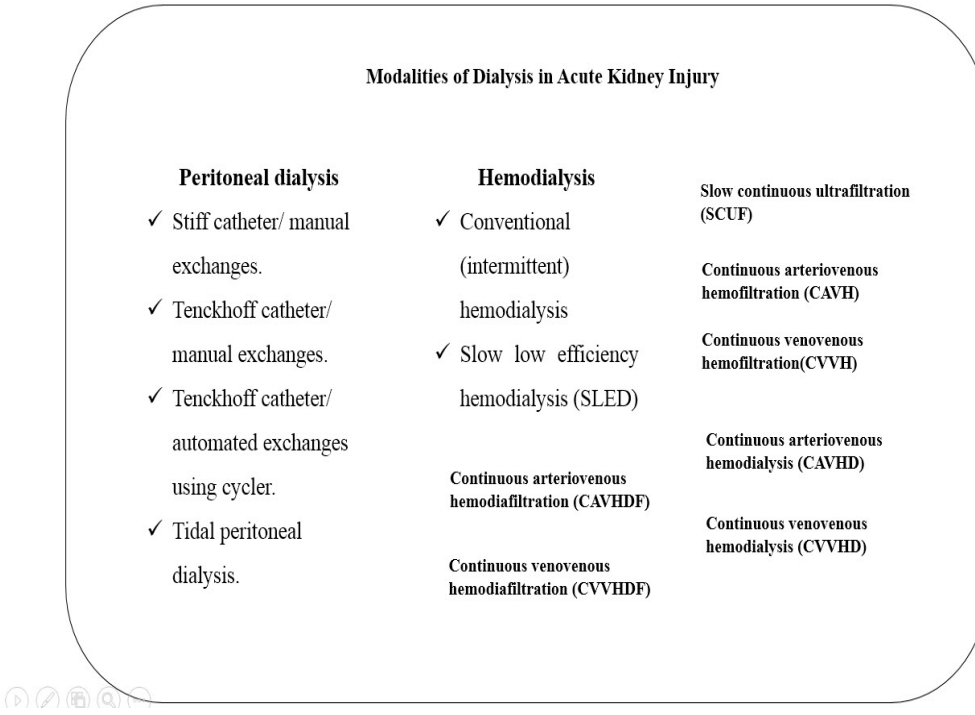

Figure 1: Modalities of dialysis in Acute Kidney Injury.

Role of Peritoneal Dialysis

PD was the first form of dialysis tried for AKI due to its simplicity [6]. PD has several advantages which could be beneficial in certain situations. The lack of need for a vascular access makes this a better choice in the pediatric population as well as in the patients having problems in getting a vascular line. This makes its use feasible even in remote areas and places where doctors trained in placing vascular accesses are not available [7]. Even nursing staff with minimal training can initiate and continue PD. As there is no need for electricity, it could be used in AKI developing in underdeveloped areas and low income countries where reliable electric supply may not be available [8]. As conventional hemodialysis (HD) often needs a water treatment facility to treat raw water, PD could be an option if this facility is not available [9]. AKI is a common accompaniment in multiorgan failure. This is especially so in the intensive care units (ICU). It is not uncommon for critically ill patients to be on multiple supports including inotropes and ventilators. Very often, HD machines may not be available in the ICUs, which necessitates transferring the critically ill patients to the dialysis units or shifting the HD machine to the ICU. As PD can be started in the ICUs itself, these can be avoided [10]. Thrombocytopenia, coagulation abnormalities and bleeding from various sites are common when AKI occurs following sepsis and multiorgan failure [11]. Need for

anticoagulation during HD adds to the risk. PD offers a significant advantage of not needing anticoagulation. Another clinical situation where PD has benefits is in those with hemodynamic disturbances, where conventional HD is often not tolerated.

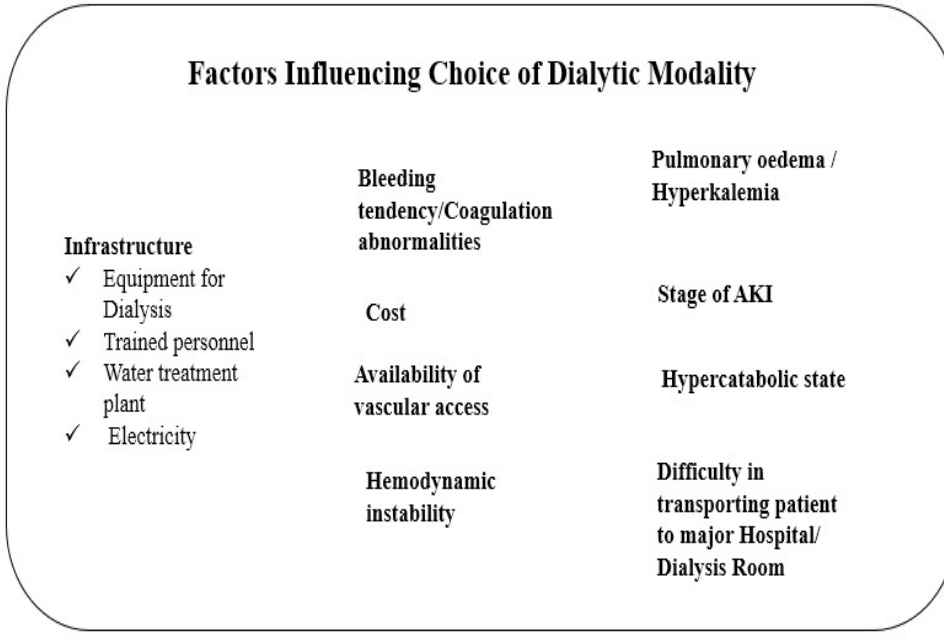

Figure 2: Factors influencing the choice of dialystic modalities.

Yet, with time, use of PD has diminished [12], especially in the developed countries, mainly due to the concerns about lower efficacy of PD with faster clearance of solute and fluids offered by the subsequent development of HD. This has been shown by calculating solute clearance using the formula KT/V where K is the Urea clearance, T the time on dialysis and V is the volume of distribution. However, PD can be used for prolonged periods and thus clearance can be increased. Conventional HD done for 4 hours every alternate day gives approximately 12 hours of HD per week. Assuming a KT/V of 1 for every 4 hours of HD, this would work out to a weekly KT/V of around 4. Use of PD with 2 L exchanges every 2 hours can provide a similar weekly KT/V [13]. Thus, patients with azotemia can be maintained on PD which gives a slow but prolonged correction. However, patients with life threatening pulmonary edema or hyperkalemia may need HD as the preferred dialysis modality. Septic patients with AKI are often hypercatabolic, making PD seem less ideal. This is especially true if dialysis is started at later stages of AKI where the blood urea and serum creatinine are high. There are however, reports that it is possible to do PD even in

hypercatabolic patients with some modifications like using a flexible catheter with a cycler [14]. Modifying the dialysis prescription by adding Tidal Peritoneal dialysis where the entire PD fluid is not drained could be another modification to increase efficiency [15].

In hemodynamically unstable patients, conventional HD may not be feasible. Alterations like slow continuous ultrafiltration (SCUF) could be tried when fluid overload is the major concern. Continuous arteriovenous hemofiltration (CAVH), or pump assisted continuous venovenous hemofiltration (CVVH) with replacement fluid may increase the urea clearance marginally by convective clearance. An additional solute removal by dialysis can be obtained by continuous arteriovenous dialysis (CAVHD) or continuous venvenous dialysis (CVVHD). Adding replacement fluid to this could combine solute and fluid removal and may be preferred in AKI occurring in the critically ill, hemodynamically unstable patient [11]. When falciparum malaria was the major cause of infection associated AKI, PD with a stiff PD catheter, an open drainage system, and manual exchanges of 2 L with 30 minute dwell time was found to be inferior to CVVHDF with regard to resolution of acidosis and renal failure and mortality was high [16]. This suggested that PD is unsuitable in this setting. However, it is possible that falciparum malaria infection might have blocked the peritoneal capillaries resulting in inefficient PD which might account for the poor outcome in this study. Another drawback suggested in this study was the use of a stiff PD catheter with manual exchanges [8]. Use of high volume PD using a Tenckhoff catheter and possible use of cycler performing automated exchanges was suggested as a modification to improve the outcome of PD in such situations [17]. In an open prospective randomised study of 50 patients with acute kidney injury (AKI) done in our centre, where the causes of AKI were predominantly sepsis and acute tubular necrosis, there was no significant difference in the composite outcome between PD and CVVHDF. The use of PD in AKI has thus seen a resurgence in recent times [18].

PD has also been compared to daily HD in those with severe ischemic or nephrotoxic acute tubular necrosis. Similar metabolic control, patient outcome and renal recovery were observed with a flexible (Tenckhoff) catheter using an automated cycler delivering 2 L exchanges with 30 -50 min dwell [19]. As metabolic acidosis is often associated with AKI, it is important that PD should tackle this problem. Use of PD fluid containing bicarbonate could correct metabolic acidosis by diffusion. However, lactate based PD fluid is more commonly available and is cheaper. Lactate gets converted in the liver to eventually yield bicarbonate. PD fluid containing lactate can also correct acidosis, though it takes time and the liver should be functioning normally. We have shown correction of metabolic acidosis with a lactate based PD fluid [20]. Lactate based PD and replacement fluids are however preferably avoided in those with hepatic dysfunction.

Initial reports suggested that high dose ultrafiltation rates of around 35 ml/kg/hour may be beneficial in sepsis associated renal failure due to removal of inflammatory cytokines [21]. It was hence felt that CAVHDF or CVVHDF would be better than

PD in such patients as ultrafiltration rates for PD are significantly lower [10]. This has however not been substantiated in subsequent studies with standard ultrafiltration rates of 20 ml/kg/hour being equally effective [22]. Even in sepsis, ultrafiltration rates of 20 ml/kg/hour are not inferior [23]. Such ultrafiltration rates can be obtained by PD fluids using hypertonic solutions.

Ensuring an adequate dose is thought to be important in assessing the dialysis adequacy. It is suggested that a standard weekly KT/V of 2.1 should be the minimum target to be achieved in AKI. This can be achieved by PD also, despite lesser efficiency than HD [24]. Clearance of middle molecules may be even better for PD than conventional HD and its role in management of sepsis associated AKI needs further study.

Use of a flexible biocompatible Tenchkoff catheter has advantages as it can be used for prolonged periods with less chances of obstruction and faster flow [13, 14]. Its insertion however needs more expertise and training than a stiff PD catheter. This can be done using a peel away sheath, Trocar, peritoneoscope or surgical insertion. If one anticipates a shorter duration of PD as when being used as a bridge to HD or till the patient becomes hemodynamically stable, a stiff catheter may suffice. A cycler may be used in the ICU which may increase the efficiency, decrease risk of peritonitis as well as save on nursing time [18].

PD carries a risk of peritonitis and is considered to be a reason for its decline [3]. However, using the flush before fill technique has decreased the risk of peritonitis [10]. Utilising flexible catheters with transfer sets and automated cyclers can further decrease this risk. This often needs the use of commercial CAPD bags which can increase the cost. When conventional PD fluid manufactured locally was used, the cost was only a third of the cost of CVVHDF [10]. The main justification of using CAPD bags over conventional PD bags made from polyvinylchloride (PVC) by the local hospital pharmacies has been the fear that plasticisers like diethylhexylpthalate can damage the peritoneal membrane in the long run [25]. However, in AKI, this concern is minimal as only short term dialysis is required. Use of locally made sterile PD fluid bags with a flexible catheter may achieve a better uremic correction at a lower cost in the developing countries.

Other situations where PD may be preferable is in AKI associated with intraabdominal hypertension (IAH).When the intraabdominal pressure is >15 mmHg, there is a risk of AKI as it can reduce the kidney perfusion [26]. In such patients, judicious use of PD following partial drainage can reduce IAH. Raised IAH can contribute to AKI in some cases of acute pancreatitis [27]. We have reported better outcome with PD compared to HD in IAH following acute pancreatitis [28].

To conclude, PD appears to be a viable mode of dialysis in the selected cases of AKI. It has advantages in the critically ill patients with AKI in the ICU as it requires minimally trained staff and infrastructure (**Figure 3**). Due to lesser fluid

shifts, it may need less intensive monitoring than CVVHDF. Yet, it has some disadvantages like less efficiency compared to HD and CVVHDF.

Advantages

- ✓ Minimum infrastructure: Equipment, Trained Personnel, electricity, water treatment.
- ✓ Cheap.
- ✓ Anticoagulation not required.
- ✓ Shifting critically ill patients to hemodialysis centres can be avoided.
- ✓ Can be done even in primary health centres and hospitals without dialysis facilities.

Disadvantages

- ✓ Cannot be done following abdominal surgery where peritoneum is opened
- ✓ Risk of Peritonitis
- ✓ Mechanical complications: obstruction causing poor inflow or outflow/blood stained effluent
- ✓ Less efficient clearance of Urea / Creatinine
- ✓ Not ideal in pulmonary oedema

Figure 3: Advantages and disadvantages of Peritoneal Dialysis.

The following guidelines may help in deciding the clinical situations where PD may be better suited:

1. PD may be best suited in early stages of renal failure when the urine output starts to decrease and blood urea and serum creatinine are marginally elevated. It is also effective in correcting metabolic acidosis. This may often suffice as the sole form of CRRT, but may need shifting to other forms of dialysis later. Using a flexible Tenckhoff catheter with or without a cycler could be considered when the duration of dialysis is likely to be prolonged.

2. PD may not be ideal if patients are in significant fluid overload where a more rapid removal of fluid is needed. This should also be less preferred when the patient is hypercatabolic with significantly raised blood urea and serum creatinine. This situation often arises when nephrologists are consulted from other departments fairly late. PD may be less preferred in life threatening hyperkalemia.

3. Shifting patients to conventional hemodialysis or CVVHDF could be considered if correction of metabolic parameters is delayed or as soon as patients are hemodynamically stable, initially with a lower pump speed if needed. This will reduce the overall cost, mortality and is less taxing when limited personnel are available.

4. PD has advantages in the underdeveloped and the economically backward countries with limited resources and can be considered as a first form of dialysis.

References

1.Schieppati, A., N. Perico, and G. Remuzzi, 2015: Eliminating treatable deaths due to acute kidney injury in resource poor settings. *Semin. Dial.,* **28,** 193-197.

2.Chertow, G. M., E. Burdick, M. Honour, J. V. Bonventre, and D. W. Bates, 2005: Acute kidney injury, mortality, length of stay and costs in hospitalized patients. *J. Am. Soc. Nephrol.,* **16,** 3365-3370.

3.Mehta, R. L., J. Cerda, E. A., M. Tonelli, G. García-García, V. Jha, P. Susantitaphong, M. Rocco, R. Vanholder, M. S. Sever, D. Cruz, B. Jaber, N. H. Lameire, R. Lombardi, A. Lewington, J. Feehally, F. Finkelstein, N. Levin, N. Pannu , B. Thomas, E. Aronoff-Spencer, and G. Remuzzi, 2015: International Society of Nephrology's 0 by 25 initiative for acute kidney injury: zero preventable deaths by 2025: a human rights care for nephrology. *Lancet*, **385,** 2616-2643.

4.Ponce, D., and A. Balbi, 2016: Acute kidney injury: risk factors and management challenges in developing countries. *Int. J. Nephrol. Renovasc. Med.,* **9,** 193-200.

5.Jha, V., and S. Parameswaran, 2013: Community acquired acute kidney injury in tropical countries. *Nat. Rev. Nephrol.,* **9,** 278-290.

6.Maxwell, M. H., R. E. Rockneey, and C. R. Kleeman, 1959: Peritoneal Dialysis. Techniques and applications. *JAMA,* **170,** 917-924.

7.Sharma, S. K., D. Manandhar, J. Singh, H. S. Chauhan, B. Koirala, M. Gautam, L. H. Ghotekar, B. Tamang, and S. Gurung, 2003: Acute peritoneal dialysis in Eastern Nepal. *Perit. Dial. Int*., **23,** 196-199.

8.Ponce, D., M. N. Berbel, C. Regina de Goes, C. T. Almeida, and A. L. Balbi AL, 2012: High-volume peritoneal dialysis in acute kidney injury: indications and limitations. *Clin. J. Am. Soc. Nephrol.,* **7,** 887–894.

9.Olowu, W. A., A. Niang, C. Osafo, G. Ashuntantang, F. A. Arogundade, J. Porter, S. Naicker, and V. A. Luyckx, 2016: Outcomes of acute kidney injury in children and adults in sub-Saharan Africa: a systematic review. *Lancet Glob. Health.,* **4,** 242–250.

10. George, J., S. Varma, S. Kumar, J. Thomas, S. Gopi, and R. Pisharody, 2011: Comparing continuous venovenous hemodiafiltration and peritoneal dialysis in critically ill patients with acute kidney injury: a pilot study. *Perit. Dial. Int.,* **31,** 422–429.

11. Mehta, R. L., 1993: Renal replacement therapy for acute renal failure: matching the method to the patient. *Seminars dial.,* **6,** 253-259.

12. Hyman, A., and D. C. Mendelssohn, 2002: Current Canadian approaches to dialysis for acute renal failure in the ICU. *Am. J. Nephrol.,* **22,** 29-34.

13. Ponce, D., M. N. Berbel, R. C. Goes, C. Regina de Goes, C. T. Almeida, and A. L. Balbi, 2012: High volume peritoneal dialysis in Acute kidney injury: Indications and limitations. *Clin. J. Am. Soc. Nephrol.,* **7,** 887-894.

14. Gabriel, D. P., J. T. Caramori, L. C. Martim, P. Barretti, and A. L. Balbi, 2009: Continuous peritoneal dialysis compared with daily hemodialysis in patients with acute kidney injury. *Perit. Dial. Int.,* **29,** 62-71.

15. Chitalia, V., A. F. Almeida, H. Rai, M. Bapat, K. V. Chatalia, V. N. Acharya, and R. Khanna, 2002: Is peritoneal dialysis adequate for hypercatabolic acute renal failure in developing countries? *Kid. Int.,* **61,** 747-757.

16. Phu N. H., T. T. Hien, N. T. H. Mai, T. T. H. Chau, L. V. Chuong, P. P. Loc, C. Winearls, J. Farrar, N. White, and N. Day, 2002: Hemofiltration and peritoneal dialysis in infection associated acute renal failure in Vietnam. *N. Eng. J. Med.,* **347,** 895-902.

17. Gabriel, D. P., J. T. Camori, L. C. Martim, P. Baretti, and A. L. Balbi. High volume peritoneal dialysis vs daily hemodialysis-A randomized control trial in patients with acute kidney injury. *Kid. Int*., **73,** 87-93.

18. Ponce, D., and A. L. Balbi, 2007: Peritoneal dialysis in acute kidney injury: a viable alternative. *Perit. Dial. Int.,* **27,** 277-282.

19. Gabriel, D. P., J. T. Caramori, L. C. Martim, P. Barretti, and A. L. Balbi, 2009: Continuous peritoneal dialysis compared with daily hemodialysis in patients with acute kidney injury. *Perit. Dial. Int*., **29,** 62-71.

20. George, J., V. P. Sathyanathan, R. N. Potty, and R. Pisharody, 1998: Formic acid poisoning: does early peritoneal dialysis have a role. *Ind. J. Nephrol.,* **8,** 22-24.

21. Cole, L., R. Bellomo, D. Journois, P. Davenport, I. Baldwin, and P. Tipping, 1992: High volume hemofiltration in human septic shock. *Inten. Care Med.,* **18,** 235-240.

22. Tolvani, A. J., R. C. Campbell, B. S. Stefan, K. R, Lai, R. A. Oster, and K. M. Willie, 2008: Standard versus high dose CVVHDF for ICU related acute renal failure. *J Am Soc Nephrol*., **19,** 1233-1238.

23. The VA/NIH Acute Renal Failure Trial Network, 2008: Intensity of renal support in critically ill patients with acute kidney injury. *N. Eng. J. Med.,* **359,** 7-20.

24. Chionh, C. Y., C. Ronco, F. O. Finkelstein, S. S. Soni, and D. N. Cruz, 2010: Acute peritoneal dialysis: what is the adequate dose for acute kidney injury? *Nephrol. Dial. Transplant.,* **25,** 3155-3160.

25. Mettang, T., C. Pauli Magnus, D. M. Alscher, J. Kirchgessner, R. Wodarz, A. W. Rettenmeier, and U. Kuhlmann, 2007: Influence of plasticizer free CAPD bags and tubings on serum, urine and dialysate levels of pthalic acid esters in CAPD patients. *Perit. Dial. Int.,* **27,** 267-276.

26. De Waele, J. J., E. Hoste, S. I. Blot, J. Decruyenaere, and F. Colardyn, 2005: Intraabdominal hypertension in patients with severe acute pancreatitis. *Crit. Care,* **9,** 452-457.

27. Li, H., Z. L. Qian, Z. Liu, H. Liu, X. Han, and H. Kang, 2010: Risk factors and outcome of acute renal failure in patients with severe acute pancreatitis. *J. Crit. Care,* **25,** 225-229.

28. Nath, J. P., J. George, M. Das, N. Gracious, S. Kumar, and N. S. Vineetha, 2014: Successful management of acute kidney injury in severe acute pancreatitis with intraabdominal hypertension using peritoneal dialysis. *Ind. J. Crit. Care Med.,* **18,** 834.

Chapter 49

Peritoneal Dialysis in Obese Patients

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Peritoneal Dialysis in Obese Patients

Introduction

Worldwide, obesity is reaching epidemic proportions and it is a well-known risk factor for developing type-2 diabetes and hypertension [1]. Both these latter entities are the main causes of CKD and ESRD in the world today [2]. It is estimated that nearly 70% of the diabetic population are obese.

Obesity and metabolic syndrome are increasing even in the developing world where it co-habits with malnutrition and cachexia. This is more prevalent in the urbanareas; e.g., in India nearly 30-65% of adults are either overweight, obese or have abdominal obesity [1].

The cut off for obesity in terms of BMI is different for Asian (including Indian) and the Caucasian population. Indian guidelines suggest that BMI of 23-24.9 kg/m^2 should be classified as overweight, while obesity should be labelled as BMI $>25kg/m^2$ [1].

Patients on dialysis have a significantly higher mortality as compared to the general population. Nearly, a fifth of the patients die per year on dialysis in the US, mainly due to cardiovascular diseases [3].

As obesity and metabolic syndrome are strong risk factors for cardiovascular disease, it is presumed that obese patients on dialysis fare worse. Paradoxically, obese patients on haemodialysis (HD) have a survival advantage; whether the same is true for CAPD is not very clear. Not many studies are there looking at the survival of obese patients on PD, neither is there a randomised controlled trial comparing HD and PD [4]. In this era, when obesity is increasingly prevalent in the dialysis population, it would be interesting to assess whether peritoneal dialysis (PD) is to be offered to these patients and what are the points to consider before the decision.

The main concerns amongst nephrologists about PD in obese patients are a concern aboutadequate solute clearance in obese patients on PD, higher chance of PD peritonitis or exit site infections and quality of life (QoL) and survival. All these has led to PD not being offered freely as a modality to obese incident dialysis patients [5]

What Parameter of Obesity Measure is Best Suited for Dialysis Patient?

Worldwide, obesity is most commonly described by the body mass index (BMI) which is calculated in Kg/m^2 and the waist circumference (WC) [6]. It is also well known that Asians (including Indians) have more abdominal obesity and the cardiovascular risks are more evident at lower BMI's. Hence, the Indian guidelines defines normal BMI: 18.0-22.9 kg/m^2, overweight: 23.0-24.9 kg/ m^2, obesity: >25 kg/m^2 [1]. WC is preferred over waist hip ratio as a measure of

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central obesity and is better in terms of predicting the cardiovascular complications. The cut-offs of WC for Asians and Indians are 90 cm for men and 80 cm for women, while a WH ratio more than 0.95 for men and more than 0.85 in women is abnormal. However, in patients on PD, because of PD fluid inside and the lax abdominal wall, BMI according to the ethnicity of the patient is a better marker [6].

How is Obesity Harmful?

Central obesity is much more harmful than peripheral obesity. It is consistently associated with insulin resistance, dyslipidaemia and cardiac complications. While, visceral fat has been shown to produce and release higher quantities of pro-inflammatory cytokines like TNF-α, IL-6 and CRP, lower levels of adiponectin in insulin resistant diabetic patient are present, both of which predispose to higher rates of cardiovascular events [4, 6].

PD itself Causes Obesity

Patients on PD generally gain about 7-10% of their initial body weight, which they had at the start of dialysis. The weight gain is noticed mainly in the initial period, if the PD is functioning well and the effect wears out by one and a half year after startof dialysis [7]. Nearly, 100-200 gm. of glucose is absorbed every day from the dialysate which adds about 400-800 Kcal. Good solute clearances increases the patients' appetite resulting in a good calorie intake per day. All this may lead to a significant weight gain in some patients. In a study from Brazil, it was found that 60 % of patients on PD had >3% increase in weight in the first year, while 20% had >7% weight gain; moreover weight gain had no adverse impact while weight loss had [8].

Concerns about Initiating Peritoneal Dialysis in Obese Patients

The main concerns about starting CAPD in obese patients is that they may not get an adequate dose of dialysis as prescribed in the (NKF)-KDOQI guidelines; particularly when they become anuric (Table1). Secondly, the general perception is that with inadequate doses of dialysis, it would lead to a poorer QoL and resulting morbidity and mortality [5]. The other widely held belief is that CAPD in obese patients leads to an increased peritonitis and exit site infection, as the patient may not have a good view of the exit-site because of obesity. Added to these are the issues of peri-catheter leaks and increased risk of hernia formation. The issues of uncontrolled hyperglycaemia and other complications of metabolic syndrome can also get worse on PD but can be tackled with proper follow-up.

On the other hand, the possible advantages of PD in obese patients could be that one does not need a vascular access for dialysis which could be difficult in this group. Moreover, any patient with severe vascular access failure could find PD to be a boon. The other advantages of PD like better preservation of residual renal

function, hemodynamic stability and others also apply to this group. The advantages and concerns regarding the PD in obese patients are enlisted in **Table 1**.

What is the Adequate Dose for Peritoneal Dialysis in Obese Patients?

The general perception is that in the obese patients, a larger total body water and body surface area exists. If one calculates the normalised weekly urea (Kt/V) and weekly creatinine clearances basing on these values, it becomes essential to use huge drain volumes to achieve the targeted clearances. Using mathematical modelling, one may find that even a 3 L exchange 4 times per day may not provide enough dialysis for an 80 kg patient [5].

Table 1: Peritoneal Dialysis in Obese Patients

Advantages	**Concerns**
No vascular access needed ,particularly useful in patients with access failure	Inadequate dose of dialysis delivered
Better preservation of residual renal function	Poor solute clearance causing poor quality of life and increased mortality
Gentler form of dialysis, better haemodynamic stability	Increased risk of peritonitis and exit sit infections
Can be done at home	Catheter leaks
	Increased Hernia Risk
	Rapid weight gain and metabolic complications worsening

Nolph *et al,* calculated that 4 exchanges of 2, 2.5 and 3 litres may not achieve the weekly Kt/V urea >1.6 in patients weighing more than 64, 77.6 and 91 kg [9]. However, in practice it is seen that a majority of patients may actually achieve their targets of solute clearance using standard dialysis prescription. The reason could be that many patients now have significant residual renal functions and may use APD with enhanced clearances. Shibagaki et al have reported that more than 80 % of their obese patients were able to achieve their Kt/V and WC targets and these included anuric patients [10].

This discrepancy can be better answered if we understand that one group who are primarily obese have more body fat (and less total body water), while the other group are more muscular and have higher total body water. In the former group, the majority of patients achieve the set clearance targets, while the ones who are well built and muscular (with more total body water), it may be more difficult to achieve the targets [5].

With this information, it is reasonable to presume that Indian and other Asian patients may achieve their clearance targets easily as they fit into the primarily obese group with less total body water. In this context, it is appropriate to mention that as the body weight increases the proportion of TBW decreases; this is because fat has very low water content. Though, there is confusion about the best formula to calculate the total body water, for PD patients (including those with obesity), Watson's formula to estimate volume seems to be the most suited.

As per recent KDOQI recommendations, a weekly Kt/V of 1.7 without considering the WCC is all that is necessary. These targets are lesser than the previous targets and easier to achieve.

The Association between Obesity and Survival in PD Patients

There is conflicting data in the literature between the association of BMI and survival rates on PD **(Table 2)**.

While the general perception is that PD is better than HD, particularly in the first 2 years after initiation of PD, the data is divided on the impact of obesity on PD.Vonesh et al reviewed 9 studies comparing HD and PD. They found that PD had lower mortality in the first 1-2 years, but diabetes, age and co-morbidity significantly affected the outcomes [11]. Interestingly, Termorshuizen et al. found no significantly different outcomes of PD and HD patients till 2 years after starting dialysis; after that they found increased mortality on PD particularly in patients who were more than 60 yrs of age [12].

Ananthakrishnan *et al,* retrospectively compared the effect of weight in 43 pair matched patients on PD, comparing those weighing more than 90Kg to those less than 90 kg.They found no difference in outcomes between the two groups and no increase in peritonitis or catheter related problems [13].

Synder *et al,* in a retrospective analysis of 41,197 PD patients from US Medicare data between 1995 and 2000 found that as compared to underweight patients (BMI<18.5) and overweight patients (BMI 25-29.9), obese patients (BMI>30) had lesser mortality over a period of 3 years [14] .

De Mutsertin in his study from Netherlands with 688 incident patients on PD found that patients who had a BMI of >30 kg/m^2 had a persistent lower mortality as compared to those with BMI<18.5 kg/m^2 [15].

Ram kumar *et al,* studied 10,140 incident patients on PD with BMI>18.5 kg/m2 and used 24 hours urinary creatinine as an indirect marker of muscle mass [16]. They found that patients with high BMI and normal or high muscle mass had a 10% lower mortality, while those with high BMI and low muscle mass had the worst outcomes suggesting that someone with a high amount of body fat and less amount of muscle have worst outcomes.

In a recent meta-analysis published in the PDI, Ahmadi have reported that as compared to underweight patients, overweight or obese patients had less chance of mortality in the first year and no significant differences from the second to the fifth year [17]. There are studies done by Beth Piranio's group which did not find any significant difference in outcomes between obese and non-obese patient [18].

Studies reporting worst outcomes have suggested that these patients with high BMI have increased rates of peritonitis and possibly an ethnic bias. Mc Donald *et al,* using ANZDATA Registry did a retrospective analysis of 10,709 patients spanning over 12 years. They found that higher BMI predisposes to higher peritonitis rates and that the indigenous population were more prone to it. Moreover, there was a decrease in peritonitis rates over time, the so-called vintage effect. The same group has reported that obesity leads to increased mortality and technique failure on PD, but the indigenous population seemed not to be affected [19].

There seems to be a distinct pattern of outcomes seen in Asian patents on PD based on their BMI. In a recent meta-analysis, Liu *et al,* reviewed 7 cohort studies and included 3610 patients.The obese group (BMI 25-29.9 kg/m^2) was associated with a 46% higher risk of all-cause mortality and cardiac mortality compared to the normal group (BMI 18.5-22.9 kg/m^2). The underweight group (BMI<18.5 kg/m^2) also had an increased risk of all-cause mortality, while the overweight group (BMI23-24.9 kg/m^2) seems to be protected. Thus, a U-shaped trend in mortality is evident in this group [20].

The findings of other studies from this area are also similar. Zhou H et al from China studied the association of BMI and survival in patients on PD comparing between those with BMI 18.5-24.9 kg/m^2 with those with BMI 25.0-29.9 kg/m^2. They found the former group had a lesser mortality [21].

A study from Hong Kong looked at the survival of 274 incident patients on PD between 2001-2008. Patients with an inadequate dialysis and those with early deaths was excluded. They found that the mortality was increased in both the underweight and obese patients. However, in the obese group those with diabetes and CVD had worse outcomes [22].

In the only study available from India Prasad *et al,* followed 328 incident patients on PD for 20± 14.3 months. In this study, 17.4% of patients were obese (BMI>25 kg/m^2) and 52% were diabetic. Their observation was that while the chances of death was much more in the underweight category, those with obesity had higher rates of peritonitis [23].

So in regards to Asian patients on PD, a distinct pattern is observed. There is a "V-shaped" curve in the relationship between all-cause mortality and BMI in this group (Figure 1). Both the underweight and obese patients have an increased all-cause mortality as compared to normal BMI patients. Obese patients were also likely to have high CVD mortality, may due to an increased visceral fat and central obesity

in this group. It is easy to understand that underweight patients are malnourished, may have chronic inflammation and may be prone to infections and poor outcomes.

The "reverse epidemiology phenomenon" seen in patients on HD where higher BMI is associated with a better survival, is not so obvious in PD patients, more so in the Asian population. While the studies of obesity in HD have been mainly in Caucasian patients, the PD studies from Asia look at a different group of people altogether. It is important to note that when the outcomes in obese Asian population on hemodialysis in the US was looked at, the survival advantage seemed to be missing.

Looking at obese patients on PD, more so in the Asians, abdominal obesity is predominant. This visceral fat mass increases 11-23% in the first year after PD. Central obesity and visceral fat are primarily responsible for insulin resistance, release of adipokines and cardiovascular complications in the population at large and that may be causing all the outcome differences in these patients too.

Are Obese Pd Patients More Prone to Infections?

It is thought that obese patients may have difficulty in visualising their exit-sites, and cleaning the area leading to a high chance of infections. Many of them ask their care givers to clean the site or use mirrors to visualise.

Again, there is a difference in the results seen in the various regions. Piraino et al found similar peritonitis and exit site infections in patients with greater than 110% of ideal body weight. Nessim *et al,* from Toronto in their analysis of the causes of peritonitis did not find obesity to be a contributing factor [24].

Studies from Australia and Europe have identified obesity as a risk factor for PD peritonitis.

Similarly, in multiple studies done from Asia, obesity was found as a significant risk factor for causing peritonitis. This was well documented in a study from India and from other countries in the region [23, 25].

The reason for increased peritonitis rates observed consistently in these regions may be because of the tropical humid climate in many of these places, predominant abdominal obesity, difference in surgical technique, difference in level of PD training imparted, level of basic understanding of PD and exit site care. It is difficult to pin point the exact cause unlesssystematic analysis is done.

Quality of life

There are no studies which have looked specifically into the QoL in these obese patients on PD However, in a meta-analysis of studies looking at both HD and PD, there was no significant difference between the two [26]. Reports from one centre say that there was no significant difference in QoL between the obese and other patients on PD.

Peri-catheter Leaks and Risk of Hernia Formation

There is not much data about the incidence of peri-catheter leaks in obesity, though previous studies had mentioned it. Recent studies did not find it to be an important risk factor, probably as surgical techniques are better now.The incidence of hernia formation was not of any concern in these patients, in fact one study stated that the chances are lesser in this group.

Conclusion

Obese patients on HD do uniformly better, however those on PD may not always do so well. Studies, mainly from Asia have reported worse outcomes in obese patients on PD. The two main problems are increased peritonitis and cardiovascular deaths. The way forward is to ensure better patient training and education to ensure proper exit site and catheter care, use of APD may further help reduce infections. Proper lifestyle management, supervised exercise schedules with resistance training to help build muscles may reduce cardiac mortality. Use of Icodextrin may reduce the glucose load and further decrease the cardiac risk factors.

Solid diamond -HR from individual study; Hollow diamond-the overall summary HR. Horizontal line-the study specific 95% CI. HR-adjusted hazard risk for obese group vs. normal BMI group based on Asian BMI categorization.

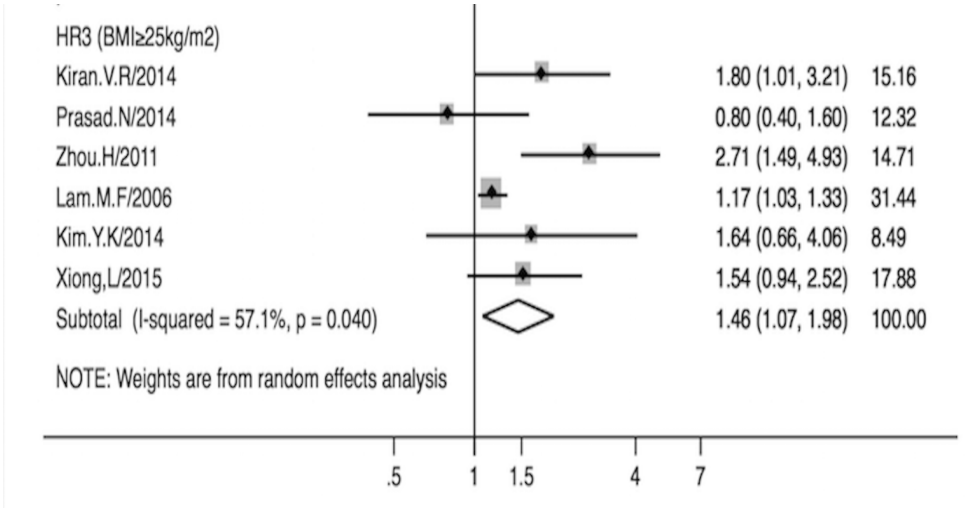

Figure 1: Pooled HR with 95%CI of all-cause mortality in high BMI group (BMI ≥25kg/m2) in Asian patients

Table 2: Studies looking at outcomes of Obese Peritoneal Dialysis Patients [Modified from 20].

Studies reporting better outcomes			
Synder *et al*	Retrospective analysis of 41,197 pts	Follow up of 3 years	Overweight and obese patients had better survival
Johnson DW	Prospective observational study of 43 pts	Follow up of 3 yrs	Patients with BMI > 27.5 had better survival
deMutsert *et al*	Prospective cohort study of 688 pts.	Follow up of 5 yrs.	Patients with BMI> 30 had better survival.
Ramkumar *et al*	10,140 Incident PD pts		High BMI >25 with high muscle mass had least mortality, while those with low muscle had highest mortality
Ahmadi *et al*	Meta-analysis and systematic review	Follow up upto 5 yrs	In the short term Obesity had lower mortality, in the long term there was no difference
Studies finding no difference in outcome			
AnanthKrishnan *et al*	43 pair matched PD pts analysed retrospectively	Included patients over a period of 10 yrs	No difference in outcome between those more than 90 kg and those less than 90 kgs. Catheter loss and peritonitis rates similar
Fried L *et al*	Prospective cohort study in 340 pts with 660 yrs on PD	Included patients enrolled between 1979-1995	No difference in outcomes between patients with low or high body weight
Aslam N *et al*	Prospective study of incident PD patients. 104	Followed up for 2 yrs	No difference in outcomes at 2 yrs based on BMI

	pts with BMI >27 were matched with 104 with <27	
Studies reporting worse outcomes		
McDonalds *et al*	Analysis of incident 9679 dialysis patientsbetween1991-2002 from ANZDATA Base	Reported worst patient and technique survival in the obese patients
Liu *et al*	Meta-analysis of 7 cohort studies with 3610 pts from Asia	Obese patients with BMI 25-29.9 had higher all-cause and cvs mortality
Zhou *et al*	159 pts studied for 5 yrs	Patients with obesity had worse outcomes
Kiran VR	Survival of 274 incident Asian PD pts between 2001-2008 were analysed	Mortality in obese patients was increased,those with diabetes and CVD were worse affected
Prasad N	Followed 328 incident PD pts for 20±14.3 months	Patients with high BMI had higher rates of peritonitis, while mortality was higher in the underweight group. Only study from India
LM Ong *et al*	Prospective observational study over 1yr period with 1603 participants in 15 centres in Malaysia	Obesity was a significant risk factor for development of peritonitis

Importants points to keep in mind

1. Obesity is quite common in dialysis patients.

2. Obese patients on haemodialysis have better outcomes.

3. The outcomes in obese PD patients are varied.
4. While western data suggest good outcomes.
5. Studies from Asia report poor outcomes.

6. Excess of both PD infections and cardiovascular disease are reported in studies from Asia.

7. The impact of central obesity in Asians may be contributing to these adverse outcomes even at moderately high BMI's.

8. The impact of weather, poor socioeconomic conditions, poor literacy and training levels may also be contributing.

9. Achieving adequacy targets is usually not difficult particularly in those with more fat and less muscle mass.

CAPD can be offered to obese patients, particularly in those with access problems

- Proper exit site care procedures have to be ensured.
- APD may ensure easier delivery of dialysis dose and reduce infections.
- Proper lifestyle management including muscle building exercises may help.
- Use oficodextrin to reduce the glucose load may further improve outcomes.

References

1.Misra, A., P. Chowbey, B. M. Makkar, N. K. Vikram, J. S. Wasir, and D. Chadha, 2009: Consensus Statement for Diagnosis of Obesity, Abdominal Obesity and the Metabolic Syndrome for Asian Indians and Recommendations for Physical Activity. *JAPI*, **57,** 163-170.

2. Jha, V., G. Garcia-Garcia, K. Iseki, Z. Li, S. Naicker, and B. Plattner, 2013: Chronic kidney disease: global dimension and perspectives. *Lancet*, **382,** 260–272.

3. Maric-Bilkan, C., 2013: Obesity and diabetic kidney disease. *Med. Clin. North Am.,* **97,** 59-74.

4. Ekart, R., and R. Hojs, 2016: Obese and diabetic patients with end-stage renal disease: Peritoneal dialysis or hemodialysis? *Eur. J. Intern. Med.,* **32,** 1-6.

5 Shetty, A. K., 2011: Logistics of peritoneal dialysis in the obese population. *Dial. Transplant.,* **40,** 364–366.

6 Li, P. K. T., B. Ching-Ha Kwan, C. C. Szeto, and G. T. C. Ko, 2008: Metabolic syndrome in peritoneal dialysis patients. *NDT Plus*, **1,** 206–214.

7. Diaz-Buxo, J. A., and W. P. Burgess, 1992: Is the weight gain in most chronic peritoneal dialysis patients? *Adv. Perit. Dial.,* **8,** 334-339.

8. Maria, N., F. da Silva Fernandes, M. G. Bastos, I. M. Regina, G. Franco III, and A. Chaoubah, 2013: Body size and longitudinal body weight changes do not increase mortality in incident peritoneal dialysis patients of the Brazilian peritoneal dialysis multicenter study. *Clin.,* **68,** 51-58.

9 Nolph, K. D., R. A. Jensen, R. Khanna, and Z. J. Twardowski, 1994: Weight limitations for weekly urea clearances using various exchange volumes in continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **14,** 261-264.

10. Shibagaki, Y., M. D. Faber, G. Divine, and A. Shetty, 2002: Feasibility of adequate solute clearance in obese patients on peritoneal dialysis: A cross sectional study. *Am. J. Kid. Dis.,* **40,** 1295-3000.

11. Vonesh, E. F., J. J. Snyder, R. N. Foley, and Collins, 2006: Mortality studies comparing peritoneal dialysis and hemodialysis: what do they tell us? *Am. J. Kid. Int. Suppl.,* **103,** 3-11.

12. Termorshuizen, F., J. C. Korevaar, F. W. Dekker, J. G. Van Manen, E. W. Boeschoten, and R. T. Krediet, 2003: Hemodialysis and peritoneal dialysis: comparison of adjusted mortality rates according to the duration of dialysis: analysis of The Netherlands Cooperative Study on the Adequacy of Dialysis. *J. Am. Soc. Nephrol.,* **14,** 2851-2860.

13. Ananthakrishnan, S., N. Sekercioglu, R. M. Elias, J. Kim, D. Oreopoulos, M. Chu, and J. M. Bargman, 2014: Peritoneal dialysis outcomes in a modern cohort of overweight patients. *Int. Urol. Nephrol.,* **46,** 183-189.

14 Snyder, J. J., R. N. Foley, D. T. Gilbertson, E. F. Vonesh, and Collins, 2003: Body size and outcomes on peritoneal dialysis in the United States. AJ. *Kid. Int.,* **64,** 1838-1844.

15. de Mutsert, R., D. C. Grootendorst, E. W. Boeschoten, F. W. Dekker, and R. T. Krediet, 2009: Is obesity associated with a survival advantage in patients starting peritoneal dialysis? *Contrib. Nephrol.,* **163,** 124-131.

16. Ramkumar, N., L. M. Pappas, and S. Beddhu, 2005: Effect of body size and body composition on survival in peritoneal dialysis patients. *Perit. Dial. Int.,* **25,** 461-469.

17. Ahmadi, S. F., G. Zahmatkesh, E. Streja, R. Mehrotra, C. M. Rhee, and C. P. Kovesdy, 2016: Association of Body Mass Index With Mortality in Peritoneal Dialysis Patients: A Systematic Review and Meta-Analysis. *Perit. Dial. Int.,* **36,** 315-325.

18 Aslam, N., J. Bernardini, L. Fried, and B. Piraino, 2002: Large body mass index does not predict short-term survival in peritoneal dialysis patients. *Perit. Dial. Int.,* **22,** 191-196.

19. McDonald, S. P., J. F. Collins, and D. W. Johnson, 2003: Obesity is associated with worse peritoneal dialysis outcomes in the Australia and New Zealand patient populations. *J. Am. Soc. Nephrol.,* **14,** 2894-2901.

20. Liu, J., X. Zeng, H. G. Hong, Y. Li, and p. Fu, 2017: The association between body mass index and mortality among Asian peritoneal dialysis patients: A meta-analysis. *PLoS One*, **12,** e0172369.

21. Zhou, H., L. Cui, G. Zhu, Y. Jiang, X. Gao, Y. Zou, M. Yang, H. Liu, J. Di, Y. Zong, and J. Pan, 2011: Survival advantage of normal weight in peritoneal dialysis patients. *Renal. Failure,* **33,** 964-968.

22. Kiran, V. R., T. Y. Zhu, T. Yip, S. L. Lui, and W. K. Lo, 2014: Body mass index and mortality risk in Asian peritoneal dialysis patients in Hong Kong—impact of diabetes and cardiovascular disease status. Perit. Dial. Int., **34,** 390-398.

23. Prasad, N., A. Sinha, A. Gupta, R. K. Sharma, D. Bhadauria, and A. Chandra, 2014: Effect of body mass index on outcomes of peritoneal dialysis patients in India. *Perit. Dial. Int.,* **34,** 399-408.

24. Nessim, S. J., P. Komenda, C. Rigatto, M. Verrelli, and M. M. Sood, 2013: Frequency and microbiology of peritonitis and exit-site infection among obese peritoneal dialysis patients. *Perit. Dial. Int.,* **33,** 167-174.

25. Ong, L. M., C. C. Chang, Wee, H. C., P. Subramaniam, H. Zainal, and B. L. Goh, 2017: Risk of Peritoneal Dialysis-Related Peritonitis in a Multi-Racial Asian Population. *Perit. Dial. Int.*, **37,** 35-43.

26. Liem, Y. S., J. L. Bosch, and M. G. Hunink, 2008: Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis. *Value Health,* **11,** 733-741.

Chapter 50

Peritoneal Dialysis in Diabetic End Stage Renal Disease

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Peritoneal Dialysis in Diabetic End Stage Renal Disease

The number of patients with ESRD is increasing in the world due to aging populations, longer life expectancy, increasing access to renal replacement therapies (RRT), and higher incidence of diabetes mellitus and hypertension.

Presently, dialysis is the main therapy to prevent death from uremia, because donor kidneys are in short supply, and survival of these patients is still a major concern. Diabetes mellitus is a leading cause of ESRD even in India. In fact, diabetic nephropathy was found to be the commonest cause of ESRD in India accounting to 31% of total ESRD aetiologies [1].

As per recent Indian Council of Medical Research data, prevalence of diabetes in Indian adult population has risen to 7.1%, (varying from 5.8% in Jharkhand to 13.5% in Chandigarh) and in urban population (over the age of 40 years), the prevalence is as high as 28% [2, 3, 4].

Potential benefits of Peritoneal Dialysis (PD) in diabetics

1. Home based continuous therapy which is beneficial over centre based therapy [5].
2. Slow sustained ultrafiltration which is more physiological leading to better quality of life [6, 7].
3. PD avoids complications inherent to HD (because of rapid, intermittent removal of solutes and water & extracorporeal circuit) like dialysis induced hypotension, coronary ischemia and arrhythmias [8].
4. PD is not associated with complications like "HD induced myocardial stunning, a new aspect of cardiovascular disease in CKD [9, 10].
5. No need for vascular access and thereby avoiding related complications like thrombosis and infections.
6. Avoids peripheral and coronary steal syndromes.
7. Cardiac load due to an arteriovenous fistula on heart is avoided.
8. Diabetes is an independent factor for faster decline in RRF [11].
9. "PD first" is a rational way to preserve reduced renal function (RRF) in diabetics with ESRD [12, 13].
10. The risk of RRF loss is 65% lower in PD patients than in HD [14].
11. RRF translates into decreased fluid overload, low cardiac stress and better elimination of advanced glycosylation end products and decreased risk of glucose degradation product accumulation.
12. Less chance of progressive diabetic retinopathy.
13. Fewer events of haemorrhagic retinopathy, as there is no need for systemic heparinization [15].

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14. PD allows good haemoglobin targets maintenance at lower erythropoietin doses, with both clinical and economic advantages [16].
15. Lower risk of contracting certain blood-borne diseases, like hepatitis C; the prevalence of anti-HCV antibodies in patients on dialysis was significantly lower in PD than in HD patients [17].
16. PD is associated with lower rates of delayed graft function after transplantation possibly due to lower risk of hypotension and hypervolemia particularly relevant in diabetic patients prone to hemodynamic intolerance [18].
17. PD protects patients from the HD-induced recurrent regional ischemia that leads to increased endotoxin translocation from the gut. Resultant endotoxemia is associated with systemic inflammation, markers of malnutrition, cardiac injury, and reduced survival [19].

Potential disadvantages of PD in diabetics:

1. Glucose absorption from dialysate:

Overall, 60–80% of glucose-containing PD solution instilled into the peritoneal cavity is absorbed, corresponding to daily intake of 100–300 g glucose.
– Hyperglycemia

– Weight gain

– Hypertriglyceridemia

– Peritoneal membrane changes

- Exposure to advanced glycosylated end products

(AGEs) and glucose degradation products (GDPs)

All these factors trigger the production of reactive oxygen species (ROS) and induce an inflammatory cascade leading to blockade of insulin action and normal lipoprotein metabolism [20].

Waist circumference is not a correct parameter to evaluate obesity due to the presence of the Tenchkoff catheter and potential residual peritoneal dialysate inside the abdominal cavity.

The use of body mass index (BMI) is also a biased factor. Increased body mass is mainly due to fat and has a different prognostic meaning than body mass related to more muscle.

Patients on PD with a high BMI with high muscular mass have a survival advantage, compared with those with high BMI but low muscular mass and have an enhanced risk of cardiovascular death [21].

Patients on PD frequently gain weight (fat mass), especially during the first year of PD therapy and particularly if they have diabetes or have a high BMI at initiation.

This is not always related to glucose absorption. This can be countered by the use of icodextrin solution in the first 36 months [22].

Factors associated with the higher percentage of fat mass gain over time on PD were age, diabetes, gender (female) and non-icodextrin group.

HbA1c was the significant risk factor for all-cause mortality after related variables were adjusted and also significantly predicted mortality in these patients [23]. HbA1c underestimates the glucose level in diabetic patients on PD which is secondary to the use of erythropoietin (means a larger proportion of circulating erythrocytes have not been around long enough for sufficient glycosylation of haemoglobin).

A greater predictive value can be achieved with the use of glycated albumin which measures glycemic control over the preceding 2 weeks and is not affected by serum albumin concentrations [24].

Blood glucose measurements in patients receiving icodextrin must be done with a glucose-specific method to avoid interference by maltose, a metabolite of icodextrin. Glucose dehydrogenase pyrroloquinolinequinone or glucose dye oxidoreductase-based methods must not be used.

Diabetic patients have a minimal increase in insulin requirement after initiation of PD *per se*, but the dosage of insulin increases markedly after exposure to hypertonic glucose solution [23].

Fluid overload (hyperglycemia activates thirst mechanism): In turn, fluid overload implies use of more hypertonic bags negatively impacting glycemic control and peritoneal integrity, therefore creating a vicious circle

Peritoneal albumin loss

Hyperinsulinemia

Central obesity

Peritoneal infection

Membrane fast transport status (GDP-inflammation-Neoangiogenesis-increased permeability-fast transporter status).

Neutral effects of dialysis modality in diabetics

1. No consistent evidence exists to show that diabetics have more infections (peritonitis or exit site).
2. No consistent evidence exists to prove a higher incidence of EPS in diabetic *vs.* non-diabetics on PD.

Choice of PD fluid in diabetics

Glucose containing solutions have two main effects that have a great bearing on diabetes control and its downstream consequences: All glucose containing solutions (1.5, 2.5 and 4.5) produce hyperglycemia and hyperinsulinemia irrespective of peritoneal membrane status, which is further modified as per peritoneal membrane transporter status. With use of Icodextrin (**Table 1**), the two main effects of glucose containing solutions, **i.e,** hyperglycemia and hyperinsulinemia can be avoided [26].

Table 1: Icodextrin as a PD Fluid

CHO:carbohydrate per 2L	**Icodextrin 150 gm**	**2.5% dextrose 45.4 gm**	**4.5% dextrose 77.2 gm**
% Absorbed/8hour dwell	25	86	86
Approx.g of CHO absorbed/dwell	37.5	39	66
Approx. Kcal/dwell	150	156	266

Redrawn from: Gokal *et al*, 2002.

What makes Icodextrin unique?

- Icodextrin is a glucose polymer.
- Least absorbed through peritoneum.
- Only way of absorption is through peritoneal lymphatics.
- Minimal extracellular metabolism in humans due to absence of enzyme maltase extracellularly.
- No perceivable hyperglycemia or hyperinsulinemia.
- Small amount that forms glucose occurs intracellularly.
- Icodextrin is functionally a "non-glucose" osmotic agent [27].
- Improves glycemia control and reduces total insulin requirement per day
- Absence of fluctuations in blood glucose levels improves ultrafiltration in patients with poor glycemic control [28].
- Icodextrin use is also seen useful in long term control of diabetes and better preservation of CAPD as witnessed by reduction is serum insulin levels and enhanced insulin sensitivity when used as a long night dwell in CAPD [29].
- Lower weight gain in long term as compared to glucose containing solutions [30].
- Lipid composition also varies: Hyperglycemia and hyperinsulinemia both favour production of apolipoprotein B and thereby increase LDL indirectly. This is not seen with icodextrin [31].

Icodextrin also scores better to glucose in terms of metabolic and laboratory interactions of PD solutions (**Table 2**).

Table 2: Metabolic and Laboratory Interactions of PD Solutions

	Dextrose solutions	Icodextrin
Metabolic Effects		
Glucose absorption	Yes	No
Hyperglycemia	Yes	No
Hyperinsulinemia	Yes	No
Increased insulin sensitivity	No	Yes
Hyperlipidemia	Yes	No
Weight gain	Yes	No
Laboratory Effects		
Dilutional hyponatremia	No	Yes
Increased plasma osmolality	No	Slight
Increased alkaline phosphatase	No	Slight
Apparent decrease in serum amylase activity	No	Yes
Interference in enzymatic glucose assays	No	Yes
Interference with creatinine analysis	Yes	No

Redrawn from: Gokal *et al,* 2002.

Survival and outcomes in diabetic patients on PD

Large disparity exists in the results of studies evaluating the outcomes of diabetics on PD versus HD. Some studies have shown benefit of one modality over the other, while others showed no difference. Large heterogeneity is reported in the study design, patient background (including age, dialysis vintage, comorbidities) and statistical methods used.

Vonesh *et al,* systematically reviewed 6 large scale registries and 3 prospective cohort studies that compared mortality among ESRD patients on HD *vs* PD, conducted in the US, Canada, Denmark and the Netherlands [25].

- Non-diabetics and younger diabetics (18-44 years) have superior or equivalent survival rates with PD compared with HD.
- In the U.S.A., diabetic ESRD patients > 45years have a better survival with HD than PD, whereas in Canada and Denmark, there is no survival difference between PD and HD in this group.
- PD offers an equal or lower mortality rate overall compared to HD in the first 1-2 years of dialysis therapy; thereafter the results vary by subgroup.
- In addition to DM status, both age and the presence of co-morbidities influence the effect of dialysis modality on survival.

Outcome studies in Indian patients:

Outcome studies in Indian population are limited; a study from India comparing quality of life and outcomes in a cohort of mixed diabetic and non-diabetic population between HD and PD was published in 2015 [32].

Diabetic CAPD patients have significantly better quality of life (QoL) in physical as well as psychological aspects and have significantly lower mortality when compared with patients on HD [32].

Strategies to improve outcomes of PD in diabetic ESRD patients

1. Preservation of RRF: Avoiding nephrotoxins like contrast exposure, NSAIDS, aminoglycosides and intravascular volume depletion
2. Mininmising cardiovascualr risk: Diet counselling, promoting physical activity to avoid obesity; control of dyslipidemia (ACEI/ARB, statins, β-blockers and apsirin).
3. Patient education.
4. Early nephrologist referral (when eGFR falls < 30 ml/min/1.73m^2).

PD specific strategies

1. Control of Fluid Overload***:*** Control of blood pressure, weight and oedema (using high dose loop diuretics, use if icodextrin and APD).
2. Use of low GDP solutions, glucose sparing regimens and individualized low calcium solutions: Avoidance of hypertonic bags; use of Bi/Tri compartment bag solutions.
3. Nutritional evaluation and support: Using SGA (subjective global assessment), nPNA (protein equivalent of nitrogen appearance, serum albumin and lipid profile. Enteric supplements and peritoneal supplement (nutirneal once a day).
4. RAAS blocking drugs for all: ACEI and ARB should be used as first antihypertensive drugs due to possible protective effects in the peritoneal membrane status [33].
5. Increasing PD technique survival: Optimising PD solutions as per PET status.

Our centre (SVIMS) experience of PD in diabetic CKD patients:

Data from 138 patients of SVIMS in the past 5 years (2012-2017) is presented in **Table 3**.

Table 3: Patient Data from SVIMS

	DIABETIC ESRD	**NON-DIABETIC ESRD**
Total Patients (138)	85	53
Peritonitis (Episodes Per Catheter Year)	3.9	3.1
Catheter Removals (11)	4	7
Shifted To Hd (1)	0	1
Underwent Renal Transplanation	0	4
Death (20)	16	4

References

1. Rajapurkar, M. M., G. T. John, A. L. Kirpalani, G. Abraham, S. K. Agarwal, A. F. Almeida, S. Gang, A. Gupta, G. Modi, D. Pahari, R. Pisharody, J. Prakash, A. Raman, D. S. Rana, R. K. Sharma, R. N. Sahoo, V. Sakhuja, R. R. Tatapudi, and V. Jha, 2012: What do we know about chronic kidney disease in India: first report of the Indian CKD registry. *BMC Nephrol.,* **13,** 10-17.

2. Raman, R., S. Ganesan, S. S. Pal, V. Kulothungan, and T. Sharma, 2014: Prevalence and risk factors for diabetic retinopathy in rural India. Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study III (SN-DREAMS III), report no 2. *BMJ Open Diabetes Res. Care,* **2,** e000005.

3. Anjana, R. M., R. Pradeepa, M. Deepa, M. Datta, V. Sudha, R. Unnikrishnan, A. Bhansali, S. R. Joshi, P. P. Joshi, C. S. Yajnik, V. K. Dhandhania, L. M. Nath, A. K. Das, P. V. Rao, S. V. Madhu, D. K. Shukla, T. Kaur, M. Priya, E. Nirmal, S. J. Parvathi, S. Subhashini, R. Subashini, M. K. Ali, and V. Mohan, 2011: Prevalence of diabetes and prediabetes (impaired fasting glucose and/or impaired glucose tolerance) in urban and rural India: phase I results of the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study. *Diabetologia,* **54,** 3022-3027.

4. Mendelssohn, D. C., and A. Pierratos, 2002: Reformulating the integrated care concept for the new millennium. *Perit. Dial. Int.,* **22,** 5–8.

5. Kutner, N. G., R. Zhang, H. Barnhart, and A. J. Collins, 2005: Health status and quality of life reported by incident patients after 1 year on haemodialysis or peritoneal dialysis. *Nephrol. Dial. Transplant.,* **20,** 2159–2167.

6. Selby, N. M., and C. W. McIntyre, 2007: The acute cardiac effects of dialysis. *Seminars Dial.,* **20,** 220–228.

7. Dorairajan, S., A. Chockalingam, and M. Misra, 2010: Myocardial stunning in hemodialysis: what is the overall message? *Hemodial. Int.,* **14,** 447–450.

8. Selby, N. M., and C. W. McIntyre, 2011: Peritoneal dialysis is not associated with myocardial stunning. *Perit. Dial. Int.,* **31,** 27–33.

9. Bernardo, A., I. Fonseca, A. Rodrigues, M. J. Carvalho, and A. Cabrita, 2009: Predictors of residual renal function loss in peritoneal dialysis: is previous renal transplantation a risk factor? *Adv. Perit. Dial.,* **25,** 110–114.

10. Lang, S. M., A. Bergner, M. Topfer, and H. Schiffl, 2011: Preservation of residual renal function in dialysis patients: effects of dialysis-technique-related factors. *Perit. Dial. Int.,* **21,** 52–57.

11. Jansen, M. A. M., A. A. M. Hart, J. C. Korevaar, F. W. Dekker, E. W. Boeschoten, and R. T. Krediet, 2002: Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kid. Int.,* **62,** 1046–1053.

12. Moist, L. M., F. K. Port, S. M. Orzol, E. W. Young, T. Ostbye, R. A. Wolfe, T. H. Sheron, C. A. Jones, and W. E. Bloemberger, 2000: Predictors of loss of residual renal function among new dialysis patients. *J. Am. Soc. Nephrol.,* **11,** 556– 564.

13. Sato, K., and T. Babazono, 2000: CAPD in diabetic patients. *Clin. Dial.,* **16,** 2137–2142.

14. Richardson, D., D. Ford, J. Gilg, and A. J. Williams, 2009: UK renal registry 11th annual report (December 2008): chapter 9 haemoglobin, ferritin and erythropoietin amongst patients receiving dialysis in the UK in 2007: national and centre specific analyses. *Nephron Clin. Prac.,* **111,** 149–183.

15. Pereira, B. J. G. and A. S. Levey, 1997: Hepatitis C virus infection in dialysis and renal transplantation. *Kid. Int.,* **51,** 981–999.

16. Vanholder, R., P. Heering, A. Van Loo, W. V. Biesen, M. C. Lambert, U. Hesse, M. V. D. Vennet, B. Grabensee, 1999: Reduced incidence of acute renal graft failure in patients treated with peritoneal dialysis compared with hemodialysis. *Am. J. Kid. Dis.,* **33,** 934–940.

17. C. W. McIntyre, L. E. A. Harrison, M. T. Eldehni, H. J. Jefferies, C. C. Szeto, S. G. John, M. K. Sigrist, J. O. Burton, D. Hothi, S. Korsheed, P. J. Owen, K. B. Lai, and P. K. T. Li, 2011: Circulating endotoxemia: a novel factor in systemic inflammation and cardiovascular disease in chronic kidney disease. *Clin. J. Am. Soc. Nephrol.,* **6,** 133–141.

18. Fortes, P. C., T. P. de Moraes, J. G. Mendes, A. E. Stinghen, S. C. Ribeiro, and R. Pecoits-Filho, 2009: Insulin resistance and glucose homeostasis in peritoneal dialysis. *Perit. Dial. Int.,* **29,** 145–148.

19. van Laecke, S., N. Veys, F. Verbeke, R. Vanholder, and W. van Biesen, 2007: The fate of older diabetic patients on peritoneal dialysis: myths and mysteries and suggestions for further research. *Perit. Dial. Int.,* **27,** 611–618.

20. Cho, K. H., J. Y. Do, J. W. Park, and K. W. Yoon, 2010: Effect of icodextrin dialysis solution on body weight and fat accumulation over time in CAPD patients. *Nephrol. Dial. Transplant.,* **25,** 593–599.

21. Chen, K. H., J. L. Lin, D. T. Lin-Tan, C. W. Hsu, W. H. Huang, T. H. Yen, S. M. Weng, and C. C. Hung, 2010: Glycatedhemoglobin predicts mortality in

nondiabetic patients receiving chronic peritoneal dialysis. *Am. J. Nephrol.,* **32,** 567–574.

22. Inaba, M., S. Okuno, Y. Kumeda, S. Yamada, Y. Imanishi, T. Tabata, M. Okamura, S. Okada, T. Yamakawa, E. Ishimura, and Y. Nishizawa, 2007: Glycated albumin is a better glycemic indicator than glycated hemoglobin values in hemodialysis patients with diabetes: effect of anemia and erythropoietin injection. *J. Am. Soc. Nephrol.,* **18,** 896–903.

23. Vonesh, E. F., J. J. Snyder, R. N. Foley, and A. J. Collins, 2006: Mortality studies comparing peritoneal dialysis and hemodialysis: what do they tell us? *Kid. Int.,* **103,** 3–11.

24. Gokal, R., J. Moberly, B. Lindholm, and S. Mujais, 2002: Metabolic and laboratory effects of icodextrin. *Kid. Int.,* **62,** 62-71.

25. Holmes, C. J., and T. R. Shockley, 2000: Strategies to reduce glucose exposure in peritoneal dialysis patients. *Perit. Dial. Int.,* **20,** 31-41.

26. Mujais, S., K. Nolph, R. Gokal, P. Blake, G. Coles, Y. Kawaguchi, H. Kawanishi, S. Korbet, B. Lindholm, D. Oreopolous, B. Rippe, and R. Selgas, 2000: Evaluation and management of ultrafiltration problems in peritoneal dialysis. International Society for peritoneal dialysis Adhoc committee on Ultrafiltration Management in Peritoneal dialysis. *Perit. Dial. Int.,* **20,** 5-21.

27. Amici, G., M. Orrasch, G. Da Rin, and C. Bocci, 2001: Hyperinsulinism reduction associated with icodextrin treatment in continuous ambulatory peritoneal dialysis patients. *Adv. Perit. Dial.,* **17,** 80–83.

28. Wolfson et al, J Am SocNephrol 12:317A, 2001

29. Sniderman, A., K. Cianflone, P. O. Kwiterovich, T. Hutchinson, P. Barre, and S. Prichard, 1987: Hyperapo- betalipoproteinemia: The major dyslipoproteinemia in patients with chronic renal failure treated with chronic ambulatory peritoneal dialysis. *Atherosclerosis*, **65,** 257–264.

30. Makkar, V., M. Kumar, R. Mahajan, and N. S. Khaira, 2017: Comparison of Outcomes and Quality of Life between Hemodialysis and Peritoneal Dialysis Patients in Indian ESRD Population. *J. Clin. Diagnos. Res.,* **9,** 28–31.

31. Chiu, Y. W., and R. Mehrotra, 2010: Can we reduce the cardiovascular risk in peritoneal dialysis patients? *Ind. J. Nephrol.,* **20,** 59–67.

Chapter 51

Peritoneal Dialysis in Pregnancy

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Peritoneal Dialysis in Pregnancy

Introduction

Peritoneal dialysis (PD) can be used in three situations during pregnancy. Acute kidney injury (AKI) during pregnancy has successfully been treated with short term PD. Najar *et al,* reported from the Kashmir valley that 15% of the patients treated with PD for AKI occurring during pregnancy in 569 patients [1]. PD can also be started in a patient of chronic kidney disease (CKD) whose renal function deteriorates during pregnancy. Thirdly, a patient on CAPD can become pregnant.

Pregnancy is uncommon with advancing CKD especially in stage IV and stage V patients. This is due to the hormonal imbalance, menstrual irregularities, anaemia, loss of sexual activity, depression etc. Often the pregnancy is accidental and not planned. Very few centers in our country discuss the possibility of pregnancy in women of child bearing age with CKD. There is no clear data from our country on the conception rates. Banka et al reported the maternal and foetal outcomes of 51 pregnancies in women with CKD [2]. None of the patients were on dialysis before conception. There was a significant decline of GFR six weeks after delivery. Preeclampsia was seen in 17.6% of the patients. Three of the six patients were started on dialysis post pregnancy. Out of the 51 pregnancies 21.56% of live born infants were delivered preterm.

US Registry Data

A total of 2299 dialysis units listed by the health care finance administration in the US were surveyed to determine the frequency and course of pregnancy in the patients on dialysis [3]. This study was reported in 1998. Data was collected from 6230 women aged between 14-44 years (1699 were receiving PD and 4531 were receiving HD). Overall, 2% of the women became pregnant over a period of 4 years (2.4% of haemodialysis and 1.1% of PD patients). The infant survival was 40.2% in 184 pregnancies. It was better, *i.e.*, 73.6% in those women in whom dialysis was started after conception. The infant survival was not different between patients on HD and PD. There was a trend of better survival in women who received more aggressive dialysis. Maternal complications included two maternal deaths and five patients with hypertensive crisis. About, 79% of women had some degree of hypertension. Only 5.9% of women had a haematocrit more than 30% but only 26% women had received Erythropoietin. Overall, 84% of the infants were born premature. There was no difference in the maternal morbidity related to dialysis modality.

In the last decade pregnancy rates have gone up between 5% to 7.5% which has been reported from Saudi Arabia [4]. Similarly infant survival rates have also improved with almost 75% having
live births [5, 6].

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Diagnostic dilemma

Uremic patients have nausea and vomiting which could erroneously be attributed to it, when actually it could be due to pregnancy. There are instances where the dialysis intensity and modality were modified, assuming the symptoms were due to uraemia. Early pregnancy was missed in those cases. Ultrasound may be helpful in identifying pregnancy as well as assessing the gestational age. Human chorionic gonadotrophin (HCG) is partially cleared by the kidneys and serum levels are elevated in CKD. Hence, interpretation of HCG levels should be done with caution [7, 8].

Maternal complications

Risks to the mother and foetus are well known during pregnancy in patients on dialysis. Severe hypertension associated with its complications to the mother and prematurity are major concerns. Miscarriage, placental detachment, anaemia, infections, premature rupture of membranes, polyhydramnios, preeclampsia/eclampsia, haemorrhage and maternal death are other serious complications. Hypertension must be well controlled to maintain the diastolic blood pressure less than 80-90 mm of Hg. Hypertension due to volume overload should be managed by adequate ultrafiltration, whereas that due to preeclampsia may worsen tissue perfusion with aggressive ultrafiltration.

Complications to the mother undergoing CAPD include abdominal fullness and discomfort, poor drainage of effluent, progressive reduction in dwell volume due to increasing gestation and polyhydramnios. Bloody effluent in a non-pregnant individual is innocuous but in a pregnant woman heralds a catastrophe. Placental abruption and injury to the uterus can result in death. Peritonitis can result in preterm labour premature rupture of membranes, and stillbirth

Polyhydramnios occurs in 30-70% of the patients which is due to urea induced osmotic foetal diuresis. Increasing the dialysis dose helps in the management of this condition [9]. Patients undergoing PD have the additional mechanical influence on the uterus. Haemoglobin levels in the peritoneal fluid may be monitored for abortion or amniorrhexis.

Amenorrhea in patients on dialysis may delay the detection of pregnancy and could lead to continuation of dangerous drugs like ACE inhibitors and ARBs until late in pregnancy. This could lead to congenital malformations.

The outcome of pregnancy also depends on RRF. Since PD helps in maintaining RRF, it increases the chances of a successful pregnancy. The low rates of pregnancy in patients undergoing CAPD may be due to recurrent episode of peritonitis damaging the fallopian tubes or the hyperosmotic dialysate fluid preventing the transfer of ovum from ovary to fallopian tube [10].

Management issues

Intensive dialysis to keep the blood urea level between 34-38 mg/dl has been advocated to improve the outcome. Increasing the frequency of exchanges and reducing the dwell volumes to 800ml can help in achieving this. PD does not cause rapid shift of fluids and hence hemodynamic stability is maintained. To prevent malnutrition protein intake should be above 1.4 g/kg/day. Additional 20grams of protein is recommended for foetal growth. Energy requirement is 25 kcal/kg/day. Folic acid supplement of 1mg/day should be started from the first trimester. Placenta converts calcidiol to calcitriol and hence 25-OH vitamin D levels need to be maintained and supplemented if necessary.

Though PD is not associated with hemodynamic instability and heparin is not necessary as anticoagulant and may help in achieving a successful outcome, it has its own unique set of problems. Therefore, experts do not recommend switching haemodialysis to PD during pregnancy.

The most common maternal complication during pregnancy in patients on dialysis is hypertension occurring in about 42-80% of the patients [11]. If the patient has residual urine output, then proteinuria may appear or worsen indicating preeclampsia. Anuric patients need to be monitored closely for worsening of hypertension, as controlling it may prevent preeclampsia. The commonly used anti-hypertensive drugs include alpha methyldopa, labetalol and hydralazine, nifedipine, verapamil, clonidine and frusemide can be used safely.

Foetal complications

Prematurity, small for gestation and small birth weight infants are known to occur in patients on dialysis. Neonates have blood urea and creatinine levels higher than those born to mothers with normal renal function. This could result in osmotic diuresis and lead to significant volume depletion and electrolyte disturbances. Hence neonates should be closely monitored for such complications and treated promptly.

Peritoneal Dialysis during Pregnancy

Placing CAPD catheters during pregnancy can be done but foetal position can obstruct flow and dialysate leak may be a problem. Rigid catheters for initiating PD in pregnant women are contraindicated due to the risk of rupture of gravid uterus, laceration of blood vessels.

However, in the immediate post-partum period, careful placement of rigid catheter can be lifesaving, especially in resource poor settings. One should avoid the involuting uterus and the catheter can be placed 1-2 cm away from the fundus of the uterus. Low volume frequent exchanges can tide over the crisis until either renal function improves or HD is initiated.

Patient Reports

Cattran in 1983 reported a patient who became pregnant while on CAPD and suffered an intra uterine foetal death at 30 weeks of gestation [12]. Kioko in the same year described a diabetic patient with successful outcome when initiated on CAPD at 10 weeks of gestation [13]. PD did not interfere with the normal recovery from caesarean section. The largest series was reported in 1988 by Mark Redrow [14]. He described 8 consecutive pregnancies managed in 7 women on CAPD and or Continuous cycling peritoneal dialysis (CCPD), 5 patients were from one center and managed by the same physician. They showed that both CAPD and CCPD can be initiated during pregnancy. Based on their experience and success rate, they recommended that a patient on HD should be shifted to CAPD to achieve better outcomes. Peter Jakobi from Israel reported a patient who was initiated on PD at 24 weeks of gestation due to worsening of renal function [15]. She developed an episode of peritonitis at 34 week of gestation due to *E.coli* which was successfully treated with antibiotics and the patient spontaneously delivered a healthy baby weighing 2400 grams.

Susan Hou reported in 1993 a 20 year old woman who was initiated on CAPD at 12 weeks of gestation [16]. Although she was initially on 3 exchanges, this was increased to 4 exchanges at 32 weeks of pregnancy. Her haematocrit was well maintained with erythropoietin thrice weekly. She had mild polyhydramnios and she normally delivered a child weighing 2040 grams at 35 weeks. In 1992, Merit Gadallah reported the outcome of 3 women who became pregnant while undergoing CAPD [17]. Two of the 3 women successfully delivered healthy premature infants while the third pregnancy resulted in spontaneous abortion. The first women had a pregnancy at the age of 41 years. She was on 3 exchanges of PD. She delivered at 29 weeks of gestation spontaneously. The birth weight of the child was 1895 grams.

The second case was of a 27 year old woman who was on 4 exchanges of CAPD. This was increased to 5 exchanges per day. She remained normotensive throughout pregnancy and delivered spontaneously at 38 weeks of gestation a child of 2230 grams. The third woman was 39 year old and developed peritonitis at 24 weeks of gestation and was given intra peritoneal antibiotic. She delivered a still born baby but recovered from peritonitis later. In 2007, Karoly Schneider shared their experience of pregnancy in a patient on CAPD [18]. A 32 year old woman on CAPD with 4 exchanges daily desired to have a child and the pregnancy was planned and discussed. The diagnosis of gestation was made early and patient was regularly followed up. In the 18^{th} week of her pregnancy she underwent an amniocentesis after draining the peritoneal cavity. The amniocentesis did not show any genetic disorder. She was hospitalised in the nephrology ward from the 28^{th} week. Dialysate volume was adjusted according to her comfort. She underwent an elective caesarean section in her 35^{th} week. The PD was stopped for 24 hours and resumed later. She did not require HD. In 2013, Sharat Kumar *et al,* reported a successful outcome in a patient on CAPD from Imphal, India [19]. A 37 year old woman who was on 3 exchanges of PD was found to be pregnant at 28 weeks of

gestation. Her family wanted the child and hence the pregnancy was continued. Her exchanges were increased to 4. She was hospitalised throughout the pregnancy and delivered a pre term child normally without any complications. The child weighed 1.3 kilograms. Baby was in the neonatal ICU for 3 weeks and improved.

Conclusion

The conception rate in patients with CKD is increasing with increased longevity in dialysis patients. Counselling is important in child bearing age group women with CKD, so as to plan the pregnancy. Patients on PD pose peculiar problems during pregnancy. There is often a delay in diagnosis and increased maternal morbidity and premature delivery. CAPD can successfully be initiated and continued during pregnancy. Dose of dialysis may require to be increased however with reduced volumes. Close coordination between nephrologist, obstetrician, nutritionist and neonatologist is required to ensure a successful outcome of pregnancy.

References

1.Najar, M. S., A. R. Shah, I. A. Wani, A. R. Reshi, K. A. Banday, M. A. Bhat MA, and C. L. Saldanha, 2008: Pregnancy related acute kidney injury: A single center experience from the Kashmir Valley. *Indian J. Nephrol.,* **18,** 159-161.

2.Singh, R., N. Prasad, A. Banka, A. Gupta, D. Bhadauria, R. K. Sharma, and A. Kaul, 2015: Pregnancy in patients with chronic kidney disease: Maternal and fetal outcomes. *Indian J. Nephrol.,* **25,** 194-199.

3.Okundaye, I., P. Abrinko, and S. Hou, 1998: Registry of pregnancy in dialysis patients. *Am. J. Kid. Dis.,* **31,** 766–773.

4.Souqiyyeh, M. Z., S. O. Huraib, A. G. Saleh, and S. Aswad, 1992: Pregnancy in chronic hemodialysis patients in the Kingdom of Saudi Arabia. *Am. J. Kid. Dis.,* **19,** 235-238.

5.Jungers, P., and D. Chauveau, 1997: Pregnancy in renal disease. *Kid. Int.,* **52,** 871-885.

6.Cunningham, F. G., S. M. Cox, T. W. Harstad, R. A. Mason, and J. A. Pritchard, 1990: Chronic renal disease and pregnancy outcome. *Am. J. Obstet. Gynecol.,* **163,** 453-459.

7.Buckner, C. L., L. Wilson, and C. N. Papadea, 2007: An unusual cause of elevated serum total beta HCG. *Ann. Clin. Lab. Sci.,* **37,** 186–191.

8.Shenhav, S., O. Gemer, D. J. Sherman, R. Peled, and S. Segal, 2003: Mid trimester triple-test levels in women with chronic hypertension and altered renal function. *Prenat. Diagn.,* **23,** 166–167.

9.Luders, C., M. C. Castro, S. M. Titan, I. De Castro, R. M. Elias, H. Abensur, and J. E. Romão, 2010: Obstetric outcome in pregnant women on long-term dialysis: a case series. *Am. J. Kid. Dis.,* **56,** 77–85.

10.Hou, S. H., 2001: Conception and pregnancy in peritoneal dialysis patients. *Perit. Dial. Int.,* **21,** 290–294.

11.Hou, S. H., 1994: Frequency and outcome of pregnancy in women on dialysis. *Am. J. Kid. Dis.,* **23,** 60-63.

12.Cattran, D. C., and R. J. Benzie, 1983: Pregnancy in continuous ambulatory peritoneal dialysis patient. *Perit. Dial. Bull.*, **3,** 13-14.

13.Kioko, F. M., K. M. Shaw, A. D. Clarke, and D. J. Warren, 1983: Successful pregnancy in a diabetic patient treated with continuous ambulatory peritoneal dialysis. *Diabetes Care,* **6,** 298-300.

14.Redrow, M., L. Cherem, J. Elliott, J. Mangalat, R. E. Mishler, W. M. Bennett, M. Lutz, J. Sigala, J. Byrnes, M. Phillipe, and S. Hou, 1988: Dialysis in the management of pregnant patients with renal insufficiency. *Medicine*, **67,** 199-208.

15.Jakobi, P., G. Ohel, P. Szylman, A. Levit, M. Lewin, and E. Paldi, 1992: Continuous ambulatory peritoneal dialysis as the primary approach in the management of severe renal insufficiency in pregnancy. *Obstet. Gynecol.*, **79,** 808-810.

16.Hou, S., J. Orlowski, M. Pahl, S. Ambrose, M. Hussey, and D. Wong, 1993: Pregnancy in women with end-stage renal disease: treatment of anemia and premature labor. *Am. J. Kid. Dis.*, **21,** 16-22.

17.Gadallah, M. F., B. Ahmad, F. Karubian, and V. M. Campese, 1992: Pregnancy in patients on chronic ambulatory peritoneal dialysis. *Am. J. Kid. Dis.*, **20,** 407-410.

18.Schneider, K., S. Ferenczi, S. Vas, and Z. Papp, 2007: Pregnancy and Successful Full-Term Delivery in a Patient on Peritoneal Dialysis: One Center's Experience and Review of the Literature. *Dial. Transplant.*, **36,** 438-444.

19.Kumar, S. N., T. B. Singh, L. R. Sharma, and N. Salinita, 2013: Successful Pregnancy Outcome in a Patient Suffering from Chronic Kidney Disease Stage V Undergoing Continuous Ambulatory Peritoneal Dialysis - A Case Report. *Indian J. Perit. Dial.*, **2013,** 27-28.

Chapter 52

Peritoneal Dialysis in Cardiorenal Syndrome

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Peritoneal Dialysis in Cardiorenal Syndrome

Introduction

The incidence and prevalence rates of heart failure (HF) are rising due to population, epidemiological and health transitions. Based on disease-specific estimates of prevalence and incidence rates of HF, the estimated prevalence of HF in India due to coronary heart disease, hypertension, obesity, diabetes and rheumatic heart disease is expected to range from 1.3 to 4.6 million, with an annual incidence up to 1.8 million [1].

Both cardiac and renal diseases are extremely common in the population and frequently coexist. Cardiac disease is often associated with worsening renal function and *vice versa*. The coexistence of cardiac and renal disease significantly increases mortality, morbidity and complexity and cost of care [2]. Glomular filtration rate (GFR) has an inverse graded association with HF severity. Decreased GFR is one of the major predictors for admission for worsening HF and cardiovascular/all-cause mortality in such patients [3].

HF – Definition [4]

HF is a clinical syndrome in which patients have the following features:

1. Symptoms typical of HF: Breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling.
2. Signs typical of HF: Breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling, tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, and hepatomegaly.
3. Objective evidence of a structural or functional abnormality of the heart at rest Breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling, tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, and hepatomegaly and cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration.

Stages in the Development of HF [5]

There are several stages in the evolution of HF, as outlined by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines:

Stage A — High risk for HF, without structural heart disease or symptoms

Stage B — Heart disease with asymptomatic left ventricular dysfunction

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Stage C — Prior or current symptoms of HF

Stage D — Refractory end stage HF

Cardiorenal Syndrome – Definition

Ronco *et al*, [6] defined CRS as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of 1 organ may induce acute or chronic dysfunction of the other, and divided CRS into 5 different subtypes,

CRS type 1 (acute CRS)

Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive HF) leading to acute kidney injury.

CRS type II (chronic CRS)

Chronic abnormalities in cardiac function (e.g. chronic congestive HF) causing progressive and permanent chronic kidney disease (CKD).

CRS type III (acute renocardiac syndrome)

Abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis causing acute cardiac disorder (e.g. HF, arrhythmia, ischemia).

CRS type IV (chronic renocardiac syndrome)

CKD (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events.

CRS type V (secondary CRS)

Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction.

Pathophysiology of Cardiorenal Syndrome **(Figure 1)**

Type 2

CRS is characterised by chronic abnormalities in cardiac function (e.g., chronic congestive HF) causing progressive CKD.
The prevalence of renal dysfunction in chronic HF has been reported to be approximately 25% [7]. Chronic HF is likely to be characterised by a long-term situation of reduced renal perfusion, often predisposed to themicrovascular and macrovascular disease [8].

Renal hypoperfusion
One of the proposed mechanism is renal hypoperfusion secondary to altered hemodynamics. ESCAPE (Evaluation Study of Congestive HF and Pulmonary Catheterization Effectiveness) trial did not show any link between pulmonary artery

catheter-measured hemodynamic variables and serum creatinine in 194 patients [9]. The only link was with right atrial pressure, suggesting that renal congestion may be more important than appreciated. Clearly, hypoperfusion alone cannot explain renal dysfunction in this setting.

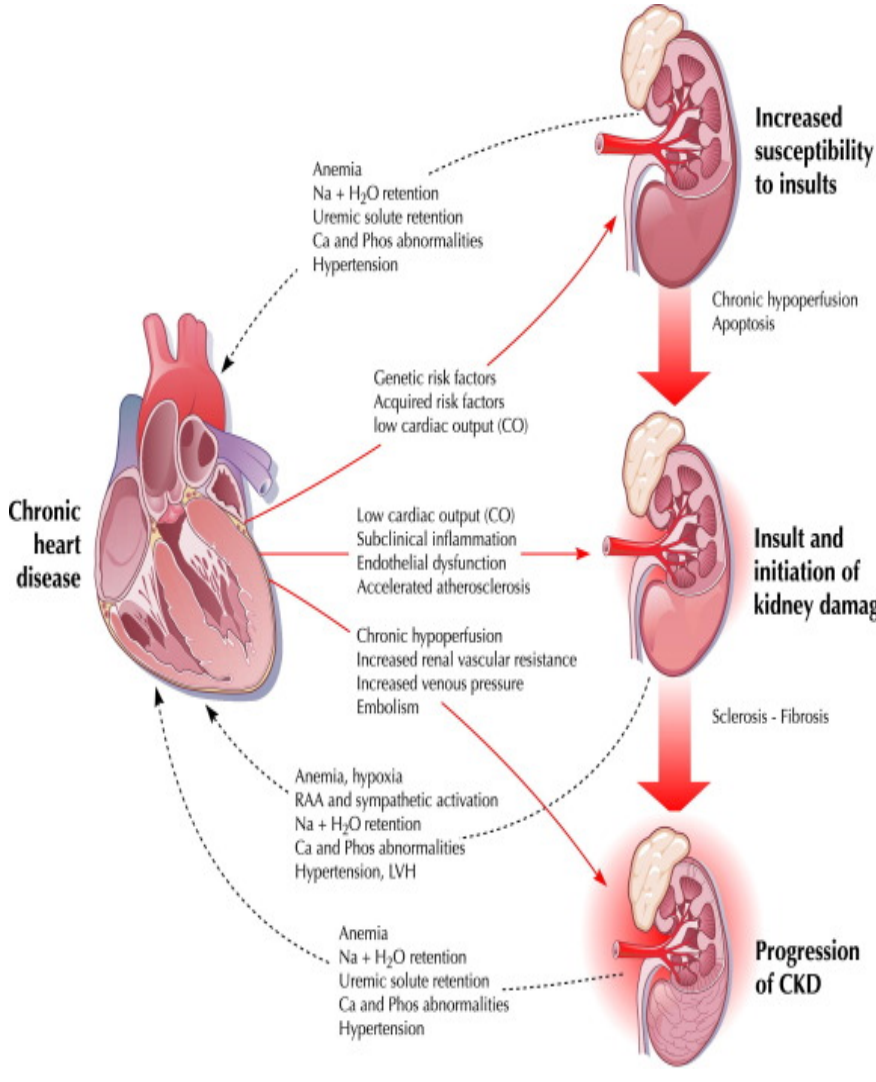

Figure 1: Pathophysiological Interactions between Heart and Kidney in Type 2 Cardiorenal Syndrome

Neurohormonal abnormalities

There is an excessive production of vasoconstrictive mediators (epinephrine, angiotensin, endothelin) and altered sensitivity and/or release of endogenous vasodilatory factors (natriuretic peptides, nitric oxide). Pharmacotherapies used in the management of HF may worsen renal function. Diuresis-associated hypovolemia, early introduction of renin-angiotensin-aldosterone system blockade, and drug-induced hypotension have all been suggested as the contributing factors [10].

Erythropoietin deficiency

There is an absolute or relative deficiency of erythropoietin which is more than expected for renal failure alone. Erythropoietin receptor stimulation in the heart may protect it from apoptosis, fibrosis and inflammation [11]. Patients with CRS type 2 receiving erythropoiesis stimulating agents not only have improvement in haemoglobin but also improved cardiac function, reduction of LV size and lowering of the B-type natriuretic peptide [12].

Drug related hemodynamic insult

The use of diuretics and vasodilators with underlying hemodynamic compromise leads to further propagation of renal dysfunction [13].

Myocardial depressant factors – role of inflammation

Both chronic heart failure (CHF) and CKD are known to cause elaboration of several pro-inflammatory mediators that can be detected at high concentrations in the tissues and blood stream. Traditional sources of inflammation include the heart and the kidneys which produce a wide range of pro-inflammatory cytokines in response to neurohormones and sympathetic activation. Elevation of TNF-α, IL-1β, and IL-6 in patients with both CKD and CHF may suggest a possible role for these cytokines in modulating inflammation incardiorenal syndrome [14].

Treatment Options

Diuretics

The standard therapy of congestive heart failure includes conventional diuretics – mainly loop diuretics combined with spironolactone in patients with GFR >30 ml/min/1.73 m^2, as well as sodium-blocking agents exerting their activity in other parts of the nephrons.

Mechanism of action

Diuretics in the treatment of congestive heart failure induce salt and water removal in a way that results in hypotonic urine, a temporary reduction of hydrostatic pressure and natriuresis [15, 16].

Problems

The long-term treatment with loop diuretics might result in electrolyte wasting, renal dysfunction and the progression of HF [15, 16]. Diuretic resistance is common. The possible causes are the delayed absorption of the diuretic, reduced secretion of the diuretic into the tubular lumen (its site of action), compensatory retention of sodium after the effective period of the diuretic and hypertrophy and hyperplasia of epithelial cells of the distal convoluted tubule [17]. The use of diuretic causes direct neurohormonal activation [18].

Ultrafiltration – extracorporeal route

Randomised controlled trials of ultrafiltration in hospitalised patients with congestion and decompensated HF have been conducted.

RAPID- CHF was a feasibility study comparing a single 8-hour course of peripheral venovenous ultrafiltration within the first 24 hours of admission to usual care with intravenous diuretics in 40 patients. This study was small but demonstrated that ultrafiltration in this setting was safe and effective compared with intravenous diuretics [19].

In UNLOAD, a larger follow-up study, 200 patients hospitalised with decompensated heart failure and congestion were randomly alloccated to either undergo early ultrafiltration or standard of care with intravenous diuretics. Even after adjusting for differences in the weight loss between the ultrafiltration and standard care groups, ultrafiltration was independently associated with improved outcomes [20].

Early Ultrafiltration in Patients with Decompensated HF and Observed Resistance to Intervention with Diuretic Agents (EUPHORIA trial) demonstrated that in patients with HF with volume overload and diuretic resistance, ultrafiltration before intravenous diuretics effectively and safely decreases the length of stay and readmissions. Clinical benefits persist at three months [17]. These studies not only suggested efficacy but also the safety of ultrafiltration in patients with refractory chronic congestive cardiac failure.

Problems with ultrafiltration by extracorporeal route

The procedure of hemodialysis (HD) exerts significant acute stress upon the cardiovascular system. There is an increasing body of evidence to suggest that subclinical ischemia is precipitated by dialysis and that this is a common phenomenon. The episodes of ischemia may potentially have a role in the development of cardiac failure, and as a trigger for arrhythmias. Therefore, reducing the acute impact of dialysis on the cardiovascular system would seem to be a desirable therapeutic target [21].

Exposure to the extracorporeal membrane during HD causes elevation of interleukin-1 (IL-1) and tumour necrosis factor alpha (TNF-α) release after

stimulation either by contaminated dialysate, non-biocompatible membrane material, or both. This release is followed by the stimulated secretion of a large number of other ILs, particularly IL-6, and the cytokine principally responsible for acute-phase protein synthesis. This pro-inflammatory state in not induced in the ultrafiltration by peritoneal route as there is no exposure to the bioincompatible material [22]. **Table 1** presents the limitations of loop diuretics and advantages of ultrafiltration [23].

Peritoneal ultrafiltration

Peritoneal ultrafiltration shows favourable results in patients with refractory HF [24, 25].

Mechanism

In this situation, an effective and gradual ultrafiltration decreases preload volume and optimises heart function [26].

Our experience with ultrafiltration by peritoneal route was effective in patients with AKI and refractory HF by improving renal and heart function, allowing to decrease the diuretic dose, stop inotropic drugs decrease ICU and hospital stay and hospital readmissions [27]. (**Table 2**)

Cytokines and humoral factors with specific myocardial depressant activity such as atrial natriuretic peptide, TNF, IL-1, and IL-6 have also been implicated in the development and progression of HF in these patients [28]. The molecular weight of those myocardial depressant factors ranges between 500 and 30,000 Daltons, which would allow their transperitoneal transfer and removal [24, 29-31].

Table 1: Limitations of Loop Diureticsand Advantages of Ultrafiltration

Limitation of loop diuretic	Advantages of ultrafiltration
Elimination of hypotonic Urine	Removal of isotonic plasma water
Diuretic resistance: lack of dosing guidelines	Precise control of rate and amount of fluid removal
Electrolyte abnormalities	No effect on plasma concentration of electrolytes
Reduced GFR	Improved GFR
Direct neurohormonal activation	No direct neurohormonal activation
Neither safety nor efficacy demonstrated in randomised controlled trials	Randomised controlled trial demonstrating safety, efficacy, and improved outcomes
Photosensitivity Skin rashes	
Hearing loss	
Bone loss	

Table 2: Summary of Experience with PD in 10 Patients with Heart and Renal Failure at Care Hospitals, Hyderabad, India

Pt	Gender	Age (years)	Cardiac diagnosis	EF% (before PD)	EF% (after PD)	Days of hospitalisation (before PD)	Days of hospitalisation (after PD)
1	M	63	ICMP	25	40	83	5
2	F	54	RHD	25	55	59	0
3	F	60	ICMP	20	30	52	17
4	F	57	ICMP	25	35	109	40
5	M	63	ICMP	25	55	120	8
6	M	58	ICMP	25	35	90	12
7	M	57	DCMP	18	30	12	0
8	M	59	RHD	22	28	36	0
9	M	70	DCMP	33	46	33	0
10	M	63	DCMP	26	40	40	0

Patient study

A 49 year old man was referred from cardiology department for persistent congestion (NYHA grade IV) despite on maximal dose of diuretic. He was bed ridden for last many months with NYHA grade IV breathlessness. He had ischemic dilated cardiomyopathy with ejection fraction of 25%. He was admitted in the hospital thrice during last one year because of recurrent congestive cardiac failure. He was dependent of diuretic and dobutamine infusion for last 7 days. There was a progressive worsening of azotemia (creatinine level increased from 2.2 to 4.8 mg/dl), hyponatremia (serum sodium 122 meq/L) and hyperkalemia (serum potassium 5.9 meq/L). This is a common scenario with patients with recurrent HF (cardiorenal syndrome type 2). Here, diuretic use is no longer effective and leads to a persistent fluid overload and azotemia.

In view of persistent congestion, despite on optimal dose of diuretic, worsening azotemia and dysectrolytemia, he was started RRT. He underwent two sessions of SLED followed by bedside percutaneous Tenchoff catheter by the nephrologist. CAPD exchanges started on the same day in ICU using automated cycler. Within 2 days, the inotropes were weaned off and the patient was shifted to the ward.

During the follow up after four weeks, he was symptom free (NYHA grade I) and on a single manual exchange per day. The left ventricular ejection fraction improved from 25% to 45%. Peritoneal ultrafiltration not only helped in symptomatic improvement due to decongestion but also recurrent hospitalisation could be avoided. There were no further events of HF requiring hospitalisation. The predicted one year mortality was 78% as per EFFECT HF Mortality Prediction. (www.ccort.ca/CHFriskmodel.aspx) [32]. This was symptom free at one year of follow up.

We studied 30 similar cases of refractory HF (**Table 3**). The data was analysed before starting peritoneal ultrafiltration and later four weeks after the treatment. There was a significant improvement in the clinical parameters. The predicted one year mortality of these patients based on EFFECT HF scores improved from 80% to around 10%.

Table 3: Summary of Clinical Improvement of Study Patients [33]

Parameters	**Pre- ultrafiltration (n= 30)**	**Post- ultrafiltration (n=30)**	**P- value**
Hb (g/dl); Mean ±SD	9.1 ± 1.17	10.7 ± 1.5	0.0001
Ejection fraction; Mean ±SD	29.3 ± 7.4	48.5 ± 11.8	0.0001
Duration of stay in hospital (days); Median ±SD	75.8 ± 43.3	7.8 ± 12.4	0.0001
Hospitalisation rate	30 (100%)	13(43.4%)	0.0001
NYHA Class III & IV	30 (100%)	14(46.6%)	0.0001

Hb=haemoglobin, NYHA = New York Heart Association

The symptomatic improvement (NYHA grade) and reduction in the days of hospitalisation was remarkable in improving the quality of life (QoL).

We had documented a significant decrease in the level of myocardial depressant factors (IL-1, IL-6, and TNF) after peritoneal ultrafiltration (**Table 4**). This helps to correct the underlying pathophysiological mechanism of inflammation (**Figure 2**) [33].

Treatment Protocol for Peritoneal Ultrafiltration

The patient with refractory HF usually needs 2 or 3 sessions of SLED or SCUF. The Tenckhoff catheter can be placed by the percutaneous or surgical method. Peritoneal fluid exchanges can be started on the same day. Automated cycler can be used initially as it allows small volume exchanges and avoids infections in the ICU. The cycler can be switched over to manual exchanges once the patient is out of ICU (**Figure 3)**. The prescription is modified for patients individually and depends on the volume status and native urine output.

Table 4: Effect of Peritoneal Ultrafiltration on Myocardial Depressant Factors [33]

Parameters	Pre-ultrafiltration (n= 30)	Post-ultrafiltration (n=30)	Mean difference	P- value
IL-1	24.1 ± 14.7	8.1 ± 4.04	-15.9 ± 12.1	0.0001
IL-6	130.6 ± 155.4	23.7 ± 17.6	-106.8 ± 156.5	0.001
TNF- alpha	44.6 ± 12.06	14.9 ± 5.07	-29.7 ± 10.5	0.0001
NT pro-BNP	3917.5 ± 4575.6	506.6 ± 594.9	-3410.8 ± 4620.4	0.0001

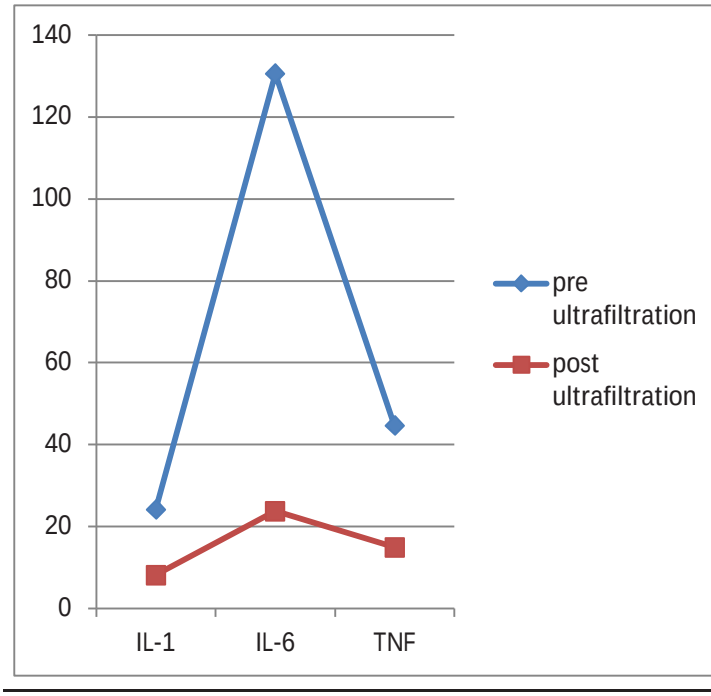

Figure 2: Decrease in Level of Myocardial Depressant Factors
IL-1 = interleukin 1, IL-6 = interleukin 6, TNF = tumour necrosis factor

Following fluids are used
2.5% Dextrose (2 litres) Dianeal bags

1.5% Dextrose (2 litres) Dianeal bags

7.5% Icodextrin (2 litres) Extraneal bags

Most of the patients initially require 2-3 exchanges per day which gradually decreases to 1-2 exchanges per day over 2-3 weeks.

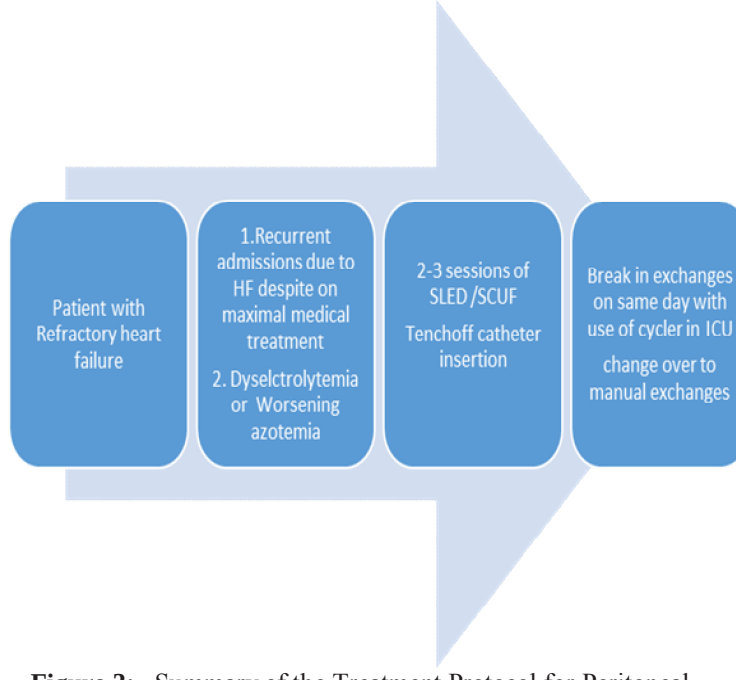

Figure 3:– Summary of the Treatment Protocol for Peritoneal Ultrafiltration
HF= HF, SLED=slow low efficiency dialysis, SCUF=slow continuous ultrafiltration

Advantages of Peritoneal Route over Extracorporeal Route

Many studies have shown that residual renal function is lost more rapidly in patients performing HD than in those on peritoneal dialysis (PD) [12-14]. Hence, ultrafiltration by peritoneal route has the advantage of preserving renal function and does not cause any cardiac adverse events. The removal of middle molecular weight

myocardial depressant factors (IL-1, IL-6, TNF-alpha) including atrial natriuretic peptide helps to correct the underlying pathophysiology [25].)

Conclusion

There is a more clear understanding of the cardiorenal syndrome with the central role of myocardial depressant factors in pathophysiology. The conventional treatment with diuretics and vasodilators is associated with a significant dyselectrolytemia and worsening renal parameters. The diuretic resistance which is a common phenomenon makes decongestion even more difficult. Ultrafiltration has a clear role in this situation. Peritoneal route clearly scores over extracorporeal route as it is associated with less hemodynamic stress on the myocardium and preserves residual renal function. The removal of myocardial depressant factors by peritoneal route helps in correcting underlying pathophysiology. There is a significant improvement in HF score and hence decreased mortality. Hence, ultrafiltration by peritoneal route seems to be an effective and safe alternative in patients with refractory chronic congestive cardiac failure.

References

1. Huffman, M. D., and D. Prabhakaran, 2010: Heart failure: epidemiology and prevention in India. *Natl. Med. J. India*, **23,** 283-288.
2. Forman, D. E., J. Butler, Y. Wang, W. T. Abraham, C. M. O'Connor, S. S. Gottlieb, E. Loh, B. M. Massie, M. W. Rich, L. W. Stevenson, J. B. Young, and H. M. Krumholz, 2004: Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J. Am. Coll. Cardiol.,* **43,** 61-67.
3. Shiba, N., and H. Shimokawa, 2011: Chronic kidney disease and heart failure--Bidirectional close link and common therapeutic goal. *J. Cardiol.*, **57,** 8-17.
4. The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology, 2008: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. *Eur. Heart J.,* **29,** 2388-2442.
5. Hunt, S. A., W. T. Abraham, M. H. Chin, A. M. Feldman, G. S. Francis, T. G. Ganiats, M. Jessup, M. A. Konstam, D. M. Mancini, K. Michl, J. A. Oates, P. S. Rahko, M. A. Silver, L. W. Stevenson, and C. W. Yancy, 2009: 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. *J. Am. Coll. Cardiol.,* **53,** 1-90.
6. Ronco, C., M. Haapio M, A. A. House, N. Anavekar, and R. Bellomo, 2008: Cardiorenal syndrome. *J. Am. Coll. Cardiol.,* **52,** 1527-1539.
7. Hillege, H. L., D. Nitsch, M. A. Pfeffer, K. Swedberg, J. J. McMurray, S. Yusuf, C. B. Granger, E. L. Michelson, J. Ostergren, J. H. Cornel, D. de Zeeuw, S. Pocock, and D. J. van Veldhuisen, 2006: Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circul.*, **113,** 671–678.
8. Bhatia, R. S., J. V. Tu, D. S. Lee, P. C. Austin, J. Fang, A. Haouzi, Y. Gong, and P. P. Liu, 2006: Outcome of heart failure with preserved ejection fraction in a population-based study. *N. Eng. J. Med.,* **355,** 260–269.
9. Nohria A, Hasselblad V, Stebbins A, D. F. Pauly, G. C. Funarow, M. Shah, C. W. Yanky, R. M. Callif, L. W. Stevenson, and J. A. Hill, 2007: Cardiorenal interactions—insights form the ESCAPE trial. *J. Am. Coll. Cardiol.,* **51,** 1268–1274.
10. Liang, K. V., A. W. Williams, E. L. Greene, and M. M. Redfield, 2008: Acute decompensated heart failure and the cardiorenal syndrome. *Crit. Care Med.,* **36,** 75–88.
11. Jie, K. E., M. C. Verhaar, M. J. Cramer, P. K. Vander, C. A. Gaillard, P. A. Deovandans, H. A. Koomans, J. A. Joles, and B. Braams, 2006: Erythropoietin and the cardiorenal syndrome: Cellular mechanisms on the cardiorenal connectors. *Am. J. Physiol. Renal. Physiol.*, **291,** 932–944.
12. Palazzuoli, A., D. S. Silverberg, F. Iovine, A. Calabrò, M. S. Campagna, M. Gallotta, and R. Nuti, 2007: Effects of betaerythropoietin treatment on left

ventricular remodeling, systolic function, and B-type natriuretic peptide levels in patients with the cardiorenalanemia syndrome. *Am. Heart J.,* **154,** 9–15.
13. Butler, J., D. E. Forman, W. T. Abraham, S. S. Gottlieb, E. Loh, B. M. Massie, C. M. O'Connor, M. W. Rich, L. W. Stevenson, Y. Wang, J. B. Young, H. M. Krumholz, 2004: Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am. Heart J.,* **147,** 331–338.
14. Colombo, P. C., A. Ganda, J. Lin, D. Onat, A. Harxhi, J. E. Iyasere, N. Uriel, and G. Cotter, 2012: Inflammatory activation: cardiac, renal, and cardio-renal interactions in patients with the cardiorenal syndrome. *Heart Fail. Rev.,* **17,** 177.
15. Loon, N. R., C. S. Wilcox, and R. J. Unwin, 1989: Mechanism of impaired natriuretic response to furosemide during prolonged therapy. *Kid. Int.,* **36,** 682–689.
16. Domanski, M., J. Norman, B. Pitt, M. Haigney, S. Hanlon, and E. Peyster, 2003: Diuretic use, progressive heart failure, and death in patients in the Studies of Left Ventricular Dysfunction (SOLVD). *J. Am. Col. Cardiol.,* **42,** 705– 708.
17. Costanzo, M. R., S. Mitchell, J. O'Sullivan, and P. Sobotka, 2005: Early Ultrafiltration in Patients with Decompensated Heart Failure and Observed Resistance to Intervention with Diuretic Agents. *J. Am. Col. Cardiol.,* **46,** 2047-2051.
18. Ikram, H., W. Chan, and E. A. Espiner, 1980: Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure. *Clin. Sci.,* **59,** 443-449.
19. Bart, B. A., A. Boyle, A. J. Bank, I. Anand, M. T. Olivari, M. Kraemer, S. Mackedanz, P. A. Sobotka, M. Schollmeyer, and S. R. Goldsmith, 2005: Relief for Acutely Fluid Overloaded Patients With Decompensated Congestive Heart Failure. *J. Am. Col. Cardiol.,* **46,** 2043-2046.
20. Costanzo, M. R., M. E. Guglin, M. T. Saltzberg, M. L. Jessup,B. A. Bart, J. R. Teerlink, B. E. Jaski, J. C. Fang, E. D. Feller, G. J. Haas, A. S. Anderson, M. P. Schollmeyer, and P. A. Sobotka, 2007: Ultrafiltration versus IV Diuretics for Patients Hospitalized for Acute Congestive HF: A Prospective Randomized Clinical Trial. *J. Am. Col. Cardiol.,* **49,** 675-683.
21. McIntyre, C. W., Effects of hemodialysis on cardiac function. *Kid. Int.,* **76,** 371–375.
22. Horl, W. H., 2002: Hemodialysis Membranes: Interleukins, Biocompatibility, and Middle Molecules. *J. Am. Soc. Nephrol.,* **13,** 62–71.
23. Bart, B. A., 2009: Should Ultrafiltration Be Used Preferentially Instead of Diuretics for the Initial Treatment of ADHF Patients? *Circul. Heart Fail.,* **2,** 499-504.
24. Cnossen, N., J. P. Kooman, C. J. Konings, J. M. van Dantzig, F. M. van der Sande, and K. Leunissen, 2006: Peritoneal dialysis in patients with congestive heart failure. *Nephrol. Dial. Transplant.,* 21, 63–66.
25. Gotloib, L., R. Fudin, M. Yakubovich, and J. Vienken, 2005: Peritoneal dialysis in refractory end stage congestive heart failure: a challenge facing a no win situation. *Nephrol. Dial. Transplant.,* **20,** 32–36.

26. Gabriel, D. P., J. Ferna´ndez-Cean, and A. L Balbi, 2007: Utilization of peritoneal dialysis in the acute setting. *Perit. Dial. Int.,* **27,** 328–331.
27. Vikranth, R., A. Thet, M. Harikrishna, and R. Chakravarthi, 2009: Role of CAPD in refractory congestive heart failure. *Ind. Soc. Perit. Dial. Cong.,* (abstract).
28. Diwan, A., T. Tran, A. Misra, and D. L. Mann, 2006: Inflammatory mediators and the failing heart: a translational approach. *Curr. Mol. Med.,* **3,** 161–182.
29. Horl, W. H., and W. Riegel, 1993: Cardiac depressant factors in renal disease. *Circul.,* **87,** 77– 82.
30. Zemel, D., A. L. Imholz, D. R. de Waart, C. Dinkla, D. G. Struijk, and R. T. Krediet, 1994: Appearance of tumor necrosis factor-alpha and soluble TNF-receptors I and II in peritoneal effluent of CAPD. *Kid. Int.,* **46,** 1422–1430.
31. Fincher, M. E., H. T. Campbell, A. H. Sklar, R. J. Caruana, B. O. Lightfoot, P. L. Cheek, K. L. Smith, and C. P. Hess, 1989: ANP is removed by peritoneal dialysis in humans. *Adv. Perit. Dial.,* **5,** 16–19.
32. Chakravarthi, M. R., H. Santosh, P. R. Vikranth, and M. Piyush, 2013: Ultrafiltration by peritoneal route in refractory chronic congestive cardiac failure. *J. Nephrol. Therapeutic.*, **2013,** 3-5.
33. Lee, D. S., P. C. Austin, J. L. Rouleau, P. P. Liu, D. Naimark, and J. V. Tu, 2003: Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA,* **290,** 2581-2587.

Chapter 53

Peritoneal Dialysis in Special Situations

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Peritoneal Dialysis in Special Situations

Peritoneal dialysis (PD) is now a well established, mature treatment modality for advanced chronic kidney disease (CKD). The 5 year survival of patients on peritoneal dialysis is currently equivalent to that of those on Hemodialysis [1]. PD as a therapeutic modality has carved out a niche for itself where it is considered equal to or superior to other renal replacement therapy (RRT) modalities. Discussed below are some of the special situations where PD may contribute substantially to the patient care.

Peritoneal Dialysis in Heart failure

The commonly used modalities to treat heart failure include non-pharmacological measures like salt and fluid restriction and use of pharmacological agents like diuretics, ACEI, ARB, vasodilators and beta-blockers. Most of the patients respond to these strategies, nevertheless, a small proportion are resistant to the above said measures [2].

In these patients, further aggressive approaches are needed like intravenous inotropes, cardiac resynchronization with dual chamber pacing, mechanical circulatory support to mention a few. With advanced therapeutic options becoming available and more affordable, the care of patients with ischemic heart disease has improved manifold with a resultant increased survival and growth in the number of prevalent patients with heart failure. The presence of co-existing renal impairment further complicates management of these patients [3].

Isolated ultrafiltration techniques have shown promise in the treatment of diuretic-resistant heart failure either by PD or with the help of extra corporeal circuits. There was initial enthusiasm for intermittently applied extracorporeal UF strategies following the EUPHORIA study [4].

Following it two randomised controlled trials, UNLOAD and CARRESS-HF, with a total of 388 patients were disappointing. UNLOAD showed greater weight loss in the UF group (5.0± 3.1 *vs.* 3.1 ± 3.5 kg; $p = 0.001$), and fewer re-hospitalisations (0.22 ± 0.54 *vs* 0.46 ± 0.76; $p< 0.05$), but no difference in secondary endpoints including dyspnea scores, renal function, 6-minute walking tests, or mortality [5]. CARRESS-HF study showed that UF was inferior to a stepped drug-based algorithm in preserving renal function at 96 hours. Ultrafiltration was also associated with a higher rate of adverse events (AEs) like renal failure, bleeding and catheter-related complications with no significant differences in the composite rate of death or rehospitalisation for HF (38% and 35%, respectively; P = ns) [6]. PD has been proposed as a therapeutic intervention for heart failure since 1949 but only recently has the interest in PD as a therapeutic modality for resistant heart failure has been rekindled [7].

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Possible Advantages of Peritoneal Dialysis in heart failure

A few benefits have been proposed while using PD in resistant heart failure:

1. PD offers slow removal of water and solute from intravascular compartment allowing for an adequate time for refilling from extra-vascular spaces which avoids hypotension in patients with vulnerable hemodynamics.

2. PD contributes to an enhanced potassium removal which may allow reinstitution of an ACEI/ARB or aldosterone antagonist which have proven mortality benefits in HF [2].

3. Higher diuretic doses leads to intravascular volume depletion and worsening of renal dysfunction which have been implicated in mortality in heart failure. A reduction in diuretic doses is possible with concomitant use of Isolated Ultrafiltration [8].

4. PD achieves ultrafiltration cheaply and is largely performed at home with its attendant benefits on lifestyle and economic independence.

5. PD does not activate the sympathetic nervous system, renin-angiotensin-aldosterone systems, often seen with diuretics and may even result in better preservation of residual renal function [3].

6. There is also a speculation that other harmful mediators may also be removed including urate, atrial natriuretic peptide, tumor necrosis factor (TNF), alpha-monocyte chemoattractant protein-1 (MCP -1) and interleukin 6 (IL-6), and a so-called myocardial depressant factor [9].

7. The peritoneal catheter acts as an access for draining ascites in cases of intractable right heart failure, thereby, reducing the intra abdominal pressure which has been shown to improve the renal function [10].

8. PD avoids the risks related to a vascular access with regards to catheter related blood stream infections in a patient with prosthetic heart valves and potential negative effects on cardiac function with high flow arterio venous fistulas [3].

PD regimens prescribed for heart failure use fewer exchanges, aimed predominantly at ultrafiltration, without the need to consider other solute removal targets. Furthermore, PD can be instituted in these patients with a percutaneous catheter approach avoiding general anaesthesia. In patients with no overt need for RRT, a single daily peritoneal exchange with Icodextrin has been shown to be efficacious to achieve the required fluid removal [11]. There is an added advantage of it being a home-based treatment and definitely offers obvious advantages over extracorporeal treatments performed in the hospitals or clinics.

Outcome of Heart Failure on Peritoneal Dialysis

There is convincing evidence that PD is an excellent therapy for HF. German Society of Nephrology feels that PD should be the treatment of choice for such patients [12] and have set up a registry for these patients. While a number of RCTs have been proposed, none as yet have been completed or reported, and the total number of patients in the literature remains relatively low.

Some argue that the encouraging results with PD in patients with heart failure is merely a 'Hawthorn effect' and that the benefits of PD may be due to ongoing and usually exceptional care of the PD team in addition to perhaps an interested research team [3].

Few observational studies have shown that PD reduces the duration of hospitalization with some showing a reduction in hospital days by almost 83% [14]. The improvement in symptoms with PD is not only due to the relief of pulmonary and tissue congestion as has been shown by few studies which have examined its effects on the heart by echocardiography. Improvements have been demonstrated in various parameters of cardiac function including LVEF [15], with icodextrin in particular showing a favorable effect on hemodynamics and left ventricular end-diastolic diameter [15]. Almost all the studies report symptomatic improvement and a reduction in NYHA grading in survivors [15].

Given the study designs of the published work, at the moment, it is unknown whether a therapeutic strategy including peritoneal dialysis improves the survival rate for this patient population[16]. The quality of life as assessed by Minnesota Living with Heart Failure Questionnaire was definitely better in patients on PD as compared to those on conservative measures.

Registry data from U.S and France have shown that patients with renal failure and heart failure do better on HD than on PD. However, in these large registry studies selection bias cannot be controlled for, nor can we know the UF prescribed or achieved, and there is no data on the osmotic agent used as early studies using mainly glucose-based regimes are likely to have been a lot less successful than those using icodextrin [3].

Another important factor determining the outcomes of patients on PD is patient selection. To ensure successful outcomes, one has to pick the correct patients at the right moment in their natural history [2]. The higher mental function, strength, and dexterity required to learn and perform the technique of PD and practice it successfully is often the only selection criterion on which to offer treatment, as this is the major player in determining outcomes.

Peritoneal Dialysis in Cirrhosis

The exact prevalence of CKD in patients with hepatic cirrhosis is not known. There is a definite increase in the frequency of the occurrence of this association due to the growing prevalence of both diseases [17].

Ascites is also a common accompaniment in patients with Chronic Kidney disease. The various causes of ascites include: coexisting liver disease, coexisting cardiovascular disease, peritonitis, severe protein depletion, and idiopathic ascites. RRT in these patients should be considered after weighing in certain factors which are more prevalent in them.

The optimal time for commencing dialysis in these patients is difficult to determine, since

1. Symptoms such as anorexia and weight loss could be due to both uremia and liver disease
2. Over-estimation of renal glomerular filtration rates (GFR) leads the physician to attribute the symptoms to the liver disease more than to uremia [18].

No clinical trials have yet been carried out that accurately evaluate the impact of the different dialysis options available to patients with CKD and cirrhosis. These patients pose a unique challenge with regards to maintaining hemodynamic stability in the presence of CKD, especially during hemodialysis sessions [17].

Cirrhotic patients with CKD are more prone to intradialytic hypotension during HD. These patients already have a reduced peripheral intravascular resistance which further compounds hemodynamic instability especially when there is a sudden decrease in the intravascular volume as occurs during ultrafiltration in hemodialysis.

They are characterized by the presence of intractable coagulopathy due to thrombocytopenia secondary to hypersplenism and deficiency of clotting factors due to failing liver function, contributing to increased risk of hemorrhage as well as gastrointestinal bleeding, thereby, limiting the use of heparin during hemodialysis.

Another inconvenience of HD is the sudden drastic changes in osmolarity and electrolyte levels that produce severe alterations in cerebral water levels, with consequent increased risk for developing encephalopathy [19, 20].

PD offers significant advantages with regards to several aspects in Cirrhotic patients with CKD. Some of them include:

1. PD being a continuous modality of therapy causes lesser hemodynamic instability and less rapid fluid and electrolyte shifts with its attendant benefits in cirrhotic patients.

2. It also allows for drainage of ascitic fluid thereby providing much needed symptomatic relief.

3. There is a lower risk of acquiring HCV infection among PD patients as this technique requires fewer blood transfusions and absence of vascular access points and extracorporeal blood circuits, which reduces the risk of parenteral exposure to the virus during this outpatient procedure [21, 22].

4. Patients on PD exhibit better preservation of residual renal function than those on hemodialysis with its attendant benefits.

5. In patients with failing liver function, complementary glucose input with the use of dextrose containing PD fluid is an added advantage [19].

Limitations of Peritoneal Dialysis

There are, however, few limitations to routine use of PD in these patients

1. Inadequate ultrafiltration and removal of solutes in the presence of ascites,

2. Increased risk of bacterial peritonitis due to transmigration of colonic bacteria

3. Protein loss in the dialysate further worsening already existent hypoalbuminemia [19, 20].

Durand *et al*, [23] described the functional behaviour of the peritoneum in four patients, observing an initial increase in UF capacity and high solute clearance. Selgas *et al,* [17] and Durand *et al,* [23] described a higher UF capacity in cirrhotic patients than in non-cirrhotic patients.

One of the problems associated with the loss of proteins through the effluent produced in these patients is the risk of malnutrition. However, in the study of cirrhotic patients treated with PD by Selgas *et al*., they observed an initial loss of proteins in the peritoneal membrane at the start of dialysis treatment as high as 30g per day but this loss later decreased to a mean of 7-15 g/day. This effect was observed during the first three months of dialysis treatment; later, the reduced protein loss was correlated with increased serum albumin levels and the patient's recovered body weight [17].

There are also some discrepancies regarding the higher rate of peritonitis associated with cirrhotic patients with ascites compared to the rate of peritonitis in patients without cirrhosis. The predominant type of organism causing peritonitis is also different in the study groups, with some showing a predominance of Gram positive Staphylococcus whereas others showing a predominance of Gram negative organisms.

De Vecchi *et al*, observed that the majority of the isolated microorganisms were Gram-positive, primarily Staphylococcus, and only two episodes were caused by

Gram-negative bacteria [24]. This result differs from other studies in which the more frequent cause was Gram-negative bacteria [17].

Spontaneous bacterial peritonitis, the pathology most frequently associated with ascites, is primarily caused by gram-negative bacteria. It is difficult to differentiate the infectious episodes that are due to the dialysis technique used from those secondary to the liver disease itself. In any case, continuous visualisation of the peritoneal liquid through a daily drain allows for an earlier diagnosis based on the turbidity of the dialysate and avoids the need for paracentesis in the case of suspected SBP [25].

Outcomes with Peritoneal Dialysis

Survival of patients who are on PD with hepatic cirrhosis is not well established. Few case series have suggested that these patients do relatively well when compared to those on conservative measures. Some studies have compared survival on patients on PD with and without hepatic cirrhosis and reported similar survival [24]. In spite of the scarce clinical observations, PD can be considered as a viable and effective dialysis technique for this group of patients.

Peritoneal Dialysis in Acute Kidney Injury

Acute kidney injury occurs in hospitals and is seen in up to 5% of hospitalized patients. 0.5% of the patients with AKI require dialysis [26]. Acute kidney injury occurs more frequently in ICU as part of the multi organ failure and is associated with higher mortality rate and increased dialysis requirement in ICU setting. PD has been in use since 1970 in patients with acute kidney injury especially in those who are [40].

1. Hemodynamically unstable
2. At risk of bleeding because of bleeding tendency
3. In pediatric patients with AKI both in ICU and non ICU settings
4. In patients with vascular access failure

PD as a therapy is simple and easy to use. PD is not commonly used in management of AKI in developed world due to the availability of newer HD techniques like continuous renal replacement therapies. The preferred modality in Dialysis requiring AKI usually is HD, though there are some circumstances where PD may be preferred over HD, like:

1. Acute PD is the preferred mode of RRT in children [27].
2. In patients with hemodynamic instability, PD is preferred over conventional HD [28]. PD can maintain adequate fluid, electrolyte, solute clearances, and acid base balance in patients with AKI.
3. In patients with AKI complicated by fulminant liver failure, PD has been used because it avoids need for anticoagulation. It reduces the risk of hypoglycemia and

hypothermia and corrects fluid and electrolyte disorders [29]. It may assist in the removal of toxins like ammonia, bilirubin, and free fatty acids.

4. PD can be used as route for delivery of nutrients like glucose and amino acids in severely ill patients admitted to ICU, may not be enough in severely malnourished individuals though [30-32].

5. Patients with AKI complicated by clinically significant hypothermia or hyperthermia who do not respond to conventional therapy may be managed with PD where heated or cold peritoneal solutions can be used to maintain core temperature [33].

6. In acute hemorrhagic pancreatitis, PD may help in removing bioactive substances presumed to be responsible for systemic inflammation [29]. However, a multicenter prospective study found no difference in the mortality or complication rate for patients who received standard supportive therapy with or without hourly 2-L PD exchanges for 3 days [34].

Outcomes with Peritoneal Dialysis in AKI

Earlier studies have shown that patients treated with PD had lower mortality rates and a higher incidence of renal recovery than did similar patients treated with HD [40]. Furthermore, some recent studies from the developing world conducted in AKI patients with PD have given promising results. A prospective study with 30 AKI patients was performed in Brazil in which the role of high volume continuous PD in patients with AKI was assessed [35]. Patients were assigned to a high-dose continuous PD *via* a flexible PD catheter and automated PD with a cycler. They concluded that High Volume Continuous PD was an effective therapy for AKI and it provided appropriate metabolic and acid-base control as well as adequate dialysis dose and fluid removal.

Another prospective, randomised, crossover study from India enrolled 87 patients with AKI and compared two different modalities of PD, tidal PD versus continuous PD [36]. It showed that both these modalities were adequate in mild to moderate hypercatabolic AKI patients from developing countries.

Studies comparing acute PD to other modalities of RRT are limited and the results of the conducted studies are conflicting. A prospective, randomised, controlled trial from Brazil compared high volume PD with daily hemodialysis in RRT of AKI due to ischemic ATN associated with sepsis in the majority of the patients [37, 38]. Hospital mortality was 58% in patients who were treated with high volume PD and 53% in patients who were randomly assigned to daily hemodialysis (P =0.71). Overall, 83% of the surviving patients in the PD group recovered kidney function as compared with 77% in the hemodialysis group and time to renal recovery was shorter in HVPD group as compared to DHD (7.2±2.6 *vs.* 10.6±4.7 days, P = 0.04), thereby yielding comparable results.

Phu *et al,* performed an open, randomised comparison of pumped venovenous hemofiltration and PD in patients with infection-associated AKI in an infectious

disease referral hospital in Vietnam [39]. Mortality rate of patients on PD was 47% compared to 15% on CRRT. The need for further RRT was higher in survivors of PD than those of hemofiltration. To conclude, PD remains an acceptable alternative to hemodialysis and CRRT for acute kidney injury especially in countries where technology for IHD and CRRT is not readily available.

References

1. Davies, S. J. 2013: Peritoneal dialysis—current status and future challenges. *Nat. Rev. Nephrol.,* **9,** 399-408.
2. Yancy, C. W., M. Jessup, B. Bozkurt, J. Butler, D. E. Casey, M. H. Drazner, G. C. Fonarow, S. A. Geraci, T. Horwich, J. L. Januzzi, M. R. Johnson, E. K. Kasper, W. C. Levy, F. A. Masoudi, P. E. McBride, J. J. V. McMurray, J. E. Mitchell, P. N. Peterson, B. Riegel, F. Sam, L. W. Stevenson, W. H. W. Tang, E.J. Tsai, and B.L. Wilkoff, 2013: ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circ*., **128,** 240–327
3. Puttagunta, H., and S. G. Holt**,** 2015: Peritoneal Dialysis for Heart Failure**.** *Perit. Dial. Int.,* **35,** 645–649
4. Costanzo, M. R., M. Saltzberg, J. O'Sullivan, and T. Kotsos, 2004: EUPHORIA trial: early ultrafiltration therapy in patients with decompensated heart failure and observed resistance to intervention with diuretic agents. *J. Card. Fail.,* **10,** 78.
5. Costanzo, M. R., Guglin, M. T. Saltzberg, M. L. Jessup, B. A. Bart, J. R. Teerlink, B. E. Jaski, J. C. Fang, E. D. Feller, G. J. Haas, 2007: Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J. Am. Coll. Cardiol.,* **49,** 675–83.
6. Bart, B., S. R. Goldsmith, K. L. Lee, M. M. Givertz, C. M. O'Connor, D. Bull, M. M. Redfield, A. Deswal, J. L. Rouleau, M. M. LeWinter, E. O. Ofili, L. W. Stevenson, M. J. Semigran, G. M. Felker, H. H. Chen, A. F. Hernandez, K. J. Anstrom, S. E. McNulty, E. J. Velazquez, J. C. Ibarra, A. M. Mascette, and E. Braunwald, 2012: Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N. Engl. J. Med.* **367,** 2296–304
7. Schneierson, S. J., 1949: Continuous peritoneal irrigation in the treatment of intractable edema of cardiac origin. *Am. J. Med. Sci.,* **218,** 76–79.
8. Eshaghian, S., T. B. Horwich, and G. C. Fonarow, 2006: Relation of loop diuretic dose to mortality in advanced heart failure. *Am. J. Cardiol.,* **97,** 1759–1764.
9. Ross, E. A., and A. Kazory, 2012: Ultrafiltration therapy for cardiorenal syndrome: physiologic basis and contemporary options. *Blood Purif,* **34,** 149–157.
10. Mullens, W., Z. Abrahams, G. S. Francis, D. O. Taylor, R. C. Starling, and W. H. Tang, 2008: Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. *J. Card. Fail.,* **14,** 508–514.
11. Basile, C., D. Chimienti, A. Bruno, S. Cocola, P. Libutti, A. Teutonico, and F. Cazzatto, 2009: Efficacy of peritoneal dialysis with icodextrin in the long-term treatment of refractory congestive heart failure. *Perit. Dial. Int.,* **29,** 116–118.
12. Schwenger, V., and A. B. Remppis, 2012: Renal replacement therapy for refractory heart failure. *Internist (Berl),* **53,** 823–832.
13. Davies, S., F. Lally, D. Satchithananda, U. Kadam, and C. Roffe, 2014: Extending the role of peritoneal dialysis: can we win hearts and minds? *Nephrol. Dial. Transplant,* **29,** 1648–1654.

14. Courivaud, C., A. Kazory, T. Crépin, R. Azar, C. Bresson-Vautrin, J. M. Chalopin, D. Ducloux, 2014: Peritoneal dialysis reduces the number of hospitalization days in heart failure patients refractory to diuretics. *Perit. Dial. Int.,* **34,** 100–108.
15. Paniagua, R., O. Orihuela, M. J. Ventura, M. Ávila-Díaz, A. Cisneros, M. Vicenté-Martínez, M. D. C. Furlong, Z. García-González, D. Villanueva M-.d.-C. Prado-Uribe, G. Alcántara, and D. Amato, 2008: Echocardiographic, electrocardiographic and blood pressure changes induced by icodextrin solution in diabetic patients on peritoneal dialysis. *Kid. Int.,* **73,** 125–130.
16. François, K, R. Claudio, and J. M. Bargman, 2015: Peritoneal Dialysis for Chronic Congestive Heart Failure. *Blood Purif,* **40,** 45–52.
17. Selgas, R., M. A. Bajo, G. Del Peso, R. Sánchez-Villanueva, E. González, S. Romero, E. Olivas, and C. Hevia, 2008: Peritoneal dialysis in the comprehensive management of end-stage renal disease patients with liver cirrosis and ascites: practical aspects and review of the literature. *Perit. Dial. Int.,* **28,** 118-122.
18. Howard, C. S., and I. Teitelbaum, 2005: Renal replacement therapy in patients with chronic liver disease. *Semin. Dial.,* **18,** 212-216.
19. Chaudhary, K., and R. Khanna, 2007: Renal replacement therapy in end-stage renal disease patients with chronic liver disease and ascites: role of peritoneal dialysis. *Perit. Dial. Int.,* **28,** 113-117.
20. Howard, C.S., and I. Teitelbaum, 2005: Renal replacement therapy in patients with chronic liver disease. *Semin. Dial.,* **18,** 212-216.
21. Sun, J., R. Yu, B, Zhu, J. Wu, and S. Larsen, 2009: Hepatitis C infection and related factors in hemodialysis patients in China: systematic review and meta-analysis. *Ren. Fail.,* **31,** 610-612.
22. Natoy, S. N., and B. J. Pereira, 2005: Hepatitis C virus in chronic dialysis patients. *Minerva Urol. Nephrol.,* **57,** 175-197.
23. Durand, P. Y., P. Freida, and J. Chanliau, 1993: Long-term follow-up in cirrhotic patients with chronic renal failure undergoing CAPD. *Perit. Dial. Int.,* **13,** 47.
24. De Vecchi, A. F., P. Colucci, F. Salerno, A. Scalamogna, and C. Ponticelli, 2002: Outcome of peritoneal dialysis in cirrhotic patients with chronic renal failure. *Am. J. Kid. Dis.,* **40,** 161-168.
25. Ruiz, S. R., E. G. Vilchez, T. P. G. Frías, T. M. M. Velázquez, L. B. Martos, T. J. Salcedo, and D. H. Marrero, 2011: The role of peritoneal dialysis in the treatment of ascites. *Nefrologia*, **31,** 648-655.
26. Brady H. R. and G. G. Singer, 1995: Acute renal failure. *The Lancet*, **346,** 1533–1540.
27. Reznik, V. M., R. W. Griswold, B. M. Peterson, A. Rodarte, M. E. Ferris, and S. A. Mendoza, 1991: Peritoneal dialysis for acute renal failure in children. *Pediat. Nephrol.*, **5,** 715–717.
28. K. D. Nolph, 1988: Continuous versus intermittent therapy for acute renal failure. Peritoneal dialysis for acute renal failure. *ASAIO Transact.*, **34,** 54–55.
29. R. Mactier, 1992: Non-renal indications for peritoneal dialysis Advances in peritoneal dialysis. *Conference on Peritoneal Dialysis*, 141–144.

30. De Graaff, M., A. H. Zegwaard, M. M. Zweers, A. Vlijm, D. R. de Waart, F. Vandemaele, D. G. Struijk and R. T. Krediet, 2010: The effects of a dialysis solution with a combination of glycerol/amino acids/dextrose on the peritoneal membrane in chronic renal failure. *Perit. Dial. Int.,* **30,** 192–200.
31. Asola, M., K. Virtanen, K. Nagren, S. Helin, M. Taittonen, H. Kastarinen, B. Anderstam, J. Knuuti, K. Metsärinne, and P. Nuutila, 2008: Amino-acid-based peritoneal dialysis solution improves amino-acid transport into skeletal muscle. *Kid. Int.*, **108,** 131–136.
32. Tjiong, H. L., T. Rietveld, J. L. Wattimena, J. W. van den Berg, D. Kahriman, J. van der Steen, W. C. Hop, R. Swart, and M. W. Fieren, 2007: Peritoneal dialysis with solutions containing amino acids plus glucose promotes protein synthesis during oral feeding. *Clin. J. Am. Soc. Nephrol.*, **2,** 74–80.
33. Reuler, J. B. and R. A. Parker, 1979: Peritoneal dialysis in the management of hypothermia. *J. Am. Med. Assoc*., **240,** 2289–2290.
34. Mayer, A. D., M. J. McMahon, and A. P. Corfield, 1985: Controlled clinical trial of peritoneal lavage for the treatment of severe acute pancreatitis. *New Eng. J. Med.*, **312,** 399–404.
35. Gabriel, D. P., G. V. R. do Nascimento, J. T. Caramori, L. C. Martim, P. Barretti, and A. L. Balbi, 2007: High volume peritoneal dialysis for acute renal failure. *Perit. Dial. Int.*, **27,** 277–282.
36. Chitalia, V. C., A. F. Almeida, H. Rai, M. Bapat, K. V. Chitalia, V. N. Acharya, and R. Khanna, 2002. Is peritoneal dialysis adequate for hypercatabolic acute renal failure in developing countries? *Kid. Int.,* **61,** 747–757.
37. Gabriel, D. P., J. T. Caramori, L. C. Martim, P. Barretti, and A. L. Balbi, 2008: High volume peritoneal dialysis vs daily hemodialysis: a randomized, controlled trial in patients with acute kidney injury. *Kid. Int.*, **108,** 87– 93.
38. Gabriel D. P., J. T. Caramori, L. C. Martim, P. Barretti, and A. L. Balbi, 2008: High volume peritoneal dialysis vs daily hemodialysis: a randomized, controlled trial in patients with acute kidney injury. *Kid. Int.,* **29,** 62–67.
39. Phu, N. H., T. T. Hien, N. T. H. Mai, T. T. H. Chau, L. V. Chuong, P. P. Loc, C. Winearls, J. Farrar, N. White, and N. Day, 2002: Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. *New Eng. J. Med.,* **347,** 895–902.
40. Ansari, N. 2011: Peritoneal Dialysis in Renal Replacement Therapy for Patients with Acute Kidney Injury. *Int. J. Nephrol*., 1- 10.

Chapter 54

Peritoneal Dialysis and Renal Transplantation

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Peritoneal Dialysis and Renal Transplantation

Introduction

Worldwide, kidney is the most commonly transplanted solid organ. As of 2008, in the United States 160,000 persons were living with a functioning kidney transplant. It is now firmly established that kidney transplantation offers the best survival advantage as compared to other available renal replacement therapies (RRT) [1]. However, there is a vast disparity between the demand and actual availability of the organs making kidney transplantation a scarce resource, even more so in the developing world. Despite active measures, the transplant waitlist timing in developing world is unlikely to change in the immediate foreseeable future. Peritoneal dialysis (PD) owing to its inherent characteristics offers a practical and viable RRT awaiting kidney transplant.

The unique characteristics of the peritoneal membrane allow its use as an endogenous dialyzing membrane. The peritoneum with a total surface are of 2 m^2 serves as a semipermeable membrane. It contains vast capillary network within the peritoneal connective tissue and is covered by a mesothelial cell layer. It allows solute and water transfer between the intravascular space and dialysate fluid dwelling in the peritoneal cavity. Since its first chronic use in the late 1970's, practice patterns of peritoneal dialysis (PD) have evolved continuously. Improvements in peritoneal access and catheter design, dialysate solutions, connectology, exit site management and peritonitis prevention strategies and the growing use of automated PD led to improved patient- and technique outcomes over the last decades.

Few of the challenges that the transplant nephrologists likely will have to deal with while maintaining patients on transplant waitlist are as below:

1. Modality education to ensure smooth initiation of most appropriate RRT
2. Preservation of residual kidney function
3. Adequate access for elective RRT initiation
4. Maintaining bacterial and viral infection free state
5. Avoiding sensitisation events
6. Effective redressal of cardiovascular comorbidity
7. Effective transfusion free anemia management
8. Hypertension management

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9. Preservation of nutritional status and attention to inflammation.

10. Autonomy of patient

11. Financial constraints of dialysis modality

PD is a patient friendly RRT that effectively addresses above issues comprehensively.

Why Peritoneal Dialysis?

Clinical Benefits of Home Peritoneal Dialysis in Potential Kidney Transplantation Candidates Survival

Data to compare survival between dialysis modalities are derived from large observational studies and registry analyses. Common findings of these studies are a similar overall patient survival between PD and HD with a potential survival benefit for PD in younger patients, non-diabetics and for patients receiving PD during their first 1-3 years of dialysis [2, 7].

A large United States Renal Data System (USRDS) analysis published by Mehrotra et al in 2011 compared survival for patients treated with in-center HD and home PD [2]. Overall, the relative risk of death for PD and HD over 5 years of follow-up was not significantly different (adjusted HR 1.03 with 95% CI 0.99-1.06) within their most contemporary cohort of patients starting dialysis between 2002 and 2004. Kumar *et al* used U.S. data from a registry of all Kaiser Permanente Southern California patients with ESRD to compare survival on PD and HD [3]. More than 1000 incident patients on PD between 2001 and 2013 were 1:1 propensity matched to incident HD patients who started dialysis after predialysis care and with a permanent vascular access.

After 9 years of follow-up, a similar survival for PD and HD was found with an early survival advantage for PD, for almost up to 3 and 2 years in an as-treated and intention-to-treat analysis, respectively [3]. Even survival data from countries that typically prescribe greater doses of HD (3 x 4hours weekly and more) confirm the overall survival similarity between PD and HD [4, 5]. Recent Canadian data do not show an early survival benefit for PD compared to HD when all patients starting dialysis had predialysis care or compared to HD patients starting dialysis with a permanent vascular access [6, 7]. A recent meta -analysis however seems to signal towards a lower 5 year mortality in PD than HD in post transplant period while there was no significant difference between the modalities in graft survival [8].

In conclusion, in the absence of randomised controlled trials and to the extent that registry data can be analysed, survival is comparable between the two modalities with a signal towards better survival from pre transplant PD modality.

Residual Renal Function

Residual renal function (RRF) not only contributes to small solute removal, but also allows for better volume control, larger molecular weight solute clearance and continued endocrine and metabolic function. Therefore, an important contributor to survival and overall health of dialysis patients is RRF [9, 10-13]. Hence, regular monitoring of RRF with 24 hours collection of urine, and strategies to preserve RRF need to be applied during follow-up of our waitlisted patients on PD [14].

Blood pressure should be well controlled while avoiding hypotensive episodes. Renin-angiotensin-aldosterone system (RAAS) blockers should be used as the first line agents if no contraindications exist. Although, diuretics have no effect on preserving solute clearance, their use will facilitate volume status control. Nephrotoxic agents such as aminoglycosides, nonsteroidal anti-inflammatory drugs and iodinated contrast agents should be avoided as far as possible. For patients with a failing kidney transplant starting PD, a plan regarding the (tapering of the) immunosuppressive regimen should be made.

Several studies suggest PD to be associated with a slower decline in RRF compared to HD [15-17]. Potential mechanisms for the superiority of PD in preserving RRF are its greater hemodynamic stability, reduced ischemic kidney insult and lack of inflammatory mediators generated from the extracorporeal hemodialysis circuit.

Dialysis Related Infectious Complications

Peritonitis remains a clinically important complication of PD. Morbidity resulting from PD-related peritonitis is significant, with some episodes being complicated by hospitalisation and temporary or permanent transfer to HD. Inflammatory processes during severe, recurrent, relapsing, repeated or refractory peritonitis can lead to peritoneal membrane failure and the need to discontinue PD. Current International Society of Peritoneal Dialysis (ISPD) guidelines recommend a PD programme's peritonitis rate to be less than 1/18 patient-months or 0.67/ year at risk [18]. Over the last decades, a declining rate of peritonitis has been described [19-21]. Major factors contributing to improved peritonitis rates are improvements in connectology, antibiotic prophylaxis before catheter insertion and at the time of invasive procedures, and antibiotics routinely at the exit site. Additional contributing factors include organizational aspects, such as continuous quality improvement initiatives and home visits [22]. PD-related peritonitis is a manageable complication, often as an outpatient, with high cure rates [21]. Hepatitis B (HBV) and Hepatitis C (HCV) have a special relationship to end stage kidney disease (ESKD) and are more prevalent in dialysis patients than the general population. Viral hepatitis is an important barrier to kidney transplantation and is a cause of significant morbidity and mortality while on transplant wait list. PD because of its inherent nature of being a home based individualised therapy with less need for blood transfusions, no reuse of dialyzers and absence of use of extra corporeal circuit is considered to be an important strategy for prevention of hepatitis and HIV

transmission in ESKD. In a study, the prevalence of anti HCV was 6.5% among CAPD patients compared to 28% among HD patients with the majority of anti HCV positive PD patients having history of hemodialysis exposure earlier on [23, 24].

Special Consideration for Patients with Congestive Heart Failure Awaiting Transplantation

Cardio vascular comorbidity is extremely common and presents a daunting task to the nephrologists to keep these patients active on the transplant waitlist. It is likely that good number of patients with uremic cardiomyopathy may benefit with transplantation. Controlling fluid status in patients suffering from congestive heart failure (CHF) complicated by progressive renal insufficiency, *i.e.,* cardiorenal syndrome type 2 (CRS2), is challenging, especially in the setting of diuretic resistance. In that case, renal replacement strategies are used for ultrafiltration. Theoretical advantages in favour of the use of PD rather than any form of intermittent or continuous hemodialysis (HD) are (i) gentle continuous ultrafiltration avoiding neurohormonal pathway activation, (ii) being a permanent outlet from the abdominal cavity and thus keeping intra-abdominal pressure and venous congestion at its lowest, (iii) removing sodium efficiently, (iv) improving potassium levels hence allowing (increased) use of RAAS-blockers and (v) offering these benefits at home. Retrospective studies evaluating clinical effects of PD in patients with CRS2 showed significant reduction in number and duration of hospitalisations after initiation of PD improved functional New York Heart Association (NYHA) classification and improvement in LVEF at an acceptable cost of PD-related morbidity [25-28]. Continuous ambulatory PD (CAPD) was the main PD modality in these studies, all limited by the absence of a comparator group treated with an alternative renal replacement modality.

A prospective study evaluating the effects of CAPD in CRS2, limited by a small sample size (n=25) and the absence of a HD comparator showed an improved quality of life (QoL), NYHA functional classification and 6 min walk test 6 and 24 weeks after the start of PD compared to baseline [29]. In the 6 months following PD start, this study also showed a decreased number of days hospitalised for acute heart failure compared to the 6 months prior to CAPD [29] Whether hospital admissions and length of stay (LOS) are reduced due to PD itself or because fluid status is better controlled, independently of the way this is achieved, is unclear. Indeed, hospitalisation number and duration for cardiovascular causes but not for all causes was reduced for both PD [Nightly intermittent PD (NIPD) or CAPD] and HD in a prospective non-randomised study evaluating beneficial effects of both the dialysis modalities. After initiation of dialysis, PD or HD, QoL and functional status improved [30]. In this study, cumulative survival of HD versus PD was not significantly different, although a beneficial trend for PD was noted. More (randomised) studies are needed to compare outcome differences between PD and HD as a strategy to control fluid balance in CRS2. Nonetheless, data regarding reduction in hospital admissions and LOS after initiation of PD in subjects suffering from CRS2 are consistent.

Therefore, PD should be considered as an excellent strategy to achieve fluid control in CRS2. Unexpectedly, a discrepancy is noted between outcomes of PD in CRS2 versus CRS4, a type of cardiorenal syndrome in which primary chronic kidney disease contributes to decreased cardiac function. A U.S. and a French retrospective registry-based study both showed higher mortality risks for patients with ESRD and CHF when treated with PD compared to HD. However, generalizability of these data is limited [31, 32]. The U.S. study applies to a 1990's population, an era prior to widespread icodextrin use, with short follow-up (2 years). Several factors warrant careful interpretation of the French study: CHF was only characterized as per nephrologists' judgement, no discrepancy was made between NYHA III and IV, and survival was only calculated from day 90, potentially underestimating HD-associated early mortality.

Nutritional Aspects of Capd Relevant To Transplantation

It is estimated that about 20-50% incident and prevalent patients on PD have protein energy malnutrition. There is a paradoxical occurrence of overweight and obesity with low visceral protein levels which may translate to perioperative morbidity. The PD fluid glucose load of 100-200g per day translating to 400 to 800 kcals has been attributed to contribute to overweight. KDOQI panel recommends a protein intake of 1.2-1.3gms/kg/day of protein in adult PD patient to maintain positive nitrogen balance [33].

Psychosocial Benefits of Home Peritoneal Dialysis

In contrast to in-center HD, PD offers greater flexibility to patients as to time management: (a) patients treated with PD are (or should be) trained to adapt the PD prescription to their daily activities if needed and (b) a PD clinic visit is scheduled every 4–12 weeks compared to thrice weekly for patients treated with in-center HD. Also, the technical simplicity of PD allows patients to perform dialysis while travelling, without the need for facility support. In every respect, PD offers increased autonomy and independence to patients suffering from ESRD compared to facility HD, and this is reflected in higher employment rates for patients treated with home PD compared to facility HD [34-36]. Evidence that the greater autonomy associated with PD leads to an improved QoL is weak although many studies suggest at least equivalent or better QoL for patients treated with PD compared to in-center HD [37-42]. As to patient satisfaction with their dialysis care, a prospective cohort study involving 37 dialysis centers in the U.S. showed patients treated with PD rated their care higher than did patients treated with facility HD [43]. Assisted PD, whereby PD is administered with the help of a trained caregiver, could support autonomy and independence of disabled or elderly persons suffering from kidney failure [44, 45]. These patient groups often experience a burden of transportation to the hemodialysis unit several times a week and might not be home hemodialysis candidates, given comorbidities or living circumstances.

Financial Benefits of Peritoneal Dialysis

The nature of PD itself, the decreased staff-to-patient ratio and lower overhead explains a lower actual cost for PD compared to HD from a healthcare system perspective, *i.e.* the payer [35, 46-51]. Both direct costs, expenditures borne by health care system, community and patient in addressing the illness, and indirect health care costs, productivity losses to society caused by the dialysis modality, are significantly reduced in patients treated with PD compared to HD [35, 49- 51]. PD bears an economic advantage even for patients presenting with PD technique failure [52]. For patients transitioning from HD to PD compared to HD only a significant financial benefit also has been described with savings mainly driven by dialysis cost savings. An important direct cost in patients on dialysis is related to the use of erythropoietin stimulating agents (ESA), modality wise it is self explanatory that the blood losses in HD clearly exceed that of PD. A large DaVita registry analysis comparing ESA use in prevalent PD and HD patients found 3-4 times higher ESA dose in HD compared to PD treated patients despite similar distribution of hemoglobin and even when adjusted for hemoglobin, case mix and malnutrition-inflammation syndrome [81]. It is evident that the actual cost for assisted PD is higher compared to self-care PD yet European and Canadian data shows assisted PD is still cost-effective when compared to in-center HD [54-56].

Few of the post transplant issues that need consideration are as below

1. Intraoperative surgical concerns relevant to PD access

2. Timing of PD catheter removal

3. PD in redo transplant waitlist candidates.

4. RRT modality and graft outcomes

Intraoperatively, the surgical team has to exercise utmost caution to avoid any breach to the peritoneum, in which case meticulous repair of the defect has to be undertaken to prevent any leakage of peritoneal or PD fluid into the graft surgical site which could lead to infection [57]. The risk factors and causative organism for post transplant peritonitis have been evaluated by Bakir *et al*, and about one third of the episodes occurred within 3 weeks of transplantation when PD was resumed [58]. Gram negative organisms were cultured in 40% while *Staphylococcus aureus* (33%), *S. epidermidis* (20%) and polymicrobial peritonitis constituted 7% of episodes. Risk factors attributed for peritonitis were previous history of peritonitis, male sex, exit site infection, peritoneal opening, visceral injury, number of rejections and permanent graft failure.

Currently, there is no consensus on the best time to remove PD catheter post transplant. The European Best Practice Guidelines are the only available guidelines that are relevant to the issue which propose that “the catheter can be left in situ 3-4 months despite a functioning graft; nevertheless, earlier removal after successful

transplantation is advisable (evidence level B)". In the absence of strong evidence based recommendations, the decision to retain PD catheter versus removal is based on transplant nephrologist's judgement based on possibility of delayed graft function (DGF) or high immunological risk scenario that might eventually lead to the possibility of continuation of PD [59].

Limited experience from Canada and United Kingdom provides strong supporting evidence that leaving PD catheters in place following renal transplantation is associated with substantially increased risk of catheter related infectious complications which occurred even when these catheters were not used post transplantation and non infectious complications with leakage of dialysate from wound site despite no disruption of peritoneal membrane impairing PD treatment in up to 20% of cases. Hence, they recommend removal of PD catheter at the time of transplantation with a caution that one would need HD support in case of DGF or acute allograft dysfunction [57]. Awaiting more robust evidence the PD catheter may be removed at the time of transplant surgery in recipients with low risk of DGF, while in those with high risk of DGF one may retain the catheter with a low threshold to remove the catheter once graft function stabilizes [57, 59].

Molnar *et al*, analysed data from scientific registry of transplant recipients (SRTR) on pre transplant dialysis modality and DGF and concluded similar DGF rates between HD and PD modalities, while all cause mortality post transplant was lower in patients on pre transplant PD modality [60]. Thomson *et al*, analysed DGF outcomes post transplantation based on dialysis modality HD versus PD and concluded that at 1, 6 and 12 months the graft functioning, patient survival, hospitalisations were similar between the two modalities [61]. A recent meta-analysis seems to suggest that pre transplantation PD was associated with lower risk of DGF compared to HD with a caveat that these results are unadjusted [8].

Each year about 2-3% kidney transplants fail and return to RRT. In failing transplant and those awaiting a redo kidney transplantation, there is a paucity of robust data on the outcomes related to PD as a RRT modality. The anecdotal recommendations available suggest a slow taper of immunosuppression (IS) with stoppage of antimetabolites on return to RRT, slow tapering of CNI over weeks and continuation of low dose prednisone while on PD to ensure preservation of residual kidney function and mitigate allograft immune intolerance. Jassal *et al*, suggest survival benefits outweigh the adverse effects of IS while on RRT [62]. Higher degree of IS is suggested to be maintained if redo kidney transplantation is expected in the foreseeable future. At times graft nephrectomy may have to be done for various reasons ranging from primary non-functioning of allograft owing to immunological, infectious or surgical complications and chronic rejection in later period. Graft nephrectomy may be straight forward early in the post transplant period but later on could pose serious technical challenges from dense pericapsular fibrosis and can lead to accidental compromise of peritoneal integrity needing temporary modality switch to HD.

In conclusion, the majority of patients presenting with kidney failure can be treated with PD while on wait list for kidney transplantation. PD is an effective dialysis modality with similar overall survival at lower cost compared to HD. Additional advantage of home PD is its intrinsic empowerment of the patient. Every patient preparing for renal replacement therapy should receive education concerning all options for dialysis including PD while awaiting kidney transplantation.

References

1. Srinivas, T. R., H. U. Meier-Kriesche, and J. D. Schold, 2010: Outcomes of Kidney and Pancreas Transplantation. In: Srinivas TR, Shoskes DA (eds.) *Kidney and Pancreas Transplantation A Practical Guide.* Current Clinical Urology. New York, USA, Springer, p. 155-177.

2. Mehrotra, R., Y. W. Chiu, K. Kalantar-Zadeh, J. Bargman, and E. Vonesh, 2011: Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Arch. Intern. Med.,* **171,** 110-118.

3. Kumar, V. A., M. A. Sidell, J. P. Jones, and E. F. Vonesh, 2014: Survival of propensity matched incident peritoneal and hemodialysis patients in a United States health care system. *Kid. Int.,* **2014**.

4. Yeates, K., N. Zhu, E. Vonesh, L. Trpeski, P. Blake, and S. Fenton, 2012: Hemodialysis and peritoneal dialysis are associated with similar outcomes for end-stage renal disease treatment in Canada. *Nephrol. Dial. Transplant.,* **27,** 3568-3575.

5. Marshall, M. R., R. C. Walker, K. R. Polkinghorne, and K. L. Lynn, 2014: Survival on home dialysis in New Zealand. *PLoS One,* **9,** e96847.

6. Quinn, R. R., J. E. Hux, M. J. Oliver, P. C. Austin, M. Tonelli, and A. Laupacis, 2011: Selection bias explains apparent differential mortality between dialysis modalities. *J Am Soc Nephrol,* **22,** 1534-42.

7. Perl, J., R. Wald, and P. McFarlane, 2011: Hemodialysis vascular access modifies the association between dialysis modality and survival. *J. Am. Soc. Nephrol.,* **22,** 1113-1121.

8. Bargman, J. M., K. E. Thorpe, and D. N. Churchill, 2001: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J. Am. Soc. Nephrol.,* **12,** 2158-2162.

9. Shemin, D., A. G. Bostom, P. Laliberty, and L. D. Dworkin, 2001: Residual renal function and mortality risk in hemodialysis patients. *Am. J. Kid. Dis.,* **38,** 85-90.

10. Szeto, C. C., T. Y. Wong, K. M. Chow, C. B. Leung, and P. K. Li, 2003: Are peritoneal dialysis patients with and without residual renal function equivalent for survival study? Insight from a retrospective review of the cause of death. *Nephrol. Dial. Transplant.,* **18,** 977-982.

11. Termorshuizen, F., F. W. Dekker, and J. G. van Manen, 2004: Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J. Am. Soc. Nephrol.,* **15,** 1061-1070.

12. Termorshuizen, F., J. C. Korevaar, and F. W. Dekker, 2003: The relative importance of residual renal function compared with peritoneal clearance for patient

survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Am. J. Kid. Dis.,* **41,** 1293-1302.

13. Blake, P. G., J. M. Bargman, and K. S. Brimble, 2011: Clinical Practice Guidelines and Recommendations on Peritoneal Dialysis Adequacy 2011. *Perit. Dial. Int.,* **31,** 218-239.

14. Moist, L. M., F. K. Port, and S. M. Orzol, 2000: Predictors of loss of residual renal function among new dialysis patients. *J. Am. Soc. Nephrol.,* **11,** 556-564.

15. Misra, M., E. Vonesh, J. C. Van Stone, H. L. Moore, B. Prowant, and K. D. Nolph, 2001: Effect of cause and time of dropout on the residual GFR: a comparative analysis of the decline of GFR on dialysis. *Kid. Int.,* **59,** 754-763.

16. Lang, S. M., A. Bergner, M. Topfer, and H. Schiffl, 2001: Preservation of residual renal function in dialysis patients: effects of dialysis-technique-related factors. *Perit. Dial. Int.,* **21,** 52-57.

17. Li, P. K., C. C. Szeto, and B. Piraino, 2010: Peritoneal dialysis-related infections recommendations: 2010 update. *Perit. Dial. Int.,* **30,** 393-423.

18. Kim, D. K., T. H. Yoo, and D. R. Ryu, 2004: Changes in causative organisms and their antimicrobial susceptibilities in CAPD peritonitis: a single center's experience over one decade. *Perit.Dial. Int.,* **24,** 424-432.

19. Perez Fontan, M., A. Rodriguez-Carmona, R. Garcia-Naveiro, M. Rosales, P. Villaverde, and F. Valdes, 2005: Peritonitis-related mortality in patients undergoing chronic peritoneal dialysis.

Perit. Dial. Int., **25,** 274-284.

20. van Esch, S., R. T. Krediet, and D. G. Struijk, 2014: 32 years' experience of peritoneal dialysis-related peritonitis in a university hospital. *Perit. Dial. Int.,* **34,** 162-170.

21. Piraino, B., J. Bernardini, and E. Brown, 2011: ISPD position statement on reducing the risks of peritoneal dialysis-related infections. *Perit. Dial. Int.,* **31,** 614-630.

22. Puttinger, H., and A. Vychytil, 2002: Hepatitis B and C in peritoneal dialysis patients. *Semin. Nephrol.,* **22,** 351-360.

23. Zacks, S. L., and M. W. Fried, 2001: Hepatitis B and C and Renal Failure. *Infect. Dis. Clin. North. Am.,* **15,** 877-894.

24. Bertoli, S. V., C. Musetti, and D. Ciurlino, 2014: Peritoneal ultrafiltration in refractory heart

failure: a cohort study. *Perit. Dial. Int.,* **34,** 64-70.

25. Courivaud, C., A. Kazory, and T. Crepin, 2014: Peritoneal dialysis reduces the number ofhospitalization days in heart failure patients refractory to diuretics. *Perit. Dial. Int.,* **34,** 100-108.

26. Rizkallah, J., M. M. Sood, and M. Reslerova, 2013: Reduced hospitalizations in severe, refractory congestive heart failure with peritoneal dialysis: a consecutive case series. *Clin. Nephrol.,* **80,** 334-341.

27. Koch, M., B. Haastert, and M. Kohnle, 2012: Peritoneal dialysis relieves clinical symptoms and is well tolerated in patients with refractory heart failure and chronic kidney disease. *Eur. J.*

Heart Fail., **14,** 530-539.

28. Nunez, J., M. Gonzalez, and G. Minana, 2012: Continuous ambulatory peritoneal dialysis as a therapeutic alternative in patients with advanced congestive heart failure. *Eur. J. Heart Fail.,* **14,** 540-548.

29. Cnossen, T. T., J. P. Kooman, and H. P. Krepel, 2012: Prospective study on clinical effects of renal replacement therapy in treatment-resistant congestive heart failure. *Nephrol. Dial.*

Transplant., **27,** 2794-2799.

30. Stack, A. G., D. A. Molony, N. S. Rahman, A. Dosekun, and B. Murthy, 2003: Impact of dialysis modality on survival of new ESRD patients with congestive heart failure in the United States. *Kid. Int.,* **64,** 1071-1079.

31. Sens, F., A. M. Schott-Pethelaz, M. Labeeuw, C. Colin, E. Villar, and R. Registry, 2011: Survival advantage of hemodialysis relative to peritoneal dialysis in patients with end-stage renal disease and congestive heart failure. *Kid. Int.,* **80,** 970-977.

32. Avesani, C. M., O. Heimburgen, P. Stenvinkel, and B. Lindholm, 2006: Nutritional aspects of adult patients treated with chronic peritoneal dialysis. *J. Bras. Nefrol.,* **27,** 232-238.

33. Helantera, I., M. Haapio, P. Koskinen, C. Gronhagen-Riska, and P. Finne, 2012: Employment of patients receiving maintenance dialysis and after kidney transplant: a cross-sectional study from Finland. *Am. J. Kid. Dis.,* **59,** 700-706.

34. Julian-Mauro, J. C., J. Cuervo, P. Rebollo, and D. Callejo, 2013: Employment status and indirect costs in patients with renal failure: differences between different modalities of renal replacement therapy. *Nefrologia,* **33,** 333- 341.

35. Muehrer, R. J., D. Schatell, B. Witten, R. Gangnon, B. N. Becker, and R. M. Hofmann, 2011: Factors affecting employment at initiation of dialysis. *Clin. J. Am. Soc. Nephrol.,* **6,** 489-496.

36. Purnell, T. S., P. Auguste, and D. C. Crews, 2013: Comparison of life participation activities among adults treated by hemodialysis, peritoneal dialysis, and kidney transplantation: a systematic review. *Am. J. Kidney Dis.,* **62,** 953-973.

37. Griva, K., A. W. Kang, and Z. L. Yu, 2014: Quality of life and emotional distress between patients on peritoneal dialysis versus community-based hemodialysis. *Qual. Life Res.,* **23,** 57-

66.

38. Merkus, M. P., K. J. Jager, F. W. Dekker, E. W. Boeschoten, P. Stevens, and R. T. Krediet, 1997: Quality of life in patients on chronic dialysis: self-assessment 3 months after the start of treatment. *Am. J. Kid. Dis.,* **29,** 584-592.

39. Wu, A. W., N. E. Fink, and J. V. Marsh-Manzi, 2004: Changes in quality of life during hemodialysis and peritoneal dialysis treatment: generic and disease specific measures. *J. Am. Soc. Nephrol.,* **15,** 743-753.

40. Cameron, J. I., C. Whiteside, J. Katz, and G. M. Devins, 2000: Differences in quality of life across renal replacement therapies: a meta-analytic comparison. *Am. J. Kid. Dis.,* **35,** 629-637.

41. Brown, E. A., L. Johansson, and K. Farrington, 2010: Broadening Options for Long-term Dialysis in the Elderly (BOLDE): differences in quality of life on peritoneal dialysis compared to

haemodialysis for older patients. *Nephrol. Dial. Transplant.,* **25,** 3755-3763.

42. Rubin, H. R., N. E. Fink, L. C. Plantinga, J. H. Sadler, A. S. Kliger, and N. R. Powe, 2004: Patient ratings of dialysis care with peritoneal dialysis vs hemodialysis. *JAMA,* **291,** 697-703.

43. Brown, E. A., 2008: Peritoneal dialysis for older people: overcoming the barriers. *Kid. Int. Suppl.,* **108,** 68-71.

44. Brown, E. A., 2010: Can quality of life be improved for the increasing numbers of older patients with end-stage kidney disease? *Expert Rev. Pharmacoecon. Outcomes Res.,* **10,** 661- 666.

45. Just, P. M., M. C. Riella, E. A. Tschosik, L. L. Noe, S. K. Bhattacharyya, and F. de Charro, 2008: Economic evaluations of dialysis treatment modalities. *Health Pol.,* **86,** 163-180.

46. Karopadi, A. N., G. Mason, E. Rettore, and C. Ronco, 2013: Cost of peritoneal dialysis and haemodialysis across the world. *Nephrol. Dial. Transplant.,* **28,** 2553-2569.

47. Baboolal, K., P. McEwan, S. Sondhi, P. Spiewanowski, J. Wechowski, and K. Wilson, 2008: The cost of renal dialysis in a UK setting--a multicentre study. *Nephrol. Dial. Transplant.,* **23,** 1982-1989.

48.Berger, A., J. Edelsberg, G. W. Inglese, S. K. Bhattacharyya, and G. Oster, 2009: Cost comparison of peritoneal dialysis versus hemodialysis in end-stage renal disease. *Am. J. Manag. Care,* **15,** 509-518.

49. Chavers, B. M., C. A. Solid, D. T. Gilbertson, and A. J. Collins, 2007: Infection-related hospitalization rates in pediatric versus adult patients with end-stage renal disease in the United States. *J. Am. Soc. Nephrol.,* **18,** 952-959.

50. Lee, H., B. Manns, and K. Taub, 2002: Cost analysis of ongoing care of patients with end-stage renal disease: the impact of dialysis modality and dialysis access. *Am. J. Kid. Dis.,* **40,** 611-622.

51. Chui, B. K., B. Manns, and N. Pannu, 2013: Health care costs of peritoneal dialysis technique failure and dialysis modality switching. *Am. J. Kid. Dis.,* **61,** 104-111.

52. Duong, U., K. Kalantar-Zadeh, and M. Z. Molnar, 2012: Mortality associated with dose response of erythropoiesis-stimulating agents in hemodialysis versus peritoneal dialysis patients. *Am. J. Nephrol.,* **35,** 198-208.

53. Oliver, M. J., R. R. Quinn, E. P. Richardson, A. J. Kiss, D. L. Lamping, and B. J. Manns, 2007: Home care assistance and the utilization of peritoneal dialysis. *Kid. Int.,* **71,** 673-678.

54. Dratwa, M., 2008: Costs of home assistance for peritoneal dialysis: results of a European survey. *Kid. Int. Suppl.,* **108,** 72-75.

55. Laplante, S., H. Krepel, B. Simons, A. Nijhoff, R. van Liere, and M. Simons, 2013: Offering assisted peritoneal dialysis is a cost-effective alternative to the current care pathway in frail elderly Dutch patients. *Int. J. Healthcare Mgmt.,* **6,** 27-36.

56. Warren, J., E. Jones, and A. Sener, 2012: Should peritoneal dialysis catheters be removed at the time of kidney transplantation? *Can. Urol. Assoc. J.,* **6,** 376-378.

57. Bakir, N., S. Surachno, W. J. Sluiter, and D. G. Struijk, 1998: Peritonitis in peritoneal dialysis patients after renal transplantation. *Nephrol. Dial. Transplant.,* **13,** 3178-3183.

58. Issa, N., and A. Kuka, 2014: Peritoneal dialysis immediately after kidney transplantation. *Adv. Perit. Dial.,* **30,** 83-86.

59. Molnar, M. Z., R. Mehrotra, and U. Duong, 2012: Dialysis modality and outcomes in kidney transplant recipients. *Clin. J. Am. Soc. Nephrol.,* **7,** 332-341.

60. Thompson, B. K., M. A. Moser, and C. Marek, 2013: Peritoneal dialysis versus hemodialysis in patients with delayed graft function.*Clin. Transplant.,* **27,** 709-714.

61. Jassal, S. V., C. E. Lok, A. Walele, and J. M. Bargman, 2002: Continued Transplant Immunosuppression May Prolong Survival After Return to Peritoneal Dialysis: Results of a Decision Analysis. *Am. J. Kid. Dis.,* **40,** 178-183.

Chapter 55

Outcomes of Peritoneal Dialysis Compared to Haemodialysis

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Outcomes of Peritoneal Dialysis Compared to Haemodialysis

The simplified technique for continuous ambulatory peritoneal dialysis (CAPD) using plastic bags was first described by Oreopoulos *et al* in 1978 [1]. It was from then that CAPD was accepted as a home based renal replacement therapy (RRT). Today approximately 11% of end stage renal disease (ESRD) patients worldwide receive peritoneal dialysis (PD) [2]. Steady improvement in clinical outcomes and tangible socioeconomic benefits have resulted in several countries adopting a "PD first" policy [3, 4].

Dialysis is a life sustaining therapy for patients with ESRD. Hemodialysis (HD) and PD are the two established forms of dialysis. It is therefore natural to compare the outcomes between the two forms of dialysis. A true comparison is not possible as there is no prospective trial randomizing incident ESRD patients to the two treatment modalities. However, such a comparison is important to decide which is better of the two. Today the choice of dialysis modality is based more on non-medical factors like financial reimbursements, insurance coverage, and physician bias [5]. Of the various parameters that could be used to compare PD and HD, the important one includes patient and technique survival, quality of life and morbidity.

Patient Survival

There has been a perceived notion that survival on PD is poorer compared to HD. This could probably be due to adverse data on PD from the US. In the CANUSA study US patients on PD had a higher mortality compared to the Canadian patients [6]. Initial USRDS data in 1991 showed no difference in survival among non-diabetic patients on HD and PD [7]. The same report suggested a higher mortality for diabetics on PD [7]. Held *et al,* [8] showed that elderly diabetic patients on PD had a higher mortality.

European studies, however, found no difference in survival on CAPD and HD [9, 10]. Fenton *et al*, reported mortality rates on HD and PD based on a sample of 11970 patients with ESRD who started dialysis between 1990 and 1994. The patients were followed for 5 years [11]. There was a higher mortality in HD for the first two years. Diabetics and patients over 65 years of age did not fare well in PD [11]. More recently Mehrotra *et al*, examined data from USRDS among patients treated with HD and PD on day 90 of ESRD (HD 620020 patients, PD 64406 patients) in three year cohorts (1996 -1198, 1999 – 2001, and 2002 – 2004) for up to 5 years [12]. The authors reported higher risk of death seen with PD in earlier cohorts which improved over years. The risk of death was similar in HD and PD in the 2002 – 2004 cohort over the five years follow up.

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All the evidence indicates that well practiced PD gives result comparable to HD or probably even better. There is bound to be differences between diabetics and non-diabetics and elderly patients.

Technique Survival

There are certain inherent problems of PD, which limit long term technique survival. They are catheter related problems, peritonitis, inadequate dialysis, ultrafiltration failure and psychosocial issues to name a few. Unlike vascular access for HD, where the options are really plenty, the peritoneal membrane if damaged, give us no alternatives. As a result, a greater proportion of PD than HD patients switch modality. Jaar*et al*, is a prospective cohort study of 262 patients from 28 PD clinics in the US found 24.8% switched to HD [13]. Prakash S inan excellent review on PD among indigenous patients concluded that technique failure appears to be higher in indigenous than in non-indigenous population globally [14].

As the time on PD increases, inadequate solute clearance and difficulty in maintaining euvolemia, standout as reasons for dropout from PD [15]. Zhe *et al*, studied the effects of peritoneal resting on peritoneal membrane transport characteristics in CAPD patients [16]. They concluded that resting the peritoneal membrane improves ultrafiltration capacity and decreases the use of hypertonic solutions. Encapsulating peritoneal sclerosis (EPS) is an infrequent complication of long term PD. It portends a high morbidity related to bowel obstruction and malnutrition. Mortality rate from EPS is approximately 50% [17, 18]. So the natural question of time limit to PD arises. Brown *et al,* in their position paper for the International Society of Peritoneal Dialysis (ISPD) concluded that there is not enough evidence to support a rule on optimal length of time on PD to avoid the risk of EPS [19].

It is therefore important to preserve the integrity of the peritoneal membrane and residual renal function. Use of biocompatible solutions, RAAS blockers, reducing peritonitis rates will probably improve the chances of maintaining long term peritoneal integrity, thereby improving long term technique survival.

Quality of life in PD

Quality of life (QoL) is a major factor which is considered in selection of the modality of RRT in ESRD patients. There are numerous ways in which QoL has been defined. This indicates the complexity of the concept. There are plenty of studies on QoL among dialysis patients [20]. Most studies show that patients on CAPD have a better quality of life than patients on in-centre HD. However, one should exercise caution in interpreting the result of these studies because none were randomized controlled studies. The reader is directed to an excellent review by Gokal *et al*, [21].

Morbidity

Hospitalisation for various reasons is a surrogate maker for morbidity in patients on PD. Hospitalization adds to the cost of therapy and impacts negatively on quality on life. This also accounts for loss of productivity in socially and economically productive individual. Coronel *et al,* have described morbidity in their patients on PD over 25 years (118 DM patients and 117 non DM patients). Hospitalisation (admission/year) were higher in diabetic patients (3.4 *vs.* 1.8 $p<0.01$) than in non-diabetics. The hospitalisation length was also more in diabetics as compared to non-diabetics (46 Vs 22 days /year $p=0.01$). Peritonitis, non-peritonitis infections, technique related reasons and cardiovascular disease were the major causes of hospitalization [22].

Szeto *et al*, looked at impact of dialysis on morbidity and mortality of anuric patients on CAPD in Hong Kong. The overall hospitalisation rate was 16 days per year. Overall, 31 of 140 patients (22.1%) were not hospitalized at all. The only independent predictors of hospitalization were low serum albumin and low creatinine clearance [23].

Conclusion

One of the reasons where HD scores over PD is the fact that vascular access sites are plenty and proper access planning from the pre dialysis stages can result in sustaining patients on HD over decades. Unfortunately once the peritoneal membrane integrity is compromised we have no option but to switch to HD. This is probably the major reason for the paucity of patients on long term PD (over 10 years).

It is very difficult to compare PD and HD head to head. Each modality has its own pros and cons. The fact that there is a wide variation in penetrance of PD as a modality of long term RRT can best be explained by non-medical factors influencing decision on therapy selection. Survival is similar and quality of life is better with PD. Peritonitis rates have come down significantly over years. Use of newer solutions like Icodextrin has improved outcomes in anuric PD patients where ultrafiltration is important. Intervention aimed at preserving peritoneal membrane integrity is likely to improve the quantum of patients on long term PD.

References

1. Oreopoulos, D. G., M. Robson, S. Izatt, S. Clayton, and G. A. de Veber, 1978: A simple and safe technique for continuous ambulatory peritoneal dialysis (CAPD). *Trans. Am. Soc. Artif. Intern. Organs,* **24,** 484-489.
2. Fresenius Medical Care 2015 Annual Report: ESRD patients in 2015 – A global prospective.
3. Li, P. K., and K. M. Chow, 2013: Peritoneal dialysis first policy made successful: Perspectives and actions. *Am. J. Kid. Dis.,* **62,** 993 -1005.
4. Dhanakijcharoen, P., D. Sirivongs, S. Aruyaptipan, P. Cheungsaman, and A. Lumpaopong, 2011: The "PD First" policy in Thailand. Three years experiences. *J. Med. Assoc. Thai.,* **94,** 153-161.
5. Nissenson, A., S. Prichard, I. Cheng, R. Gokal, M. Kubota, R. Maiorca, M. C. Riella, J. Rottembourg, and J. H. Stewart, 1997: ESRD Modality selection into the 21st Century: the importance of non-medical factors. *J. Am. Soc. Artif. Intern. Organs,* **43,** 143-150.
6. Blake, P., 1996: A critique of the Canada/USA (CANUSA) peritoneal dialysis study. *Perit. Dial. Int.,* **16,** 243-245.
7. United States Renal Data Systems. Annual Data Report 1991. National Institute of Health, National Institute of Diabetes and Digestive and Kidney Disease, Bethesda MD, 1991
8. Held, P. J., F. K. Port, M. N. Turenne, D. S. Gaylin, and R. A. Wolfe, 1994: Continuous Ambulatory Peritoneal Dialysis and hemodialysis, comparison of patient mortality and adjustment for comorbid conditions. *Kid. Int.,* **45,** 1163 -1169.
9. Maiorca, R., E. F. Vonesh, P. Caveli, A. De Vecchi, A. Giangrande, G. La Greca, L. L. Scarpioni, L. Bragantini, G. C. Cancarini, and A. Cantaluppi, 1991: A multicentre selection adjusted comparison of patient and technique survivals on CAPD and hemodialysis. *Perit. Dial. Int.,* **11,** 118-127.
10. Lupo, A., G. Cancarini, L. Catizone, A. Lupo, G. Cancarini, L. Catizone, R. Cocchi, A. De Vecchi, G. Viglino, M. Salomone, G. Segoloni, A. Giangrande, A. Limido, and F. Conte, 1992: Comparison of survival in CAPD and hemodialysis – a multicentre study. *Adv. Perit. Dial.* **8,** 136-140.
11. Fenton, S. S. A., D. E. Schaubel, M. Dermeules, H. I. Morrison, Y. Mao, P. Copleston, J. R. Jeffery, and C. M. Kjellstrand. Hemodialysis versus Peritoneal dialysis: a comparison of adjusted mortality rates. *Am. J. Kid. Dis.,* **30,** 334-342.
12. Mehrotra, R., Y. W. Chiv, K. Kalantar–Zadeh, J. Bargman, and E. Vonesh, 2011: Similar outcomes with hemodialysis and peritoneal dialysis is patents with End Stage Renal Disease. *Arch. Int. Med.,* **171,** 110-118.
13. Bernard, G. J., L. C. Platinga, D. D. Crews, N. E. Fink, N. Hebah, J. Coresh, A. S. Kliger, and N. R. Powe, 2009: Timing, causes, predictors and prognosis of switching from peritoneal dialysis to hemodialysis: a prospective study. *BMC Nephrol.,* **10,** 3-14.
14. Prakash, S., 2011: An international perspective on peritoneal dialysis among indigenous patients. *Perit. Dial. Int.,* **31,** 390-398.

15. Johnson, D. W., L. Excell, B. Livingston, K. Bannister, and S. McDonald, 2008: Peritoneal Dialysis. ANZ Data Registry Report 2008. Adelaide, South Australia: Australia and New Zealand Dialysis and Transplant Registry, 6.
16. Zhe, X. W., X. T. Tian, C. Cheng, and T. Wang, 2007: Effect of peritoneal resting on peritoneal fluid transport kinetics. *Perit. Dial. Int.,* **27,** 575-579.
17. Rigby, R., and C. Haroley, 1998: Sclerosing Peritonitis – The experience in Australia. *Nephrol. Dial. Transport.,* **13,** 154-159.
18. Balasubramaniam, G., E. A. Brown, A. Davenport, H. Cairns, B. Cooper, and S. L. S. Fan, 2009: Clinical Course and Management of encapsulating peritoneal sclerosis: a multicentre retrospective survey from the UK. *Nephrol. Dial. Transplant.,* **24,** 3209-3215.
19. Brown, E. A., W. Van Biesen, F. O. Frankelstein, H. Hurst, D. W. Johnson, H. Kawanishi, P. F. Roberto, and G. Woodrow, 2009: Length of time on peritoneal dialysis and encapsulating peritoneal sclerosis: Position paper for ISPD. *Perit. Dial. Int.,* **29,** 595-600.
20. Gokal, R., 1994: Quality of Life. *The Textbook of Peritoneal dialysis.* Gokal, R., and K. D. Nolph, Ed., Dordrecht: Kluwer Academic Publishers, 679-698.
21. Gokal, R., M. Figueras, A. Olle, J. Rovira, and X. Badia, 1999: Outcomes in peritoneal and hemodialysis – a comparative assessment of survival and quality of life. *Nephrol. Dial. Transplant.,* **14,** 24-30.
22. Coronel, F., S. Cigarran, and J. A. Herreco, 2010: Morbidity and Mortality in diabetic patients on peritoneal dialysis: Twenty five years experience at a single centre. *Nefrologia*, **30,** 626 – 632.
23. Szeto, C. C., T. Y. H. Wong, K. M. Chow, C. B. Leung, M. C. Lau, A. Y. M. Wang, S. F. Lui and P. K. T. Li, 2001: Impact of Dialysis Adequacy on Mortality and Morbidity of Anuric Chinese Patients Receiving Continuous Ambulatory Peritoneal Dialysis. *J. Am. Soc. Nephrol.,* **12,** 355-360.

Chapter 56

Organization of Peritoneal Dialysis Programme - The Nurse's Role

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Organization of Peritoneal Dialysis Programme - The Nurse's Role

Introduction

Considering the chronic nature of the disease, the patients and family members are to be motivated to self-manage and be empowered to live a productive life. It is often a challenge for the PD nurse to tailor PD training to patients of varied cultural, ethnic and educational backgrounds. Organizing and establishing an efficient PD programme should be the combined effort of the nephrologist, nurse manager and PD nurse taking into account various essential structural and functional factors.

Essential Requisites for Organizing a PD Programme.

Structural requirements

1. A designated room to demonstrate and perform PD is needed. This room should be adequately sized, preferably air conditioned with cleanable surfaces. The floor should not be slippery. Space should be adequate for two or three patients to perform PD exchanges simultaneously [1].

2. A room is to be designated for education and counseling of the patients and families. As the patients and families are being prepared for a new skill and way of life, there should be a provision in this room for video viewing, counseling and demonstration of PD on a mannequin.

3. A separate store room to stock and distribute supplies will be ideal to maintain the PD room with least traffic and contamination.

4. A waiting/ reception area for the patients and families

5. A minor OR to perform percutaneous PD catheter insertion

6. It is essential to have a clean utility room and dirty utility room where the drained fluid can be measured and discarded.

7. Doctors' room

8. Required equipment such as dialysis chairs, stands for hanging fluid bags, electronic weighing scale, automated peritoneal dialysis (APD) cycler, filing cabinets, computer, video player *etc*. [1]

Functional Requirements

1. A dedicated multidisciplinary team ideally includes a nephrologist/s, PD nurse/s, dietician, social worker, advance nurse practitioner or nurse manager is the central

core of PD programme. It is often the PD nurses who co-ordinate the efforts of the team functioning as patients' advocate. The PD nurse should be specially trained to develop knowledge and competence to provide evidence based care and education based on prepared guidelines and protocols [1].

2. Establishing protocols and standard operating procedure for practice is the combined responsibility of nephrologist, nurse manager and PD nurse.

3. Careful selection of patients for the programme is vital. The PD nurse should assess the level of motivation of the patient and the family members in learning and performing the procedure adhering strictly to aseptic techniques.

Role of Nurse

Role as Counselor

When a patient is diagnosed with chronic kidney disease (CKD) stages IV or V, the nurse educator discusses the renal replacement therapy (RRT) options, *i.e*., hemodialysis (HD), PD and renal transplantation. The patient and the family members are helped to make a choice based the information provided regarding the benefits and risks of each option. Once the patient and family decide to be initiated on PD, the PD nurse has to plan sessions with them.

Session 1: Explain about PD, understand their fears, concerns of patients and family and clarify doubts.

Session 2: Video demonstration of PD education, live-demonstration of a PD exchange (where possible), clarification of doubts.

Session 3: Obtain informed consent and prepare the patient for PD catheter insertion. The nurse should not hurry the patient and family into making a decision. She should explain about the procedure, benefits and risks involved, cost, availability of supplies etc. The patients must be allowed to express their concerns before obtaining consent. Through the initiation and maintenance phases of PD treatment, it is essential that the patients are offered psychological and spiritual support and are motivated to lead normal lives on peritoneal dialysis.

Role as Educator

The effectiveness of any PD programme depends largely on the compliance of the patients and the families to the prescribed treatment. Compliance of the patients to therapy can be ensured only through education and periodic reinforcement which is primarily the role of a PD nurse.

The nurse has to educate the patients and families on the following:

1. PD catheter insertion - Procedure, cost, pre and post procedural care.

2. PD procedure (Demonstration of exchange and observing patients' doing the exchange).

3. Setting up of a designated area for PD at home.

4. Options of PD available - APD, Continuous ambulatory PD (CAPD).

5. Dialysate fluid -types, duration of dwell and frequency of exchanges.

6. Planning of periodic follow up for assessment of dialysis adequacy and review of investigation reports.

7. Maintaining a diary with weight and fluid removal during exchanges.

8. Diet – Need to take 1.3- 1.5g protein per day, sodium and fluid restriction.

9. Signs and symptoms of fluid overload and fluid deficit.

10. Signs and symptoms of complications (peritonitis, catheter related infections, poor outflow).

11. Prevention of complications.

12. Hand washing technique using running water. Lack of clean running water for hand-washing prior to an exchange can substituted by use of water with dilute potassium permanganate [2].

Role as facilitator

After providing counselling and education, the role of PD nurse is that of a facilitator. She supervises the technique followed by the patient or the primary care giver until they are confident in performing the procedure independently. She makes herself available for the patients to clarify their doubts, ensures availability of dialysis supplies, follows up the technique and reinforces the instructions. The patients are reviewed periodically to assess dialysis adequacy and identify any complications.

Role as Patient Advocate

PD nurse coordinates care with other health care team members ensuring that patients receive excellent care in a timely manner. The concerns of patients are brought to the attention of team members and appropriate treatment plans are initiated.

Role as Researcher

PD nurses being the primary caregivers has an unparalleled role in collecting and maintaining relevant data pertaining to patients receiving PD. Electronic data available will enhance research opportunities that paves way to evidence based practice.

Responsibilities of PD Nurse- An Overview

1. Pre dialysis Education

2. PD catheter insertion- Pre operative care

Percutaneous PD catheter insertion has gained popularity now which reduces the cost, complications and period of stay in the hospital [3]. PD Nurse performs assessment and documents the following: native kidney disease, duration of CKD, co-morbidities, medication history, prior RRT history, personal history, physical exam findings and investigations (haemoglobin, platelet count, coagulation profile, renal function, electrolytes, lipid profile, iron indices, blood group, blood borne viral infection status, liver function tests, parathyroid hormone, vitamin D levels, electrocardiogram, echocardiogram, x-ray of the chest and ultrasonography of the abdomen4. An informed consent is obtained after counselling and education. Anti-platelet agents are stopped at least five days prior to procedure.

Prior to PD catheter insertion, the PD nurse ensures the following

If the patient is presently on HD, a heparin free HD is arranged on the day prior to the procedure. Preparation of skin is done from nipple line to groin on the night before the procedure. The patient is kept *nil per oral* for at least six hours prior to the procedure. Povidone iodine scrub bath is advised within two hrs before procedure. Patient is advised to skip insulin and anti diabetic agents on the morning of procedure. Prophylactic antibiotic therapy is provided prior to procedure as per protocol. Patient is advised to empty the bladder before procedure to minimize the risk of bladder injury during the procedure. A Foley's catheter may be inserted if required. Vital signs are checked to serve as base line. An intravenous access is created for administration of drugs, fluid, etc as may be needed.

If percutaneous PD catheter insertion is planned, the operating room is disinfected and kept ready with necessary articles such as sterile instruments tray, sterile drapes, introducer set, tunneler device, Veress needle, double cuffed PD catheter with adaptor, transfer set and minicap, sterile gloves, Inj. Lidocaine, sterile syringes, antiseptic solution, PD fluid bags, suture materials for subcutaneous and skin sutures, 2% chlorhexidine for cleaning, mupirocin ointment for application at the incision and exit sites.

PD catheter insertion- Intra operative care

The patient's identity is confirmed and an informed consent is obtained. PD nurse assists the doctor in performing the surgery and monitors vital signs at least every 30 minutes. At the end of the procedure, PD catheter is flushed to ensure good flow. An occlusive dressing is applied at incision and exit sites. Intra-operative events are documented. Specific instructions are given to patient and family member regarding post procedural care [3]. PD catheter insertion- Post operative care

Foley's catheter (if inserted) is removed and oral feeds are initiated 2-3 hrs following the procedure. Patient is advised rest for 24hrs post procedure. The exit site must be kept dry for two weeks. The dressing may be removed in 3-5 days and first exchange is performed in 2-3 days of catheter insertion. The ultra short break-in period is suggested to be the new standard of care [4]. Exit site care is provided and taught. Ensure that anti platelet drugs are restarted after the first successful flushing [3].

Exit site Care

The exit site dressing is changed only after 5 days to allow uninterrupted wound healing. The exit site is cleaned with a sterile gauze moistened with sterile saline in a circular motion from around the site to outside after performing hand hygiene. An antiseptic ointment is applied and a sterile gauze is placed over the site. The patient or family member is taught to follow strict aseptic techniques while doing exit site care. The patient is advised not to have bath in bath tubs, lakes or swimming pools [5].

PD adequacy

Dialysis adequacy is periodically assessed by assessing the energy level of patients, appetite, blood pressure, blood parameters of hemoglobin, phosphorous, electrolytes, albumin, etc. The prescription is optimized to achieve a minimum target Kt/V urea of 1.7, although the importance of the numerical value of this target is still debated. It is ensured that Kt/V urea is measured periodically as per institutional policy.

Kt/V protocol

24 hours dialysate sample and urine sample is collected. The fluid in all the PD bags is mixed and samples are obtained for urea and creatinine. The 24 hours' urine sample is sent for urea and creatinine analysis to estimate residual renal function.

***Peritoneal Equilibration Test* (PET)**

The peritoneal equilibration test (PET) is performed about one month after PD initiation and whenever clinically indicated. Sample for PET is collected as follows: An overnight exchange with 2.5% dextrose PD solution with a dwell time of 8-10 hrs is done. With the patient in an upright position, PD sample is collected before draining the fluid and is marked as "overnight sample". Fluid is drained and volume is recorded. 2 L of 2.5% fluid is instilled into the peritoneal cavity over 10 minutes (about 200 ml/minute) instructing the patient to roll from side to side after infusion of each 400 ml. The time at which the entire 2 L has been infused into the abdomen is recorded. This is the 0 hour dwell time. Then, 200 ml of PD fluid is drained and mixed in the bag by inverting 2-3 times. Thereafter, 10 ml of sample is drawn out using a sterile needle inserted through the medication port, and the fluid is labeled

as 0 hour dialysate sample.The remaining 190 ml of effluent is reinfused into the patient's peritoneal cavity.

Similarly, collect 10ml of PD fluid and serum sample at 2 hours and 4 hours and label it. Blood and dialysate samples are analyzed for urea, creatinine and glucose concentration. Based on PET results patient is identified as low transporter, high transporter, high average or low average transporter. Dialysis prescription is modified in consultation with the nephrologist based on PET results [6].

Prevention, identification and management of complications

PD is associated with a high risk of infection of the peritoneum, subcutaneous tunnel and catheter exit site. Although quality standards demand an infection rate <0.67 episodes/patient/year on dialysis, overall reported rate of PD associated infection is 0.24-1.66 episodes/patient/year. It is estimated that for every 0.5-per-year increase in peritonitis rate, the risk of death increases by 4% and 18% of the episodes resulted in removal of the PD catheter and 3.5% resulted in death [7]. The incidence of these complications can be greatly minimized through effective training of patients and periodic reinforcement of correct practices while handling PD catheter and exit site. The PD nurse is to teach patients regarding the signs and symptoms of complications so that early identification and management can be facilitated.

1. Fluid retention or fluid overload: Advise sodium and fluid restriction, daily weight checking. Patient is assessed for signs and symptoms of fluid retention and overload. The need to alter PD prescription is assessed [5].
2. Peritonitis: Use of aseptic techniques in handling catheter and exit site is reinforced periodically. Patients are advised to report any symptoms such as abdominal pain, cloudy drain fluid, fever, nausea, vomiting, loss of appetite and decreased fluid removal.

Collecting sample for PD fluid analysis: At least 50 ml of PD fluid sample from the first bag of cloudy solution is collected adhering to protocol and sent for culture and sensitivity test. Rapid flushing is performed to prevent block of catheter from fibrin strands. 500-1000 U/L heparin is added to each new bag till the effluent clears. Empiric antibiotic therapy is instilled usually intraperitoneally as per guideline and institutional protocol based on local antibiotic susceptibility. Signs of response to treatment as clearing of PD fluid, reducing abdominal pain, decreasing effluent cell count are assessed and documented [3].

3. Exit site infection: Patients are taught to carry out exit site care using aseptic technique. Antibiotic ointment such as mupirocin is applied once daily to prevent exit siteinfections and peritonitis. The PD nurse identifies signs and symptoms of exit site infection such as purulent discharge from exit site, redness, pain, swelling and warmth around it. The exit site is graded (0, 1, 2, 3 and 4). Discharge from the site is collected and sent for gram stain and culture. Antibiotic therapy is initiated as per nephrologist's advice. Patients are advised to soften the crusts and scabs with

saline/ clean water and gently remove them. If the exit site does not heal by three weeks, the same is reported to the nephrologist. Catheter removal or revision of exit site may be required [5].

4. Tunnel Infection: Patients are advised to report to dialysis unit if he has abdominal pain, fever or swelling along the length of subcutaneous portion of the catheter. Peritonitis or exit-site infection may also be accompanied by tunnel infection. The exit site is checked for any signs of infection. The presence of tunnel infection is confirmed by ultrasonography which shows presence of fluid in the tunnel along the catheter. Empirical antibiotic therapy is initiated according to institutional protocol. Catheter removal is often required in case of resistant or recurrent tunnel infection. The nurse must prepare the patient and family members for this possibility [3].

Handling blocked catheters

Catheter malfunction occurs in 15% -30% of patients. Drainage difficulties can be caused by kinks in the catheter, dilated intestine due to constipation or paralytic ileus, catheter malposition, excessive fibrin formation obstructing the catheter lumen, or wrapping of the omentum around the intraperitoneal portion of the catheter [8].

Poor inflow due to a fibrin clot

50 ml of heparinized saline may be instilled through a syringe and if not successful, urokinase (250,000 units in 2 ml NS for 2-4 hours) may be used to clear the fibrin clots.

Dilated intestine due to constipation

Constipation must be cleared by giving polyethylene glycol / soap and water enema or Lactulose 15 ml once or twice daily. If poor outflow persists, an x-ray is done to check the position of catheter.

Poor outflow could also result from omental wrapping or catheter migration

A flat-plate abdominal x-ray may be arranged to check the position of catheter. If catheter appear to be in position, patient may require computerized tomography (CT) of the abdomen for further assessment. When CT peritoneography is needed, a flat-plate abdominal x-ray may be arranged to check the position of catheter. If the catheter is in position, patient may be prepared for computerized tomography of the abdomen with 50 to 100 ml ionic contrast (e.g iohexol) is added into a 2-litre fluid bag. The fluid is instilled into the peritoneal cavity and the patient is made to walk around before the CT is done. This is most useful when looking for suspected leaks.

If catheter is migrated, soap and water enema is administered with oral concomitant polyethylene glycol for two days. If the catheter does not return to its appropriate position in the pelvis, the patient is prepared for repositioning of catheter with or

without omentectomy. Percutaneous bedside repositioning has been described and successfully done in several patients at our institution (unpublished data).

At the end of the training period, PD nurse has to ensure that the patient is confident in managing PD at home and knows the following:

1. Steps in performing PD exchanges using strict aseptic techniques.

2. Symptoms of inadequate PD.

3. Importance of measuring urine output and fluid intake and maintaining accurate records.

4. Exit site dressing, antibiotic ointment application, care of catheter.

5. Signs and symptoms of complications.

6. Dietary recommendations.

7. Need for regular follow up and periodic investigations.

8. Procurement of supplies (including PD fluid).

Management of minor PD related problems (troubleshooting).

Continuous Quality Improvement

It is desirable that the PD nurses are periodically updated with trends and emerging modalities of care and get certified for the specialized training. This will enable them to take autonomous roles as practitioners and be able to provide home based care and follow up.

Conclusion

A well informed and enthusiastic nurse is a blessing to the nephrologist and to the patients on PD [9]. Nurses who are sensitive to understand the needs of patients, committed to help them through the process of learning, knowledgeable and skillful to identify and manage complications play a pivotal role in organizing and maintaining a successful PD programme.

References

1.Uttley, L., and B. Prowant, Organization of a peritoneal dialysis programme — the nurses' role. *Textbook of Peritoneal Dialysis.* pp 363-386.

2. Varughese, S., G. Abraham, N. Prasad, R. Sheriff, Chronic Kidney Disease in South Asia – a clarion call for change. (Personal communication. In press.)

3. Standards of Care in Peritoneal Dialysis, Department of Nephrology, Christian Medical College, Vellore

4. George, N., S. Alexander, V. G. David, G. Basu, A. Mohapatra, A. T. Valson, S. Jacob, H. K. Pathak, A. Devasia, V. Tamilarasi, and S. Varughese, 2016: Comparison of Early Mechanical and Infective Complications in First Time Blind, Bedside, Midline Percutaneous Tenckhoff Catheter Insertion With Ultra-Short Break-In Period in Diabetics and Non-Diabetics: Setting New Standards. *Perit. Dial. Int.,* **36,** 655-661.

5.Levy, J., E. Brown, C. Daley, and A. Lawrence, Oxford Handbook of Dialysis (South Asia edition.)

6. Twardowski, Z. J., K. D. Nolph, R. Khanna, and M. P. Nielsen, 1987: Peritoneal Equibration Test. *Perit. Dial. Int.,* **7,** 138-148.

7.Jacob, A. A., 2012: Peritoneal dialysis associated infections: An update on diagnosis and management. *World J. Nephrol.,* **1,** 106–122.

8.Stringel, G., S. Olsen, and C. Cascio, 1995: Unblocking peritoneal dialysis catheters with a combination of urokinase and Fogarty catheter manipulation. *Adv. Perit. Dial.,* **11,** 200–201.

9. Oreopoulos, D. G., 1981: The peritoneal dialysis nurse: the key to success. *Perit. Dial. Int.,* **1,** 113-114.

Chapter 57

Wearable Artificial Kidney for Peritoneal Dialysis

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Wearable Artificial Kidney for Peritoneal Dialysis

Introduction

The long-term survival of patients with end stage renal disease (ESRD) on some form of dialysis is equal or worse than that of patients with malignancy. To improve patient's outcomes, the current system of weekly 12 hours hemodialysis or intermittent PD exchanges needs to be changed. To overcome short- comings of today's dialysis system, wearable dialysis devices have been developed *via* advances in nanotechnology manufacturing coupled with advances in miniaturization technique. These wearable and portable dialysis devices may revolutionize the treatment and quality of life for patients with ESRD.

It is well established that more frequent and/ or longer duration of dialysis sessions improve the cardiovascular outcomes from the available clinical trials. But the time spent for the dialysis treatment and the cost of personnel delivering health care is high which is rarely possible in majority of dialysis population even in developed nations. Hence, implementing all possible measures to increase home based treatment is necessary.

PD (CAPD/APD) is the commonest mode of home based RRT. Despite advancement in technology to improve infection rate there are major hurdles which make health care providers look away from the choice of Peritoneal Dialysis (PD).

Major hurdles in PD

Though the patients undergoing PD are free from HD machine for around 12 hours in a week, they still have to spend 20–30 minutes at least 3-4 times a day for exchanges. This frequent manipulation for dialysate exchange increases risk of introducing microorganism in to the peritoneal cavity. Moreover, it necessitates the delivery and storage of large volumes of fresh dialysate and disposal of effluent fluid. These challenges rectified to some degree with the advent of wearable artificial PD devices.

Vicenza Wearable Artificial Kidney (ViWAK)

Ronco *et al,* in 2007 introduced an innovative wearable system called "Vicenza Wearable Artificial Kidney "for peritoneal dialysis. This system requires fluid exchange only in the morning and night saving the time spent on fluid exchange during day time and reduces the risk of infection. More importantly, this system also able to regenerate the required dialysate from the spent dialysate and hence the

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required volume of fresh dialysate is reduced (**Figure 1**).

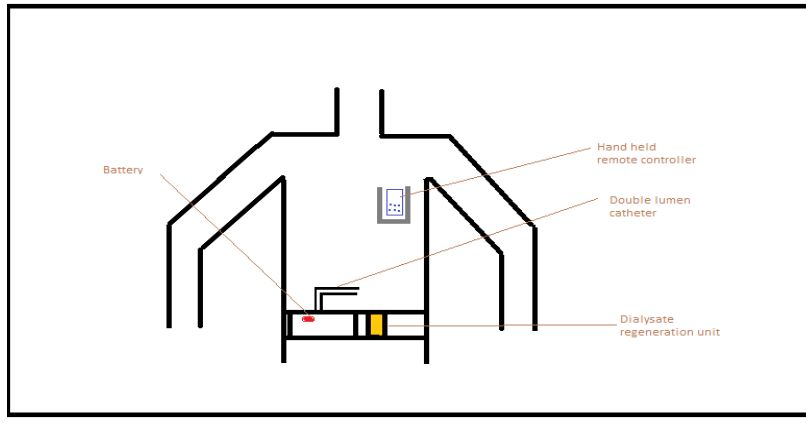

Figure 1: Vicenza Wearable Artificial Kidney (ViWAK)

This system uses a combination of continuous flow PD during the day and overnight icodextrin exchange. The ViWAK system is a daily, battery-operated adsorption system in which spent dialysate recirculates and regenerated for 10 hours. It consists of three components: 1) Double lumen PD catheter (Ronco's catheter and conventional Tenchkoff catheter), 2) Mini cycler (Regenerating unit), 3) Remote controller.

Double lumen PD catheter

The double lumen catheter used for the ViWAK where the inflow lumen ends with a diffuser while the outflow lumen begins with a spiral tube. This configuration ensures minimal intra peritoneal recirculation and maximal efficiency (**Figure 2**).

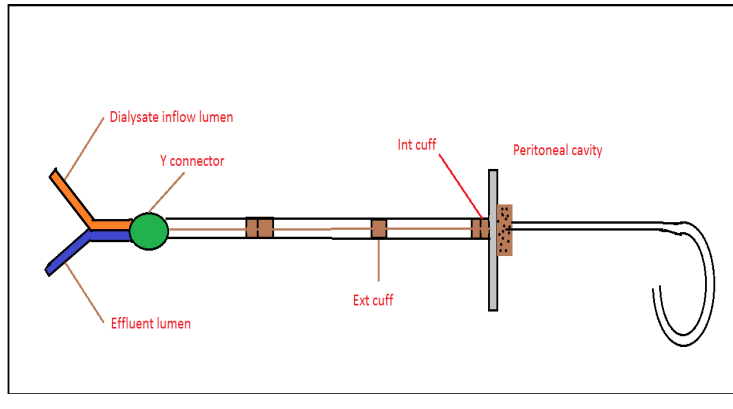

Figure 2: Double Lumen PD catheter

Mini cycler system

This is the most vital component of Ronco's system. The parts are serially connected to one another. The spent dialysate comes from out flow tract made entry into the mini cycler with the help of mini pump (**Figure 3**). This spent dialysate then flow through the filter 1 to remove any proteinacious and fibrin material. Then travel through the serially placed cartridges which contain sorbents. The original version of ViWAK sorbents consist of activated charcoal and polystyrene resin. Activated charcoal adsorbs the creatinine, uric acid, hippuric acid and vitamin B12 whereas resin will remove middle molecule toxins includingbeta-2 microglobulin, leptin, angiogenin and some interleukins. Newer cartridges contain microporous carbon, urease, Zirconium phosphate and resins.

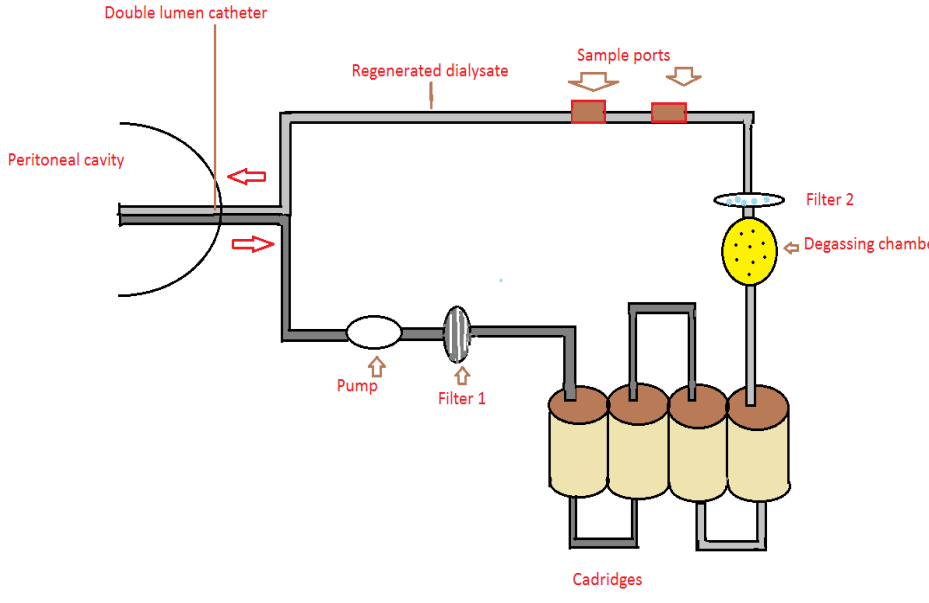

Figure 3: Mini Cycler System

Urease in the sorbent metabolizes urea in to ammonium and carbon dioxide. The ammonium then is rapidly adsorbed by zirconium phosphate. The CO_2 thus produced will form micro and macro bubbles which are easily eliminated by degassing chamber. Microporous carbon adsorbs creatinine, uric acid, chloramines, oxidants, other organic compounds, heavy metals and middle molecules include beta-β_2 micro globulin. Zirconium phosphate adsorbs ammonium, calcium, magnesium and releases hydrogen and sodium. Final effluent will flow through second filter to remove fibrin. This regenerated dialysate then checked for acid base and electrolyte content and then allowed to pass through the inlet to enter the peritoneum.

Treatment schedule

ViWAK is to be used as a mechanical supportive system to perform CAPD. Peritoneal cavity is infused with 2 liters of fresh PD fluid. After 2 hours (when approximately 50% of dialysate/plasma equilibrium has occurred) of infusion, recirculation is activated for next 10 hours at the rate of 20 ml /minute and then recirculation stopped. Glucose may be added to the solution via hand held remote controller if extra ultrafiltration is required. This fluid will be drained after 2 hours. Two liters icodextrin exchange is performed overnight to achieve further ultrafiltration. Hence daily clearance of 12 liters + 2 liters + 2 liters totaling 16 liters per day will be obtained. Such efficient clearance guarantees a weekly creatinine clearance of more than 100 liters.

Limitations with ViWAK

ViWAK system uses pre formed dialysate with standard electrolyte solution as initial fresh volume. This volume has to be refreshed with fresh dialysate or preformed bicarbonate solution to maintain acid base and electrolyte homeostasis. Further investigation is required to determine whether this addition of bicarbonate will provide satisfactory homeostasis because the amount of required bicarbonate will vary from patients to patients. The change of sorbent cartridges daily will add to the cost and complexity. Appropriate connectology is required to minimize the entry of microorganism and air in the circuit. For adequate ultra filtration, this system requires use of icodextrin which adds to cost. New proposal to insert a mechanical pump similar to that of HD machine pump to the mini cycler circuit remains to be examined in studies.

The Automated Wearable Artificial Kidney (AWAK)

The ViWAK system would require the patient to perform two standard PD exchanges per day. Due to this limitation and the costs of replacing the sorbents each day, the ViWAK has not proceeded from laboratory to clinical trials.

The automated wearable artificial kidney (AWAK) is another continuous PD device designed for continued use, which differs from the ViWAK in having single catheter lumen access, and as such dialysate flow is discontinuous, depending upon a tidal regimen requiring a reservoir for refreshed dialysate. The original AWAK system was developed by David Lee and Marty Roberts in 2008. Their current modified version, the automated wearable artificial kidney system (AWAK) is based on regenerating spent PD effluent and is under human clinical trial.

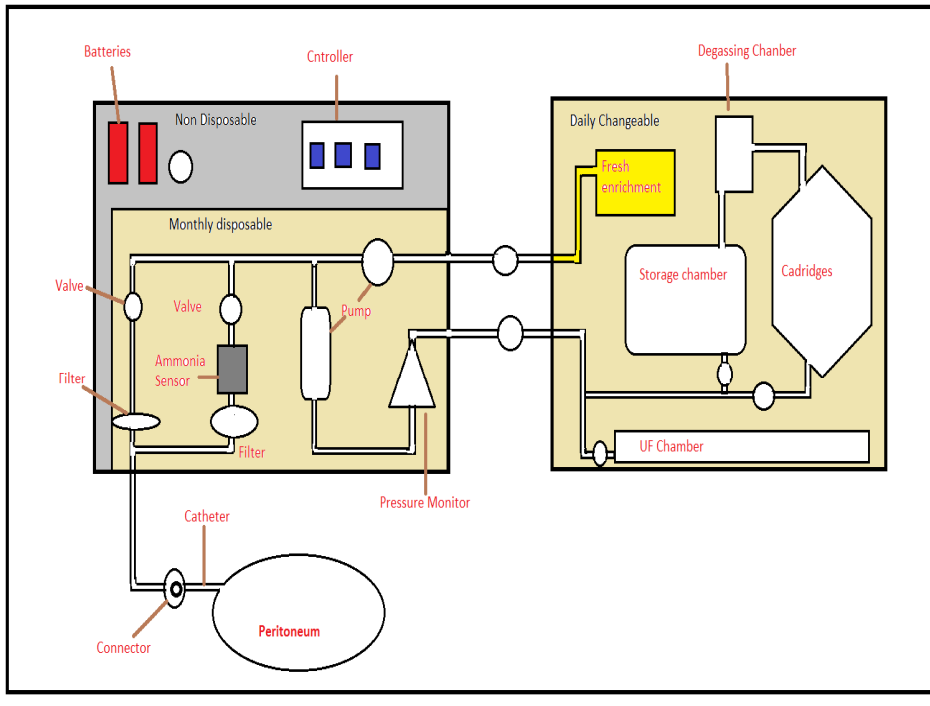

Fig AWAK system

Figure 4: The Automated Wearable Artificial Kidney (AWAK) System

The AWAK system is designed to continuously regenerate dialysate, so that a single conventional glucose-based peritoneal dialysate solution may be continuously reused for up to a month or even longer. As such, this system has an additional chamber containing electrolytes, lactate and glucose to refresh the regenerated dialysate and an ammonia sensor to monitor sorbent saturation.

Compared to the conventional PD modality, the AWAK design proposes a tidal protocol with a residual volume of 500–1,000 ml with rapid exchanges of around 250-ml aliquots aiming for exchanges of around 4 L/h. Around 750 ml of fresh dialysate is infused into the peritoneal cavity and after a period of 2 hours, the spent dialysate allowed to recirculate in a tidal manner at 4 L/h using a pump. As recycled dialysate has lower glucose and changed electrolyte composition, it must be continuously refreshed with glucose and electrolyte solutions. Ultra filtrate generated during the recirculation drained into a separate storage chamber. The AWAK is designed to have both daily and monthly disposable sections, designed for ease of replacement and to reduce the cost. The rechargeable battery life is estimated to be around 18h and requires recharging overnight. Outflow circuit **(Figure 5)** with spent dialysate effluents pumped through a fibrin filter and sorbents

and then through a degassing chamber before being retained in a storage chamber.

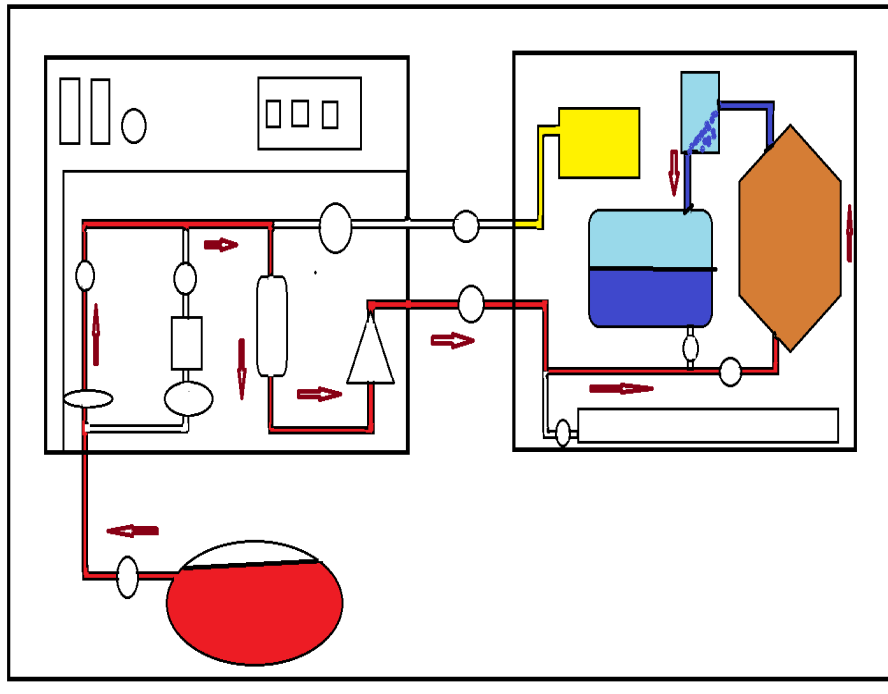

Fig showing spent PD fluid moving through circuit and finally stored in storage chamber

Figure 5: Spent PD Fluid Moving through Circuit and FInally Stored in Storage Chamber

In-flow circuit (**Figure 6**) with spent dialysate refreshed by the addition of glucose, bicarbonate and electrolytes before being passed through an ammonia sensor and then pumped back into the patient.

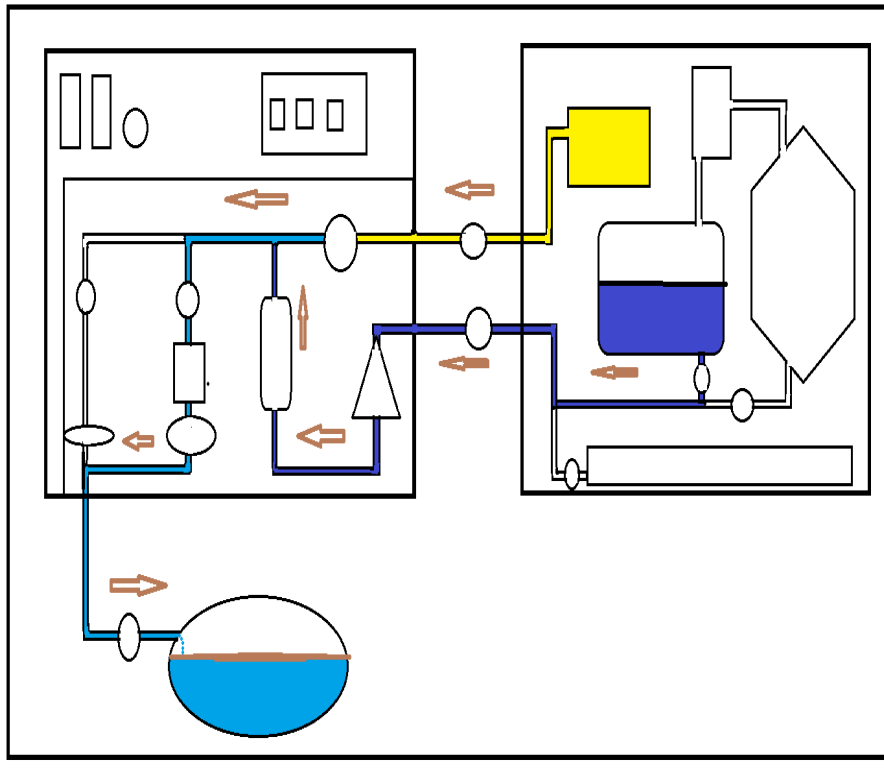

Fig showing regenerated fluid flow in to the peritoneal cavity

Figure 6: Regenerated Fluid Flow in to the Peritoneal Cavity

A 60 kg patient on dialysis with a dietary protein intake of 1g/kg is expected to produce around 9 g of urea nitrogen per day. Although, urease and 250 g of zirconium can readily catalyze and absorb 2g urea/h, this amount of urea clearance would exhaust the currently available sorbent cartridges. This necessitates more than one daily cartridge exchange. To overcome this, the AWAK device has produced two different sorbent cartridges, one designed to extract 3.5 g of urea nitrogen and another heavier cartridge to remove 10 g of urea nitrogen depending upon the patient's characteristics.

In designing a wearable device, it is important to determine the amount of sorbent to be used, as too little sorbent will lead to sorbent exhaustion needing increased frequency of sorbent exchanges, whereas additional sorbent will reduce the frequency of sorbent exchanges, it will add extra weight to the device. Thus, designers have to take care to balance what weight patients can carry around versus the inconvenience of sorbent exchange. Taking these considerations into account,

the AWAK design has two proposed versions, one weighing around 1 kg and the other 3 kg, depending on the difference in the size of the sorbent cartridges.

Replacing the sorbents currently requires the patient to drain out peritoneal dialysate and then re-instill fresh dialysate with each sorbent exchange. Thus, it is important that the sorbents last for at least 24 h to prevent the patient having to perform additional PD exchanges.

Clinical trials aimed at testing the capacity of the current sorbents are expected in 2017. Not surprisingly, the recent enthusiasm for developing wearable and portable dialysis devices has sparked new interest and research into a new generation of more effective and lighter weight sorbents.

References

1. Ronco, C., and L. Fecondini, 2007: The Vicenza Wearable Artificial Kidney for Peritoneal Dialysis (ViWAKPD). *Blood Purif.,* **25,** 383–388.
2. Ronco, C., A. Davenport, and V. Gura, 2011: The future of the artificial kidney: moving towards wearable and miniaturized devices. *Nefrologia*, **31,** 9-16.
3. Fissell, W. H., S. Roy, and A. Davenport, 2013: Achieving more frequent and longer dialysis for the majority: wearable dialysis and implantable artificial kidney devices. *Kid. Int.* **84,** 256–264
4.Davenport, A., 2012: Portable or Wearable Peritoneal Devices— The Next Step Forward for Peritoneal Dialysis? *Adv. Perit. Dial.*, **28**.

Chapter 58

Urgent Start Peritoneal Dialysis

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Urgent Start Peritoneal Dialysis

Introduction

The first report of the Chronic Kidney Disease Registry of India, published in 2012, involved 55000 patients with chronic kidney disease (CKD). About 48% of these patients presented at Stage 5 CKD. A majority (61%) were not receiving any form of RRT at the time of reporting,of the remainder, 32% were on haemodialysis (HD), 5% on PD and 2% were being worked up for transplantation [1].

India lacks a structured healthcare plan which addresses the needs of patients with CKD. Healthcare delivery takes place through both private and public systems. Even though both HD and PD are freely available in our country, the penetration of these treatment modalities is essentially restricted to the urban areas. The penetration of chronic PD as a RRT is even more uncommon with less than 20% of the CKD Stage 5 patients being on this treatment [2]. High costs and anticipated high infection rates are the two main factors that have been perceived to play a role in non-selection of PD. Jeloka *et al.* in 2013, showed that the costs of commonly prescribed PD and HD prescriptions in our country are comparable [3]. The fear that high infection rates accompany the hot and humid climate in the country and unhygienic general living conditions has remained largely unfounded. The infection rates in reported literature is acceptable and comparable to the western world [3]. Despite such findings, PD is rarely offered as a first-choice dialysis therapy with the therapy being reserved for patients with multiple comorbidities or vascular access failures who are unsuitable for HD [2].

Late presentation to healthcare, nephrologist bias against PD due to financial reasons and lack of predialysis initiation care and counselling (including dialysis access placement), have resulted in a poor popularity and high dropout rates for PD as a modality of RRT [4].

In India, the HD-centric model to RRT is prevalent. Yet, there exists a lack of pre ESRD care with inadequate permanent vascular access preparation and high reliance on the use of central venous catheters (CVC) in patients requiring emergency RRT. There are readily available facilities for the placement of CVC in most health care centres which indirectly promote the initiation of HD (haemodialysis-centric) over PD in our country.

During the last decade, there has been a change in this traditional outlook with the introduction of the concept of Urgent Start PD. Traditionally, in patients with adequate pre-ESRD care who opt for PD as the form of RRT, the peritoneal catheter is placed 2-4 weeks prior to the initiation of PD [5]. Initiation of training and the

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process of PD takes place after permitting adequate time for healing at the catheter placement site.

Definition

Urgent start PD refers to a process of initiation of PD within 2 weeks after catheter placement.

Process

The dialysis is initiated with low fill volumes using a cycler device so as to prevent pericatheter leaks. The treatment varies from alternate days to daily, typically lasting for 6-8 hoursin a day [5].The dwell volume, frequency and duration is then gradually increased depending upon the patient's tolerance of the procedure till the traditional PD prescription is reached.

Which patient is suitable for urgent start dialysis?

This modality is reserved for those patients with advanced CKD who do not require an emergent initiation of renal replacement for the traditional indications of life threatening hyperkalaemia, metabolic acidosis or volume overload, but at the same time are ideal candidates for initiation of urgent dialysis, *i.e*., within the next 2 weeks. **Table 1** gives differences between Urgent start and emergent start PD.

Ultimately, the choice of a patient for Urgent Start PD will depend on the nephrologist's discretion and would consider other factors such as local resources, clinical situation and nephrologist experience.

Table 1: Difference between Emergent and Urgent Start PD.

S.No.	Urgent Start	Emergent Start
1.	Stage CKD-V with imminent need for RRT	End Stage Renal Disease (ESRD)
2.	No plan for dialysis modality available	Usually acute presentation
3.	No life threatening indications for RRT present	Life threatening Indications for RRT present

Advantages

The advantages of PD as a modality hold true for Urgent Start PD too. It is a relatively easier technique which can achieve a gradual reduction in the electrolytes and acid- base abnormalities without precipitation of the dialysis disequilibrium syndrome. Fluid removal in the hemodynamically unstable patient or in those with

underlying heart disease may be easier. Even, the risks of a venous/arterial puncture and anticoagulation are avoided. The dextrose content of the peritoneal fluid may serve as a source of calories for the patient who may be anorexic due to long standing uraemia. Also, it is less labour intensive and requires no specialised machinery or equipment. It is a home based RRT and instils a sense of independence in the patient who participates in it to a very large extent.

Barriers to Urgent start PD

The barriers to this modality exist at various levels including the patient selection, nephrologist's perception, operator difficulties, hospital and medical centre facilities and the finances. Patient selection depends largely on the discretion of the nephrologists.

Also, there is a definite need for the involvement of the caretaker in this modality of treatment. Lack of education increases the chances of non-compliance to regular therapy and the non-adherence to the desired hygienic practices which are a must in this form of RRT [6-8].

The practising nephrologist who lacks formal training and experience in this form of therapy, may work against selection of this therapy. Absence of a consensus guideline for definition and treatment protocols for Urgent Start PD deters selection. Rapid placement of the PD catheter within 48 hours of referral could be one of the rate limiting steps [9, 10]. There exists a shortage of expertise in trained and experienced operator personnel for insertion of the PD catheters in a timely fashion [11-13]. These may include a surgeon or an interventional radiologist or a nephrologist who is trained in this aspect. There still exists a need for consensus regarding the method of placement of the PD catheter and a standardized perioperative care protocol. The usual choice of method of placement of the PD catheter is laparoscopic placement or percutaneous insertion (**Table 2**).

Hospitals need to ensure that all the infrastructure required for Urgent Start PD is in place, This would include an adequate stock of supplies needed for PD, the presence of trained personnel well-versed with the nuances of PD including trained PD nurses, the operator personnel willing to report at odd hours for the PD catheter placement and other required para medical staff. There is an important role for trained PD coordinators who would need to educate the patient and the caretaker regarding this modality and keep in touch with them even after their discharge from the hospital.

The inpatient and outpatient PD nurses need to be well-trained, aware of the complications which could been countered with Urgent Start PD patients and the techniques which would minimise the complications expected with this modality of RRT, e.g., Low volume exchanges in the recumbent position to minimise the pericatheter leaks. The hospital management must be convinced of the potential benefits of the urgent start PD and should support this therapy with adequate staff, equipment and space. The programme would require adequate allocation of a

dedicated space in the hospital, equipped with beds /chairs where the training as well as the initial sessions of PD may be carried out.

Table 2: Choice of placement method of PD catheter.

Catheter placement modalities	Laparoscopic insertion	Percutaneous placement
Patient conditions	Morbidly obese patient (BMI>35)	Multiple co-morbidities
	H/o of prior abdominal surgery	High risk anaesthesia
	Presence of abdominal hernias	Trained nephrologist/Interventional Radiologist

PD is perceived to be more expensive than HD, a belief held by both the nephrologists and the patients. This is why PD, in our country, still does not enjoy the popularity it warrants. The use of this modality remains largely restricted to areas where HD has poorly penetrated due to geographical inaccessibility in areas such as the North Eastern states of India or in patients in whom HD is poorly tolerated or with multiple vascular access failures. Contrary to this belief, a study by Jeloka *et al*, showed that no difference existed in the monthly cost of patients on thrice weekly Maintenance haemodialysis (MHD) and those on PD with thrice daily exchange. The lower cost of the HD procedure as compared to PD procedure cost was offset by the higher cost on erythropoietin requirements and transportation charges to and from the dialysis unit, resulting in equalization of the monthly costs in the two groups [3].

Contraindications to Urgent Start PD

PD, by itself, has very few absolute contraindications and most of the contraindications would be relative. The same would extend to Urgent Start PD too and include:

- Life threatening metabolic abnormalities and volume overload.
- Recent abdominal or cardiac surgery.
- Anterior abdominal wall abscess or cellulitis.
- Past history of intraperitoneal surgery which may give rise to peritoneal adhesions.
- Diaphragmatic pleural-peritoneal connections.
- Low peritoneal clearance due to any reason.

- Fungal or faecal peritonitis.
- Poorly controlled diabetes.
- Pregnancy.

Outcomes of Urgent Start PD

There appears to be no increased rates of hospitalisation, increased infective episodes or decrease in short term patient survival or technique hurdles in urgent start PD as compared to conventional PD [8, 14-19]. In a non-randomised single centre study, Ghaffari *et al,* showed that Urgent Start PD had similar short term results (90 days) as compared to elective PD with regards to Kt/V, anaemia, CKD-MBD profile and catheter and infection related complications. However, the number of minor pericatheter leaks was higher in the Urgent Start PD group [8]. In a recent single-centre, matched case-control study, See *et al.* concluded that there were no significant difference in the rates of overall and infective complications in patients on Urgent Start PD. However, there were higher rates of pericatheter leaks and catheter migrations (10-12%) as compared to the planned conventional PD patients [19]. These complications were minor, responded well to conservative methods and did not require any major surgical treatment or catheter replacement. Also, there was no significant difference in the adverse effect profile or short term patient drop-out in both the groups [19, 20].

Though the data is limited, Urgent Start PD has been shown to do as well as the patients who have been initiated on urgent HD with no significant difference (30% *vs* 42%) in the overall mortality between the two groups at the end of six months of follow up [21].

Setting up an Urgent Start PD Programme

The key elements which would play an important role in setting up a successful urgent start PD programme include:

1. Operational team support with the capabilities to place the PD catheter within 48 hours.
2. Dedicated staff and staff education regarding the use of the catheter after placement.
3. Administrative support (inpatient and outpatient setting).
4. Appropriate evidence based protocols which can be used at every step of the process (from initiation to discharge).
5. Identification of appropriate patients for urgent start PD.

Development of protocols for urgent start PD

Due to the lack of data and popularity, enough literature or guidelines to help in the process does not exist. The success of any treatment modality in medicine depends upon a protocol driven plan which may be repeated over and over again till perfection is achieved. The protocol of urgent start PD should be made based on the

requirements, infrastructure and patient profile of the local area where the modality is being offered. Inputs from the patient as well as the local PD nurse and coordinator would help in formatting a protocol suitable to the local population.

The initial assessment includes the clinical examination and routine laboratory investigations including examination for presence of severe anaemia, hyperkalaemia, fluid overload and signs and symptoms of azotaemia. This will help decide the suitability of a patient for urgent start PD as well as help the nephrologist decide how soon the process needs to be initiated after the successful placement of a PD catheter. Pre procedure preparation should include thorough aseptic technique reinforcement including site preparation, appropriate antibiotic prophylaxis and bowel preparation to avoid constipation and technique failure. Postoperative care must include local operative site dressing and care instructions and a regular bowel regimen. Local operative site should be closely monitored for post-operative bleeding and pericatheter leaks.

The patency, functionality and presence of internal bleeding must be checked immediately after catheter placement using low volume exchanges (*i.e.*, 500 ml) in a recumbent position. It should be continued till the effluent fluid is clear, following which the catheter must be secured with a sterile dressing until the need for urgent start PD. If the bleeding persists beyond three to four exchanges, further investigations for internal bleeding must be carried out.

Initial prescription for Urgent Start PD

The initial assessment of the patient will determine the urgency with which the exchanges need to be initiated. The further away the 'break- in' period is from the insertion of the catheter, lesser are the chances of mechanical complications including pericatheter leaks. The initial prescription would include low volume exchanges done in the recumbent position. If the patient is not overtly uremic, one may try to adapt a gradual and incremental approach with exchanges being done only on 3-5 days in a week either in the hospital or outpatient setting [22]. Simultaneous training must be started and imparted not only to the patient but also the care-giver. Certain volume recommendations have been given in the past based on the experience with inpatient setting [18]. The volumes and frequency of exchanges are determined based on the body surface area of the patient and the severity of the uremic symptoms and the underlying residual renal function. Patients with a smaller body surface area (BSA) of 1.65 m^2 or less can be initiated on dwell volumes of 500 mL. Dwell volumes can be increased to 750 mL in larger patients with a BSA of 1.65 - 1.8 m^2, and a 1-L dwell volume can be used in patients with a BSA exceeding 1.8 m^2. The frequency may vary between five to seven per day and total time may be five to eight hours per exchange [22-24]. Patients who require emergent initiation of RRT due to life threatening hyperkalaemia, metabolic acidosis or volume overload may be initiated on HD through a temporary vascular access placement and stabilised. Following the

stabilisation, the patient may be gradually started on the urgent start PD pathway, the so-called bimodal approach [22].

Transition to home therapy

Following the initial two weeks of initiation of therapy which is done in the recumbent position and usually under close supervision, the patient is usually ready to initiate self-care and may be changed over to the conventional continuous ambulatory peritoneal dialysis (CAPD) or automated peritoneal dialysis (APD) schedules.

Conclusion

Urgent Start PD is a modality which may popularise the use of PD amongst the ESRD patients who have a late referral to medical care and help circumvent the drawbacks of haemodialysis including the need for vascular access placement and anti-coagulation. It allows for better preservation of residual renal function and life style benefits derived from a home based therapy. It has proven to be as good as HD and may be used in isolation or as a bimodal approach which has been previously described. The barriers to this modality lie predominantly in the timely placement of the PD catheters, availability of infrastructure including resources and personnel who are trained in peritoneal dialysis and management of surgical complications including pericatheter leaks and catheter displacements. Appropriate exposure to PD during training and evidence based guidelines and protocols may help in standardising this modality of RRT.

References

1. Rajapurkar, M. M., G. T. John, A. L. Kirpalani, G. Abraham G, S. K. Agarwal, Almeida AF, S. Gang, A. Gupta, G. Modi, D. Pahari, R. Pisharody, J. Prakash, A. Raman, D. S. Rana, R. K. Sharma, R. N. Sahoo, V. Sakhuja, R. R. Tatapudi, and V. Jha, 2012: What do we know about chronic kidney disease in India: first report of the Indian CKD Registry. *BMC Nephrol.*, **6,** 10-13.
2. Jha V., 2013: Current status of end-stage renal disease care in India and Pakistan. *Kid. Int.,* **3,** 157–160.
3. Jeloka, T. K., S. Upase, and S. Chitikeshi, 2012: Monthly cost of three exchanges a day peritoneal dialysis is same as of thrice a week haemodialysis in self-paying Indian patients. *Ind. J. Nephrol.*, **22,** 39-41.
4. Jha, V., 2008: Peritoneal dialysis in India: Current status and challenges. *Perit. Dial. Int.,* **28,** 36–41.
5. Arramreddy, R., S. Zheng, A. Saxena, S. Liebman, and L. Wong, 2014: Urgent-Start Peritoneal Dialysis: A Chance for a New Beginning. *Am. J. Kid. Dis*., **63,** 390–395.
6. Casaretto, A., R. Rosario, W. R. Kotzker, Y. Pagan-Rosario, C. Groenhoff, and S. Guest, 2012: Urgent-start peritoneal dialysis: report from a U.S. Private nephrology practice. *Adv. Perit. Dial.,* **28,** 102–105.
7. Lobbedez, T., A. Lecouf, M. Ficheux, P. Henri, B. Hurault de Ligny, and J. P. Ryckelynck, 2008: Is rapid initiation of peritoneal dialysis feasible in unplanned dialysis patients? A single-centre experience. *Nephrol. Dial. Transplant.*, **23,** 3290–3294.
8. Ghaffari, A., 2012: Urgent-start peritoneal dialysis: a quality improvement report. *Am. J. Kid. Dis.*, **59,** 400–408.
9. Mehrotra, R., P. Blake, N. Berman, and K. D. Nolph, 2002: An analysis of dialysis training in the United States and Canada. *Am. J. Kid. Dis.*, **40,** 152–160.
10. Berns, J. S., 2010: A survey-based evaluation of self-perceived competency after nephrology fellowship training. *Clin. J. Am. Soc. Nephrol.*, **5,** 490–496.
11. Wong, L. P., S. E. Liebman, K. A. Wakefield, and S. Messing, 2010: Training of surgeons in peritoneal dialysis catheter placement in the United States: a national survey. *Clin. J. Am. Soc. Nephrol.*, **5,** 1439–1446.
12. Jo, Y. I., S. K. Shin, J. H. Lee, J. O. Song, and J. H. Park, 2007: Immediate initiation of CAPD following percutaneous catheter placement without break-in procedure. *Perit. Dial. Int.*, **27,** 179–183.
13. Stegmayr, B. G., 2003: Three purse-string sutures allow immediate start of peritoneal dialysis with a low incidence of leakage. *Semin. Dial.*, **16,** 346–348.
14. Jo, Y. I., S. K. Shin, J. H. Lee, J. O. Song, and J. H. Park, 2007: Immediate initiation of CAPD following percutaneous catheter placement without break-in procedure. *Perit. Dial. Int.,* **27,** 179.
15. Povlsen, J. V., and P. Ivarsen, 2006: How to start the late referred ESRD patient urgently on chronic APD. *Nephrol. Dial. Transplant.*, **21,** 56.

16. Song, J. H., G. A. Kim, S. W. Lee, and M. J. Kim, 2000: Clinical outcomes of immediate full-volume exchange one year after peritoneal catheter implantation for CAPD. *Perit. Dial. Int.*, **20,** 194.
17. Ivarsen, P., and J. V. Povlsen, 2014: Can peritoneal dialysis be applied for unplanned initiation of chronic dialysis? *Nephrol. Dial. Transplant.*, **29,** 2201.
18. See, E. J., Y. Cho, C. M. Hawley, L. R. Jaffrey, and D. W. Johnson, 2016: Early and late patient outcomes in urgent-start peritoneal dialysis. *Perit. Dial. Int.*, **36,** 171.
19. Alkatheeri, A. M., P. G. Blake, D. Gray, and A. K. Jain, 2016: Success of Urgent-Start Peritoneal Dialysis in a Large Canadian Renal Program. *Perit. Dial. Int.,* **36,** 171-176.
20. Koch, M., M. Kohnle, R. Trapp, B. Haastart, L. C. Rump, and S. Aker, 2012: Comparable outcome of acute unplanned peritoneal dialysis and haemodialysis. *Nephrol. Dial. Transplant.,* **27,** 375.
21. Ghaffari, A., V. Kumar, and S. Guest, 2013, Infrastructure Requirements for an Urgent-Start Peritoneal Dialysis Program. *Perit. Dial. Int.,* **33,** 611–617.
22. Voss, D., S. Hawkins, G. Poole, and M. Marshall, 2012: Radiological versus surgical implantation of first catheter for peritoneal dialysis: a randomized non-inferiority trial. *Nephrol. Dial. Transplant.,* **27,** 4196–4204.
23. Casaretto, A., R. Rosario, and R. W. Kotzker, Y. P. Rasario, C. Groenhoff, and S. Guest, 2012: Urgent-Start Peritoneal Dialysis: Report from a U.S. Private Nephrology Practice. *Adv. Perit. Dial.*, **28,** 102-105.

Chapter 59

Landmark Studies in Peritoneal Dialysis

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Landmark Studies in Peritoneal Dialysis

Chronic diseases have become a major cause of global morbidity and mortality. Earlier considered to be a health problem only in the developed countries, 4 out of 5 chronic disease deaths now occur in low and middle-income countries [1]. End-stage renal disease (ESRD) is a chronic, irreversible condition that will ultimately lead to death without dialysis or transplantation. According to the World Health Organisation (WHO) Global Burden of Disease Project, disease of the kidney and urinary tract contribute to global burden with approximately 850,000 deaths every year of which chronic kidney disease (CKD) is the 12th leading cause of death and 17th leading cause of disability in the world [2].

There is an epidemiological transition taking place in India as well, with the decline in communicable diseases and a growing burden of chronic diseases [3]. In India, the projected number of deaths due to chronic diseases is estimated to rise from 3.78 million in 1990 (40.4% of all deaths) to an expected 7.63 million in 2020 (66.7% of all deaths) [3]. Health programmes for prevention of chronic diseases in India had mainly focused on hypertension, diabetes mellitus and cardiovascular disease (CVD), however, the increase in the prevalence of CKD progressing ESRD has highlighted the importance of CKD and its risk factors [4, 5]. Although, the exact prevalence of CKD in India is not clear in the absence of regular national registry but according to the data from tertiary referral centres, it has been presumed that every year, nearly 100,000 new patients with ESRD are added [6].

In India, the current scenario for ERSD care is similar to other long term chronic disease states and is as listed below:

- Increasing number of patients suffering from the disease have been diagnosed.
- The level of care and costs associated with the disease increase the cost of treatment substantially.
- There is a growing need for cost effective care options with optimum care results.

Desired Goal of treatment in ESRD

- Clinical
  - Survival
  - Better preservation of RRF (Residual Renal Function)
  - Lower incidence of hepatitis B and C than HD patients
- Financial and Access

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- Lesser need for fixed and recurring expense
- Improved access to treatment for patients in remote location
- Overall Patient satisfaction
- Patient can retain employment
- Integrated in daily routine
- Reduces overall burden of disease

Treatment Options in ESRD Patients

1. Kidney dialysis

Peritoneal Dialysis- Peritoneal dialysis (PD) is a treatment for patients with severe chronic kidney failure. The process uses the patient's peritoneum in the abdomen as a membrane across which fluids and dissolved substances (electrolytes, urea, glucose, albumin and other small molecules) are exchanged from the blood. Fluid is introduced through a permanent tube in the abdomen and flushed out either every night while the patient sleeps (automatic peritoneal dialysis) or via regular exchanges throughout the day (continuous ambulatory peritoneal dialysis).

There are two major types of PD:

1. Continuous ambulatory peritoneal dialysis (CAPD)
2. Continuous cycling peritoneal dialysis (CCPD)

3.1.1 CAP

The procedure includes exchange happening manually with gravity the dialysis. It happens continuously for 24 hours a day and 7 days a week with dwell time lasting 3 to 5 hours. There are about 3-4 exchanges every day.

3.1.2 CCPD

In this procedure, the patients are attached to a machine named “cycler”; the machine accomplishes the exchange automatically based on pre-programmed settings. The patients are attached to the machine during the night when asleep and this exchange lasts 8 to 10 hours. During the daytime, exchange is done manually.

- Haemodialysis

3. Kidney Transplantation

Non- Treatment= While an option, the non-treatment choice could eventually lead to death.

Advantages of PD as a First Choice of treatment of ESRD compared to HD

- Better preservation of residual renal function (RRF) [7].
- Better hemodynamic stability [8].
- Protection from transmission of viruses [9].
- Reduced incidence of bacterial infections [10, 11].
- Reduced blood transfusions, erythropoietin need [12].
- Better quality of life with home-based dialysis therapies [13].
- Better outcome of renal transplantation [14].
- Better or equal patient survival [15].
- Another form of PD is Automated Peritoneal Dialysis (APD). The basic mechanisms of solute and fluid removal in CAPD and APD are the same. APD is designed to minimize the burden of frequent dialysate bag exchanges by using an automated cycler.

•The various types of APD are:

•Continuous therapy

CCPD (Continuous Cyclic Peritoneal Dialysis)

•Intermittent therapy

NIPD (Nocturnal Intermittent Peritoneal Dialysis)

DIPD (Daytime Intermittent Peritoneal Dialysis)

•Tidal therapy

NTPD (Nightly Tidal Peritoneal Dialysis)

CTPD (Continuous Tidal Peritoneal Dialysis)

Some important points with relation to APD are as follows:

- APD is an effective RRT for:
  - majority of patients requiring dialysis
  - patients with any peritoneal membrane transport type
  - elderly patients
  - patients with large body size

- APD is the preferred modality for pediatrics.

- In an analysis of over 4,000 PD patients from the Australia and New Zealand Dialysis and Transplant Registry, Badve *et al*, 2007 found no significant difference in patient or technique survival, between APD and CAPD [17].

- The majority of patients choose this form of dialysis because of the lifestyle benefits it can provide.

- APD is an effective dialysis therapy for all patients, and can be modified in accordance with the patient's specific peritoneal transport characteristics. APD is especially suitable for patients with high membrane transport status [18].

- In a US study examining 4 large cohorts of patients initiating PD (>40,000 patients), Mujais *et al,* 2006 found that technique survival was significantly better in APD than in CAPD ($p<0.0001$) [19].

- APD is particularly beneficial for patients who have regular commitments during the day – those who are working or studying, those caring for family members or children – because dialysis exchanges take place at night while the patient is asleep, leaving the day free for daily activities.

- APD improves quality of life. A high level of patient satisfaction and a high level of personal well-being are seen in APD patients [20, 21, 22].

Use of APD has increased significantly over the last decade

9. APD now represents more than 30% of PD use in many countries and more than 50% of use in some countries.

In the present manuscript, we summarize few landmark papers in PD and the research questions it answered; which improved our practical and clinical understanding of patients on peritoneal dialysis.

Adequacy

Canada-USA (CANUSA) Peritoneal Dialysis Study [23]

3.1.3 The objective of the study was to evaluate the relationship of adequacy of dialysis and nutritional status to mortality, technique failure, and morbidity. This was a prospective cohort study of 680 pts starting PD followed 1990 – 1993. Dialysis prescription was changed at discretion of doctor.

Overall, 98% of patients in the study were on CAPD and 2% were on CCPD.

Renal and peritoneal clearances was assumed to be equivalent, and added together (**Table 1 and 2**).

Table 1: The Variables and associated Mortality Risk

Variable Relative	Mortality Risk
Age (per year)	1.03
IDDM	1.45-1.49
CVD	2.09-2.12
Country (USA)	1.93
SGA (per 1 unit)	0.75
Kt/V(per 0.1 U/wk)	0.94
CrCl (per 5 L/wk)	0.93

Table 2: Expected 2-year patient survival according to sustained weekly kt/V and CCr (l/1.73 m^2)

Kt/V	Survival%	CCr	Survival (%)
2.3	81	95	86
2.1	78	80	81
1.9	74	70	78
1.7	71	55	72
1.5	66	40	65

The clearances of these patients revealed that with a rise of every 0.1 Kt/V value per week there is a 6% less risk of mortality, and with every 5L/wk increase in Creatinine clearance, patient gain 7 % low risk of mortality.

Limitations of CANUSA

PD adequacy studies assumed that renal and peritoneal clearances are comparable and therefore additive. Data from CANUSA were reanalysed in an effort to address this assumption.

- Observational study
- Non randomised nor Interventional
- Survival was predicted by total clearance

• Clearance data were confounded by residual renal function

• CANUSA was not designed to keep the total clearance the same as RRF declines. It is the residual renal clearance that predicts the outcome, not the peritoneal clearance

Reanalysis of CANUSA proved that neither net peritoneal ultrafiltration nor total fluid removal was associated with patient survival. Results may be explained partly, statistically, by fact that there is less variability in peritoneal clearance than in GFR. GFR is more important than the former [24].

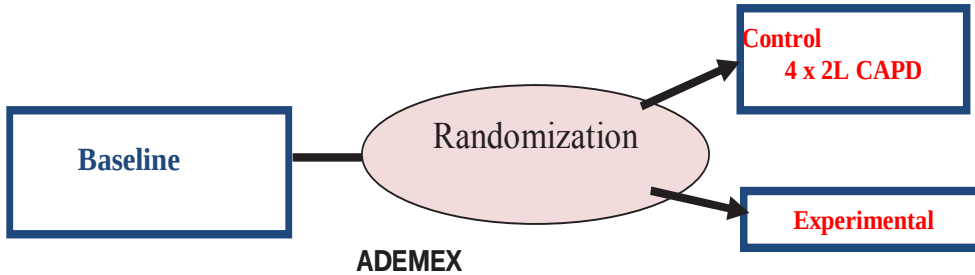
A prospective, randomised, controlled, clinical trial called ADEMEX (ADEquacy of PD in MEXico), examined the effects of increased PD small-solute clearances on mortality rates among patients with ESRD. The studies parameters included mortality as primary outcome and technique failure, hospitalisation, laboratory parameters as secondary outcomes. Overall, 965 Patients were actually randomised into two arms – one control with 4 bags of 2L and others where the goal was to achieve creatinine clearances of> 60L/wk/1.73 m^2 [25].

• Baseline:

- Patients with peritoneal CCr< 60L/week/1.73m^2

• Endpoints:

- Primary: Mortality
- Secondary: Technique Failure, Hospitalization, Labs, etc.



ADEMEX
Mean Weekly Clearances in the Two Groups

	Control Group	Treated Group
Peritoneal Kt/V	1.62	2.13
Total Kt/V	1.80	2.27
Peritoneal CrCl	46 L	57 L
Total CrCl		

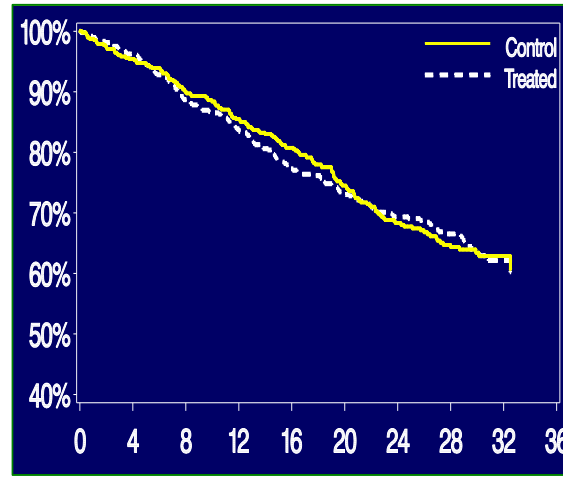


Figure 1: Follow-up: Minimum Two-year Follow-up on all Patient

Control: 1-Yr Survival=85.5%, 2-Yr Survival=68.3%

Treated: 1-Yr Survival=83.9%, 2-Yr Survival=69.3%

On studying the patient primary outcomes with intention to treat (ITT) analysis it was realized that there is no statistically significant difference between the two groups in terms of primary survival outcomes. The major clinical impact of

ADEMEX was that it showed that it is not only solute clearance which is important for long term survival, but also we must pay equal importance to other factors which are impacting the clinical outcomes. This study opened the eyes of those who seemed to be the blind followers of targets achievement in adequacy.

Various studies have shown that RRF is a better predictor of survival than peritoneal clearance. A retrospective study was conducted to analyse how the peritoneal Kt/V affected the survival of anuric patients [26].

In a study 3020 incident PD patients were categorized in to three groups and followed up for 10 years. The results showed:

- No difference in patient survival for Kt/V 1.7-2.0 *vs* >2.0 Kt/V, p=0.82
- Patient survival <1.7 Kt/V *vs* 1.7-2.0 Kt/V: p=0.054

While survival in the 1.5-1.7 group was not statistically different than the other groups, this group had more clinical problems indicating inadequate dialysis. Thus, the recommended target is 1.7/week Kt/V.

It is plausible that once a certain level of clearance is achieved, further increase may have a minimal effect on the outcome relative to the much stronger influence of other factors such as diabetes, cardiovascular disease *etc.*

The major determinant of survival in PD is residual glomerular filtration rate (GFR), much more than peritoneal solute clearances. Anuric peritoneal dialysis patients are solely dependent on the peritoneal solute clearances. The aim of the **NE**therlands **CO**operative **S**tudy on the **A**dequacy of **D**ialysis study was to analyze the effects of peritoneal small solute clearances and ultrafiltration on survival in anuric patients, and to establish the minimum levels of small solute clearances and net ultrafiltration. The study defined the lower limits of adequate peritoneal dialysis, that is $Kt/V_{(urea)}$ <1.5 per week and creatinine clearance <40 L/week/1.73 m^2 [27].

Baseline UF <750 mL/24 hr was associated with a worse patient survival (P=0.0048). The worse patient survival was also predicted by the baseline age (>65 years, P=0.001), worse nutritional status (SGA grade, P=0.0014), increased comorbidity grade (P=0.012), and diabetic status (P=0.008). Gender, and baseline body surface area, total peritoneal or residual creatinine clearance, and peritoneal solute transport status did not influence patient, technique, or combined patient and technique survival.

A 2-yr prospective European APD Outcome Study (EAPOS), multicenter, observational study, of anuric patients receiving APD was conducted to determine the factors that affect patient and technique survival in order arrive at guidelines for the treatment. Dialysis prescription was altered throughout the study, aiming to achieve both small solute clearance (Ccrea>60 L/wk per 1.73 m2) and UF (>750 ml/24 h) targets [28]. Based on Data Available: Small Solute And Fluid Removal Targets/ Recommendations **(Table 1)**

3. The target minimum delivered dose of total small-solute clearance is Kt/V urea of ≥1.7 per week.

2. In APD, an additional target of 45L/week /1.73m^2 is for creatinine clearance.

3. Minimum target for peritoneal net UF in anuric patients is 1.0 L/day.

4. Attention should be paid to both urine volume and amount of UF, with a goal of maintaining euvolemia.

Table 1: Clinical Practice Guideline Recommendations

	Weekly total Kt/V	**Weekly total Ccr**	**Continuous treatment**	**UF (per day)**
KDOQI (2006) [29]	≥1.7	NR	Yes	NR
ISPD (2006)[30]	≥1.7	APD >45L	Yes	NR
European Best Practice Guidelines (2005) [31]	≥1.7	APD>45L for patients with frequent short exchanges and slow transport status	NR	1.0L
UK Renal Association (2007) [32]	≥1.7	≥50L	NR	≥750ml
Indian Guideline (2007) [33]	≥1.7	≥45L	Yes (anuric patients)	NR

NR= No recommendation All guidelines stress on Kt/V of ≥1.7

Icodextrin

Continuous exposure of the peritoneum to hypertonic glucose solutions results in morphologic damage that may have a causative role in changes in peritoneal function. Exposure to hypertonic glucose dialysis solution, which also contains Glucose GDP and enhances the formation of Advanced Glycosylation End products (AGE) formed due to glycation of proteins in the peritoneal membrane, is one of the mechanism of peritoneal membrane injury [34, 35]. There has been a growing concern that the hyperosmolality and low pH of hypertonic glucose solution may damage the peritoneum and, thereby threaten its viability as a dialyzing membrane [36, 37]. The currently available peritoneal dialysis fluids (PDF), which are all hyperosmolar, are toxic to the cells present in the peritoneal cavity [38]. There are circumstantial evidence to support this, including AGE deposition within the

membrane, diabetiform changes in peritoneal blood vessels and the finding that sclerosing peritonitis is associated with the use of more hypertonic exchanges [39-44]. These all evidences reinforce the need of alternative dialysis solutions.

Icodextrin has a favourable effect in preserving the peritoneal environment as well as membrane integrity because of its biocompatibility profile, as reflected by preservation of cell function. It also helps reduce peritoneal glucose exposure, low GDP and reduced AGE formation [45, 46]. It is iso-osmolar to plasma and helps reduce systemic and peritoneal alterations.

Results of amulticentre trial conducted by Paniagua *et al*, showed that Icodextrin was associated with reduced glucose exposure [45]. **Figure 2** gives the reduced levels of fasting glucose with Icodextrin.

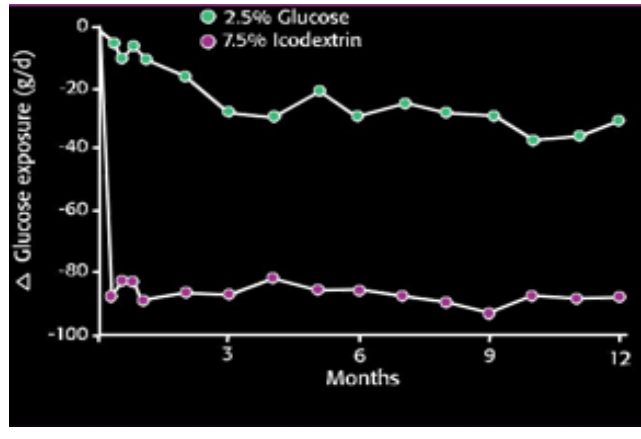


Figure 2: Reduced Fasting Glucose Level with Icodextrin

Mistry *et al*, conducted a randomised, controlled Multicenter Investigation of Icodextrin in Ambulatory Peritoneal Dialysis (MIDAS) to evaluate the long-term safety and efficacy. They compared isosmolar Icodextrin (282 mOsm/kg) with conventional 1.36% (346 mOsm/kg) and 3.86% (484 mOsm/ kg) glucose solution of different osmolarity (**Figure 3**) [47].

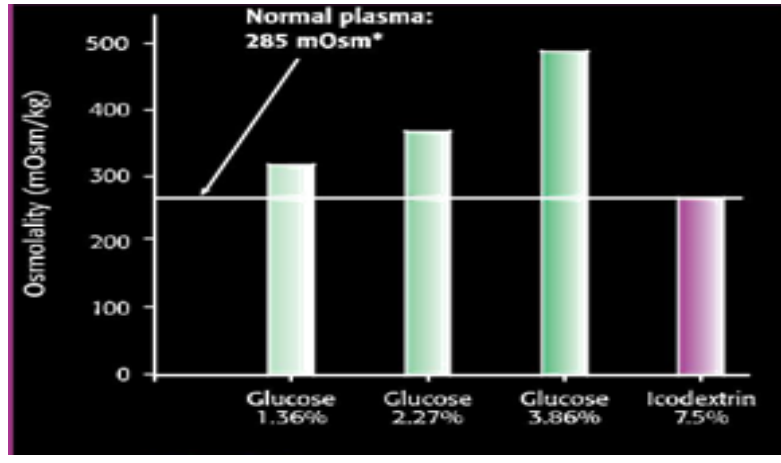


Figure 3: Icodextrin - Iso-Osmolar to Plasma

Paniagua *et al*, conducted a 12-month, multicenter, open label, randomised controlled trial to analyze the effects of Icodextrin on metabolic and fluid control in high and high-average transport diabetic patients on Continuous Ambulatory PD (CAPD). Results in this case also showed improvement in lipid profile, in addition they also showed Icodextrin was associated with reduced glucose absorption lower level of glycated haemoglobin (Hba1c) and reduced dose of insulin [48]. **Figures 4 and 5** represents the reduces glucose and insulin absorption, respectively, with icodextrin.

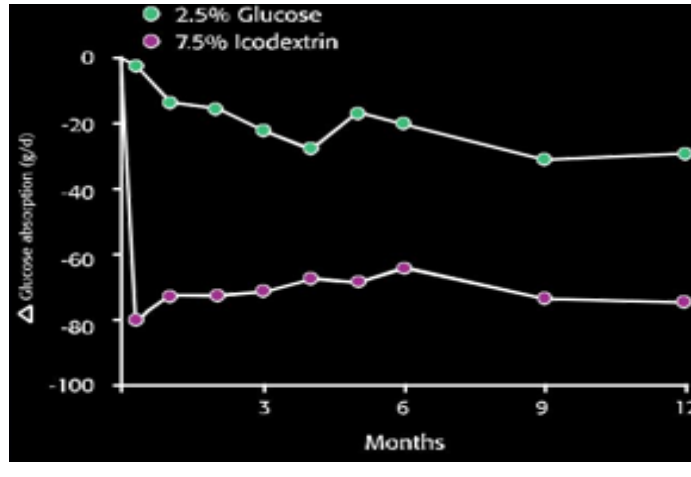


Figure 4: Reduced Glucose Absorption with Icodextrin

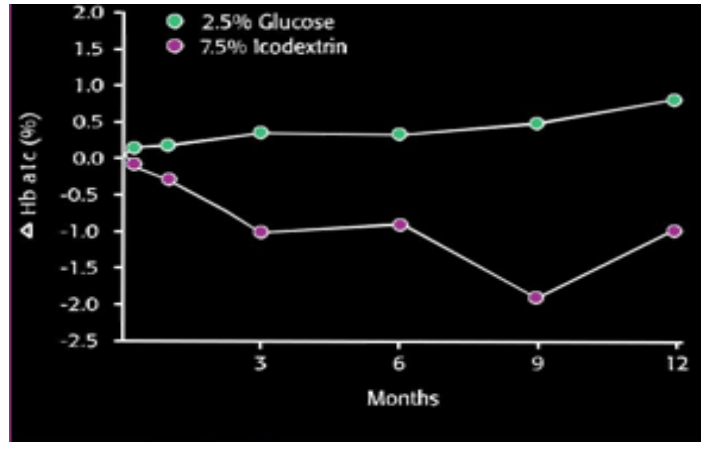


Figure 5: Reduced Insulin dose with Icodextrin.

Finkelstein *et al,* compared Icodextrin and 4.25% dextrose during the long dwell of APD. Primary objective of the study was to compare the fluid-removal capabilities of Icodextrin and 4.25% dextrose in population of APD patients who would most likely benefit from an improvement in UF. The results of this study demonstrated that use of Icodextrin for the long dwell results in highly statistically significant and clinically meaningful improvements in net UF **(Figure 6).** Although this study was limited to a 2-week observation period, but results were likely sustainable and reproducible over longer periods of observations [49].

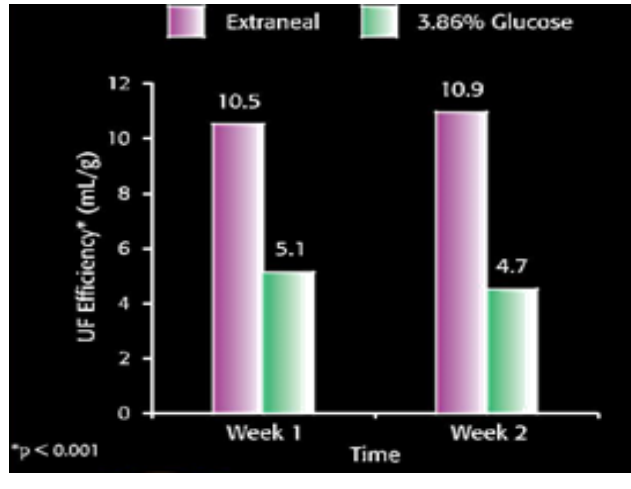


Figure 6: Enhanced UF Efficiency with Icodextrin

Davies *et al*, studied whether increased exposure to glucose preceded changes in solute transport in a selected group of long-term PD patients. Peritoneal solute transport, RRF, peritonitis rate, and peritoneal exposure to glucose were recorded prospectively in a cohort of 303 patients at a single dialysis center. In this study of long-term survivors on PD, an increase in solute transport with time was preceded by increased peritoneal exposure to hypertonic glucose [50]. **Figure 7** represents increase in solute transport with time.

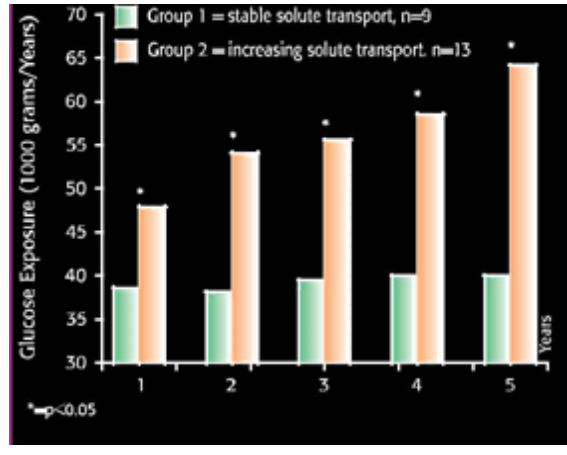


Figure 7: Increase in Solute Transport with Time Preceded by Increased Peritoneal Exposure to Hypertonic Glucose

References

1. World Health Organization: Preventing Chronic Disease: A Vital Investment. Geneva, WHO, 2005.

2.World Health Organisation-Burden of disease project available at: http://www.3.who_int/whosis/menu. cfm? path=evidence, burden and language assessed on September 2006. Cited on 2nd July, 2016.

3. Rao, M., and B. J. Pereira, 2007: Chronic kidney disease in India—a hidden epidemic. *Indian J. Med. Res.,* **126,** 6-9.

4. Grassmann, A., S. Gioberge, S. Moeller, and G. Brown, 2005: ESRD patients in 2004: global overview of patient numbers, treatment modalities and associated trends. *Nephrol. Dial. Transplant.,* **20,** 2587-2593.

5. Center for Disease Control and Prevention (CDC), 2004: Prevalence of chronic kidney disease and associated risk factors – United States, 1999–2004. *MMWR Morb. Mortal Wkly. Rep.,* **56,** 161–165.

6. Kher, V., 2002: End-stage renal disease in developing countries. *Kid. Int.,* **62,** 350-362.

7. Moist L. M., F. K. P., S. M. Orzol, E.W. Young, T. Ostbye, R. A. Wolfe, T. Hulbert-Shearon,

C. A. Jones, and W. E. Bloembergen, 2000: Predictors of Loss of Residual Renal Function among New Dialysis Patients. *JASN,* **11,** 556-564.

8. Lysaght, M. J., E. F. Vonesh, F. Gotch, L. Ibels, M. Keen, B. Lindholm, K. D. Nolph, C. A. Pollock, B. Prowant, and P. C. Farrell, 1991: The Influence of Dialysis Treatment Modality on the Decline of Remaining Renal Function. *ASAIO Transact.,* **38,** 598-604.

9. Canziani, M. E., M. C. Neto, M. A. Saragoca, J. L. Cassiolato, O. L. Ramos, H. Ajzen, and S. A. Draibe, 1995: Hemodialysis Versus Continuous Ambulatory Peritoneal Dialysis: Effects on the Heart. *Artif. Organs,* **19,** 241-244.

10. Pereira, B. J. G., and A. S. Levey AS, 1997: Hepatitis C virus infection in dialysis and renal transplantation. *Kid. Int.,* **51,** 981-999.

11. Dasgupta, M. K., 2002: Biofilms and Infection in Dialysis Patients. *Semin Dial.,* **15,** 338-346.

12. Liakopolous, V., E. Petinaki , S. Bouchlariotou , P. R. Mertens , M. Trakala, P. Kourti, J. Riehl, V. Ikonomov, and I. Stefanidis, 2004: Group B Streptococcus

(Streptococcus agalactiae) peritonitis associated with continuous ambulatory peritoneal dialysis (CAPD). *Clin. Nephrol*., **62,** 391-396.

13. House, A. A., B. Pham, and D. E. Page, 2004: Transfusion and recombinant human erythropoietin requirements differ between dialysis modalities. ***Nephrol. Dial. Transplant.,*** 13, **1763-1769.**

14. Rubin, H. R., N. E. Fink, and L. C. Plantinga, 2004: Patient Ratings of Dialysis Care with Peritoneal Dialysis *vs* Hemodialysis. *JAMA,* **291,** 697-703.

15. Meier-Kriesche, H. U., and K. Bruce, 2000: Waiting time on dialysis as the strongest modifiable risk factor for renal transplant outcomes: A Paired Donor Kidney Analysis1. *Kid. Int.,* **58,** 1311-1317.

16. Joseph, J. T., and R. M. Jindal, 2002: Influence of dialysis on post-transplant events. ***Clinical Transpl.,*** 16, **18-23.**

17. Heaf, J. G., H. Lokkegaard, and M. Medsan, 2002: Initial survival advantage of peritoneal dialysis relative to haemodialysis. *NDT*, **17,** 112-117.

18. Badve, S. V., C. M. Hawley, S. P. McDonald, D. W. Mudge, J. B. Roseman, F. G. Brown, and D. W. Johnson, 2008: Automated and continuous ambulatory peritoneal dialyses have similar outcomes. *Kid. Int.,* **73,** 480-488.

19. Rumpsfeld, M., S. P. McDonald, and D. W. Johnson, 2006: Higher peritoneal transport status is associated with higher mortality and technique failure in the Australian and New Zealand peritoneal dialysis patient populations. *J. Am. Soc. Nephrol.,* **17,** 271–278.

20. Mujais, S. and K. Story, 2006: Peritoneal dialysis in the US: Evaluation of outcomes in contemporary cohorts. *Kid. Int.,* **70,** 21-26.

21. Cameron, J. I., C. Whiteside, J. Katz, and G. M. Devins, 2000: Differences in quality of life across renal replacement therapies: A meta-analytic comparison. *Am. J. Kid. Dis.,* **35,** 629-637.

22. Juergensen, E., D. Wuerth, S. H. Finkelstein, H. Juergensen, A. Bekui, and F. O. Finkelstein, 2006: Hemodialysis and Peritoneal Dialysis: Patients' Assessment of Their Satisfaction with Therapy and the Impact of the Therapy on Their Lives. *Clin. J. Am. Soc. Nephrol*., **1,** 1191-1196.

23. Churchill, D. N., D. W. Taylor, and P. R. Keshaviah, 1996: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. *J. Am. Soc. Nephrol.,* **7,** 198 -207.24. Bargman, J. M., K. E. Thorpe, and D. N. Churchill, 2001: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: A reanalysis of the CANUSA Study. *J. Am. Soc. Nephrol.,* **12,** 2158–2162.

25. Paniagua, R., D. Amato, E. Vonesh, R. C. Rotter, A. Ramos, J. Moran, and S. Mujais. 2002: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J. Am. Soc. Nephrol.,* **13,** 1307-1320.

26. Lo, W. K., S. L. Lui, T. M. Chan, F. K. Li, M. F. Lam, K. C. Tse, S. C. W. Tang, C. B. Y. Choy, and K. N. Lai, 2005: Minimal and optimal peritoneal Kt/V targets: Results of an anuric peritoneal dialysis patient's survival analysis. *Kid. Int.,* **67,** 2032–2038.

27. Termorshuizen, F., F. W. Dekker, J. G. van Manen, J. C. Korevaar, E. W. Boeschoten, and R. T. Krediet, 2004: Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: An analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J. Am. Soc. Nephrol.,* **15,** 1061–1070.

28. Brown, E. A., S. J. Davis, P. Rutherford, F. Meeus, M. Borras, W. Reigel, J. C. D. Filho, E. Vonesh, and M. V. Bree, 2005: Survival of Functionally Anuric Patients on Automated Peritoneal Dialysis: The European APD Outcome Study. *J. Am. Soc. Nephrol.,* **14,** 2948-2957.

29. NKF-K/DOQI 2006: Clinical practice guidelines for peritoneal dialysis adequacy. Guideline 2. Peritoneal dialysis solute clearance targets and measurements. *Am. J. Kid. Dis.,* **49,** 103–116.

30. Lo, W. K., J. M. Bargman, J. Burkart, R. T. Krediet, C. Pollock, H. Kawanishi, and P. G. Blake, 2006: Guideline on targets for solute and fluid removal in adult patients on chronic peritoneal dialysis. ISPD Guidelines/Recommendations. *PDI*, **26,** 520-522.

31. 2005: European Best Practice Guidelines working group on Peritoneal Dialysis. 7. Adequacy of dialysis. *Neprol. Dial. Transpl.,* **20,** 24–27.

32. Davies, S., 2007: Clinical Practice Guidelines: 3b - Peritoneal Dialysis UK Renal Association Clinical Practice Guidelines; 5th Edition 2007. At: www.renal.org/guidelines5. Adequacy of PD

33. Prescription and Membrane Transport Characteristics. India Peritoneal Dialysis Practice Guidelines 2007. Chapter 3. Peritoneal Dialysis Society of India

34. Dawnay, A. B., and D. J. Millar, 1997: Glycation and advanced glycation end-product formation with Icodextrin and dextrose. *Perit. Dial. Int.,* **17,** 52-58.

35. Davies, S. J., L. Phillips, P. F. Naish, and G. I. Russel, 2001: Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. *J. Am. Soc. Nephrol.,* **12,** 1046-1051.

36. Duwe, A. K., S. I. Vas, and J. W. Weatherhead, 1981: Effects of the composition of peritoneal dialysis fluid on chemiluminescence, phagocytosis, and bactericidal activity *in vitro*. *Infect. Immun.,* **33,** 130-135.37. Dzo-Buxo, J. A., C. D. Farmer, and J. T. CI-Iandler, 1987: CCPD—"wet" is better than "dry." *Pent. Dial. Bull.,* **7,** 22.

38. DeFijter, C. W., H. A. Verbrugh, L. P. Oe, E. Heezius, A. J. M. Donker, J. Verhoef, and R. Gokal, 1993: Biocompatibility of a glucose-polymer-containing peritoneal dialysis fluid. *Am. J. Kid. Dis.,* **21,** 411-418.

39. Honda, K., K. Nitta, S. Horita, W. Yumura, H. Nihei, R. Nagai, K. Ikeda, and S. Horiuchi, 1999: Accumulation of advanced glycation end products in the peritoneal vasculature of continuous ambulatory peritoneal dialysis patients with low ultra-filtration. *Nephrol. Dial. Transplant.,* **14,** 1541-1549.

40. Ho-dac-Pannekeet, M. M., M. F. Weiss, D. R. de Waart, P. Erhard, J. K. Hiralall, and R. T. Krediet, 1999: Analysis of non enzymatic glycosylation *in vivo*: Impact of different dialysis solutions. *Perit. Dial. Int.,* **19,** 68–74.

41. Mahiout, A., G. Ehlerding, and R. Brunkhorst, 1996: Advanced glycation end-products in the peritoneal fluid and in the peritoneal membrane of continuous ambulant peritoneal dialysis patients. *Nephrol. Dial. Transplant.,* **11,** 2–6.

42. Krediet, R. T., M. M. Zweers, M. M. Ho-dac-Pannekeet, A. C. vander Wal, W. Smit, C. E. Douma, M. A. M. Mateijsen, and D. G. Struijk, 1999: The effect of various dialysis solutions on peritoneal membrane viability. *Perit. Dial. Int.,* **19,** 257– 266.

43. Mateijsen, M. A., A. C. van der Wal, P. M. Hendriks, M. M. Zweers, J. Mulder, D. G. Struijk, and R. T. Krediet, 1999: Vascular and interstitial changes in the peritoneum of CAPD patients with peritoneal sclerosis. *Perit. Dial. Int.,* **19,** 517–525.

44. Hendriks, P. M., M. M. Ho-dac-Pannekeet, T. M. van Gulik, D. G. Struijk, S. S. Phoa, L. Sie, C. Kox, and R. T. Krediet, 1997: Peritoneal sclerosis in chronic peritoneal dialysis patients: Analysis of clinical presentation, risk factors, and peritoneal transport kinetics. *Perit. Dial. Int.,* **17,** 136–143.

45. Paniagua, R., M. D. Ventura, M. Avila-Díaz, M. V. Martinez, M. C. Furlong, Z. G. Gonzales, D. Villanueva, O. Orihuela, M. C. P. Uribe, G. Alancatara, and D. Amato, 2009: Icodextrin improves metabolic and fluid management in high and high-average transport diabetic patients. *Perit. Dial. Int.,* **29,** 422-432.

46. Schalkwijk, C. G., P. M. ter Wee, and T. Teerlink, 2000: Reduced 1,2-dicarbonyl compounds in bicarbonate/lactate buffered peritoneal dialysis (PD) fluids and PD fluids based on glucose polymers or amino acids. *Perit. Dial. Int.,* **20,** 796-798.

47. Mistry, C. D., R. Gokal, and E. Peers, 1994: A randomized multicenter clinical trial comparing isosmolar Icodextrin with hyperosmolar glucose solutions in CAPD. MIDAS Study Group. Multicenter Investigation of Icodextrin in Ambulatory Peritoneal Dialysis. *Kid. Int.,* **46,** 496-503.

48. Paniagua, R., O. Orihuela, M. D. Ventura, M. Diaz, A. Cisneros, M. V. Martinez, M. C. Furlong, Z. G. Gonzales, D. Villanueva, M. C. P. Uribe, G. Alancatara, and D. Amato, 2008: Echocardiographic, electrocardiographic and blood pressure changes induced by Icodextrin solution in diabetic patients on peritoneal dialysis. *Kid. Int.,* **108,** 125-130.

49. Finkelstein, F., H. Healy, A. Abu-Alfa, S. Ahmad, F. Brown, T. Gehr, K. Nash, M. Sorkin, and S. Mujais, 2005: Superiority of Icodextrin compared with 4.25% dextrosefor peritoneal ultrafiltration. *J. Am. Soc. Nephrol.,* **16,** 546-554.

50. Davies, S. J., G. Woodrow, K. Donovan, J. Plum, p. Williams, A. C. Johansson, H. P. Bosselmann, O. Heimburgur, O. Simonsen, A. Devenport, A. Tranaeus, and J. C. D. Filho, 2003: Icodextrin improves the fluid status of peritoneal dialysis patients: Results of a randomised double blind randomized control trial. *J. Am. Soc. Nephrol.,* **14,** 2338-2344.

Chapter 60

Use of Information Technology in Peritoneal Dialysis

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Use of Information Technology in Peritoneal Dialysis

Introduction

Peritoneal dialysis (PD) as a treatment for patients with end-stage renal disease (ESRD) was adopted in India only in the mid-1990s. That timing was a result of initial misgivings about the viability of a home dialysis therapy in a predominantly rural, geographically vast country, with poor connectivity and access to health care, difficult sanitary conditions, and a tropical climate; however, the PD modality has shown impressive growth since then [1-3]. By conservative estimate, about 250 of the approximately 1000 nephrologists now prescribe PD to more than 6500 patients [4]. This growth contrasts with the prevailing declining trend seen in most Western countries, including the United States, which has experienced a drop in the PD utilization rate to 7% in 2010 from 14% in 1995.

Today, a major challenge affecting the acceptance and outcomes of PD is the perceived “inaccessibility” on the part of the patient to the nephrologist and to the “mother unit” (MU)—more so in geographically large countries with remote and inaccessible habitations, as typified by India, the United States, and Canada, among others.

Our PD unit has worked to innovate with practical and cost-effective solutions to overcome this barrier [5]. Rapid strides in communications connectivity have been made across the world: internet and mobile phone technology now truly penetrate almost every geographic and socio-economic boundary extant, especially in India. We are using the mobile phone short messaging service (SMS), inexpensive digital cameras, and the World Wide Web to address specific patient accessibility needs. Those technologies—coupled with a dedicated PD team (comprising medical and paramedical staff) and a regular home visit protocol [6]—have enabled us to develop a unique PD remote monitoring system. Patients are constantly in touch with their MU and nephrologist, communicating in real time, around the clock, with improved PD outcomes, especially in rural patients [7].

PD therapy has the ability to offer patients a fair deal of independence along with an improved quality of life (QoL). However, patients on PD still need to make regular visits to the PD centre to ensure proper technique and quality of therapy. Therefore, an important aspect of therapy is that the patient must be actively monitored along with daily recordings of weight, blood pressure, and fluid removal. Remote monitoring of the patient on PD offers the benefits of real-time monitoring and increased interaction with the PD centre which may facilitate both acute 'trouble shooting' as well as a means to correct any possible issues with regard to proper technique. Remote monitoring also ensures patient safety through continuous surveillance of critical portions of the treatment, compliance monitoring and

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automated collection of treatment data. Recent advances in telemedicine, telemonitoring, remote network access and sensor technologies have made such remote monitoring of the PD therapy feasible [8].

Why do we Need Telemedicine to Monitor PD Patients?

Telemedicine is the use of communication technology which may include a broad array of visual and audio platforms to allow the delivery of medical care at a distance from the health care provider. One of its goals and greatest promise is the ability to deliver high quality, affordable care to those individuals who, due to great distances or due to other reasons, would not normally have access to such benefits [9]. Such technology permits two-way communications between the patient and the medical staff over great distances with high fidelity and also allows the transmission of complex data such as medical records, images, audio, videos and physical examination findings through devices such as electronic stethoscopes, ophthalmoscopes and others. Over the last few decades, telemedicine platforms have become more widespread and now enable high quality, cost effective care in areas as diverse as cardiology, neurology, ophthalmology, dermatology, psychiatry, emergency medicine etc [10].

As we have already learnt from previous literature, PD has also shown to be more affordable than Hemodialysis (HD) in most parts of the world [11], especially in the more developed countries like the USA, and European countries where HD is commonly reported to be 1.40-1.50 times the cost of PD. However, despite these great advantages, PD is still quite underutilized. Published literature has indicated that lack of frequent nursing support unlike as in HD, less frequent interactions with the nephrologist, and lower level of clinical oversight with PD as compared to in-center HD could be possible reasons for PD underutilization [12, 13]. Therefore, a well-designed telemedicine platform can help address these 'therapy gaps' by providing an improved level of 'virtual' support with embedded educational content that continually enforces proper technique. Such additions to a PD programme can possibly lead to higher patient satisfaction, better comfort and eventually higher levels of acceptance of PD as a preferred form of RRT. Studies have already demonstrated that PD patients are willing to adopt such technology, with the belief that it could help simplify the therapy [14].

An Ideal Telemedicine Platform for PD

An ideal telemedicine platform focused on PD would have several characteristics (**Table 1 and 2**) [15]. Firstly, the system would have the capability to have two-way, rapid, real-time communications to help troubleshoot problems. This would be supplemented by the capability to regularly provide detailed assessments that allow the patient to remain at home and reduce the frequency of in-person visits to a PD center. The system would have the capability to monitor treatments when necessary and also monitor compliance with PD prescription. The system should have the capability to capture treatment data through automated collection of therapy

variables as well as the ability to analyze this data. An important, 'value-added' feature would be the ability to periodically provide educational content to retrain patients to perform optimal technique. Finally, the system would have the capability to improve outcomes such as peritonitis and exit site infection rates, volume and blood pressure control and decrease hospital admissions. By providing these functions, a telemedicine platform would allow for greater patient independence while instilling a greater degree of confidence that well-trained professionals are closely monitoring the therapy and are readily available for assistance. We would like to emphasize that, such systems may demonstrate clinical benefits even if they are merely able to increase patient satisfaction and willingness to use home therapies without significant gain in therapy outcomes.

Candidate platforms have been reported in clinical practice but are limited in their data capture ability and two-way communications [15]. A recent system described by Berman and colleagues applied to high-risk dialysis patients included remote monitoring of blood pressure, weight, glucose and pulse oximetry along with video capability that transmitted to a central location [16]. In this system, scheduled videoconferencing could occur and this was especially useful for patients in remote areas. In this pilot study, the investigators were able to demonstrate that utilization of this technology led to fewer hospitalisations, emergency room visits and health care expenditures. Currently, there are several commercially available systems designed specifically for PD. Although these systems have demonstrated considerable utility, they largely limit their focus to details of PD exchanges (volumes, timing, and alarms) and unfortunately do not incorporate any patient-specific factors or include real-time monitoring and video capture. Additionally, it should be noted that most of these systems are only available embedded within cycler technology.

Ideal Requirements for Telemedicine Monitoring of Peritoneal Dialysis

- Two-way communications with high-definition video or image capture
- Simple and intuitive alarm systems with a high degree of specificity
- Modifiable and customizable (i. e. monitoring capability at the beginning of training and for first few months may need to be more intensive and then scaled back)
- Generate useful reports
- Non-intrusive and portable.

Parameters of PD Exchanges to be Monitored

Fill and drain volumes

Fill and drain times

Blood pressure

Pulse

Oxygen saturation

Weight or bioimpedance

Time/duration of treatment dwell

Number of exchanges

Prescription of dialysis

Symptoms during therapy

Alarms and patient response to alarms

Activity during the day

Integrating Telemedicine into Care Paradigms

Telemedicine systems could ideally be included in the holistic care plan for the patient that would include home and clinic visits by the healthcare team. The theme of all PD home and clinic visit protocols would be to adequately complement the telemedicine programme with the required follow-up on each individual patient and to identify incorrect practices early before they become a serious problem. This can have a strong positive impact on PD technique survival which may eventually lead to significant cost savings. Home visit protocols are unique to and different in various PD programmes. In India, home visit schedules are prepared by the nephrology team and can be based upon medical needs and conducted by the clinical coordinators (CCs –equivalent to PD nurse). The CCs conduct a step-by-step assessment of patient well-being, monitor an exchange being performed by the patient or by the patient's primary care giver, perform a thorough check of the PD logbook/tablet application, review the most recent laboratory tests with the patients and their care-givers and are required to detect any condition that might require the attention of the nephrologist. They also check for exit site infections, signs of pedal oedema and examine the effluent bag for signs of peritonitis. Additionally, the CC also counsels the patient about their nutrition status, psychological well-being, physical fitness and rehabilitation levels after they finish their complete standardized assessment using SF-36® forms. After successful completion of the home visit, the CC enters all the details into the referral PD unit (RPU) records using their tablet computers [12]. These additions to the PD programme are to implement and do not significantly increase the cost of therapy. On an average a 100 patient programme would require 5 CC's which will impose an additional cost of USD 17,500 (including salaries, allowances, tablet computers with software licenses, USD = INR 65.00), which is roughly about USD 175 per year per patient.

Telemedicine Systems Reported in Published Literature

A study by Gallar *et al,* described the use of telemedicine in the long-term control of stable patients undergoing PD at home [17]. It described a system which made use of videoconferencing equipment installed in each patient's home, and connected to a videoconferencing unit at the hospital by three ISDN lines Another article by Nakamoto *et al,* described a fully automatic system known as an 'I-converter' which was used to collect and send data *via* cellular telephone. Later, the team upgraded the system to a newer version called the D-converter which used a 'Personal Handy-phone System (PHS)' and a 'Dopa card' [15].

These devices were described to have several advantages including high-speed data transmission, low power output, little electromagnetic interference with medical devices, and easy locating of patients. Struijk reviewed a typical remote monitoring systems making use of multiple cameras including a document scanner, video-conferencing software on a PC, an LCD monitor, integrated medical records, all connected via wireless internet [18]. He also mentioned the use of mobile applications to receive, record and store patient data for construction of a good electronic medical records (EMR) database. He also briefly described how 'e-consultations' can be very useful in managing remote patients. Schachter *et al,* described an interesting concept ofvirtual wards (VW). They described VW as a new model of integrated care that provides services to patients who are not physically admitted to hospital based on a model that would capitalize on the infrastructure built for the running of a home dialysis program (PD and Home HD). They envisaged VW to function as a pro-active, systematic management tool for vulnerable patients and also hypothesized that its implementation would mitigate gaps in care [19].

Remote Monitoring using Telemedicine in India

A tablet computer (iOS®) application for the purpose of making PD more accessible and to serve as an interactive user guide to support patients was recently developed by Nayak and co-workers [12, 20] (**Figure 1 and 2**). The latest version of the software is Health Insurance Portability and Accountability Act (HIPAA) compliant (and therefore does not compromise the patient's privacy). The earliest version of this software was first used in 2006 and had an immediate benefits for PD patients residing a thousand miles away from the MPU. Simple image transfers *via* email allowed the PD unit to diagnose and provide proper care. The current version of the software makes use of audio-visual depictions to show patients what to do at every step of a PD exchange. It is also capable of training patients before PD initiation and requires only a total of 4 hours training (i.e. four one-hour sessions spread over four days). This software can also potentially reduce training time as well as to periodically reinforce optimal technique. In addition to recording details about the PD exchange (time, volume, percentage of dextrose, and other variables), this software is also capable of recording videos and taking images. All the recorded information is automatically updated on a web based system database

that resides at the PD center. The web-based system also allows real-time interaction between patients and primary healthcare providers through online 'chats'. This 'chat' feature enables patients to use their tablet computer to discuss any other medical issue via the online system, which is visible only to the nephrologist and the CCs.

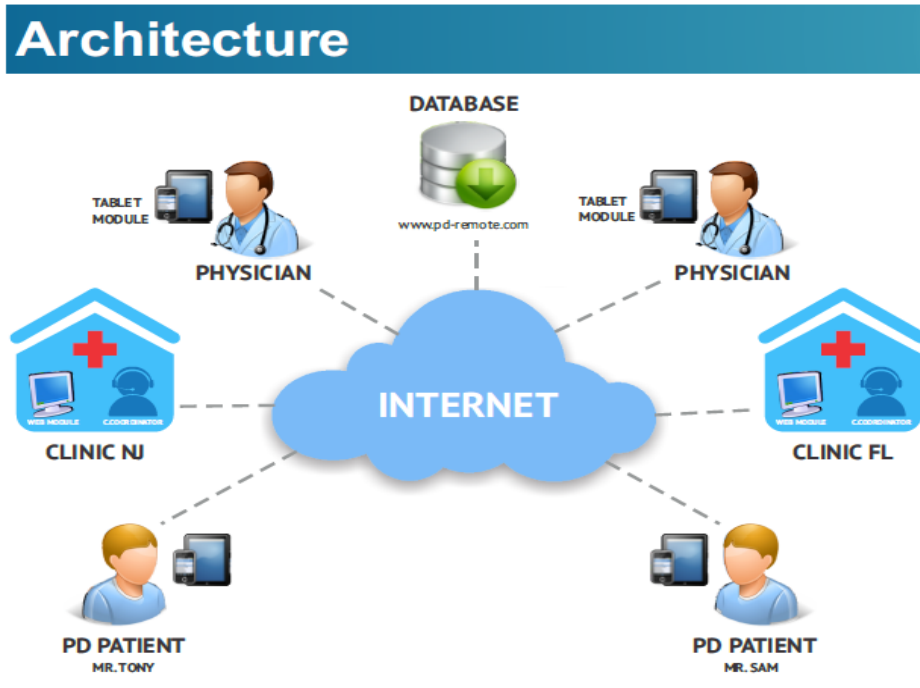

Figure 1: Software Process Architecture indicating the basic framework of the PD remote monitoring platform

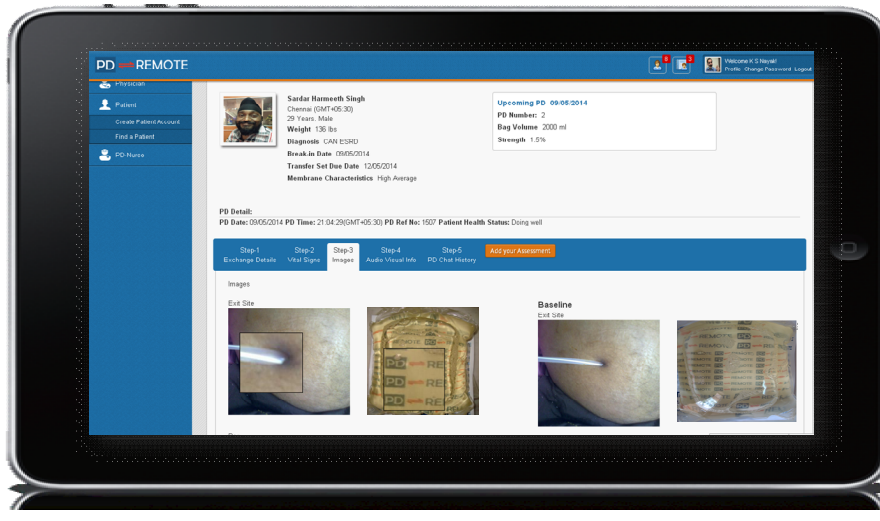

Figure 2: Snapshot of Tablet Software Showing Various Features of the Remote Monitoring Software

(Patient consent was obtained for permission to use the above image)

With this system, the care team can use the web-based system to make prescription changes, diagnose PD-related problems, and provide dietary advice, or any extra comments wherever it is required. Since there is a plethora of sensitive patient information, this database is secured, protected and is only accessible to the nephrologist and responsible PD nurses. The ultimate goal of the system is to help facilitate early diagnosis and resolution of exit site infections, peritonitis, fluid status, ultrafiltration failure or any other complications that might lead to hospitalizations if undetected. The remote monitoring system keeps caregivers aware about every patient and also enables scheduling of an emergency home visit.

Improved Clinical Outcomes and Socioeconomic Outcomes after Telemonitoring

A total of 246 PD patients, all of whom were enrolled on the earlier telemedicine system in their day-to-day care were observed and retrospectively analysed [12]. The patient cohort was divided into a rural group which included 115 patients and an urban group which included 131 patients. Mean follow-up was 4296 patient–months (2008 in the rural group, 2288 in the urban group). The final results showed similar technique survival rates, similar peritonitis rates, and similar exit site

infection rates in both groups throughout the study period. Rural patient group performed well on PD and had significantly better five year survival rates than did their urban counterparts, despite reduced proximity with respect to the PD center. Another study was designed to track quality of life and socio-economic related parameters of tele-monitored patients who performed PD in both urban and rural setting. This study also featured a comparison between the PD patients and the regular in-center HD patients under the care of the same nephrology center. Analysis of the results revealed no significant difference between rural and urban patients in terms of quality of life. It also demonstrated that rural patients had significantly reduced number of visits to the hospital, fewer hospitalized days, and lesser number of nephrologist consultations, which contributed to an overall lesser cost of therapy [20]. Future research is likely to demonstrate that implementation of such systems is accompanied by favourable clinical and socio-economic outcomes in PD patients.

Looking to the future

Although, we do not have such in-depth evidence at present, we know that telemedicine in PD shows great promise. The study by Gallar *et al,* went on to demonstrate a significant reduction in yearly hospitalisation rate during a two-year follow up period [17]. A much earlier short report by Cargill et al spoke about the use of a similar setup involving an ISDN 2E line for the transmission of images. Even though the study was conducted at a time when such technology was only available at a prohibitive cost, they were able to show that such a system could be useful for pediatric PD patients [21]. Nakamoto and team created a telemedicine system which they feel would be useful especially for elderly and handicapped patients on PD [15]. An article from Norway by Rygh *et al,* concluded by that telemedicine may potentially facilitate a communication based follow-up and improve safety within the home setting, making it easier to choose and live with home dialysis [13]. The current use of telemedicine shows promise in improving outcomes and uptake of PD across the world. However, these results have been reported in single centers and a broader clinical trial that randomises a larger number of patients to a telemedicine intervention is definitely needed. With larger trials, more substantive data on clinical and economic outcomes may be derived. However, what is currently clear is that the technology is available and may become part of standard PD care, if proved effective.

References:

1. Abraham, G., S. Bhaskaran, P. Soundarajan, R. Ravi, S. Nitya, G. Padma, and V. Jayanthi, 1996: Continuous ambulatory peritoneal dialysis. *J. Assoc. Physicians India*, **44,** 599–601.

2. Nayak, K. S., 2004: Asia, a melting pot for peritoneal dialysis practices: redefining and expanding peritoneal dialysis horizons in Asia. *Perit. Dial. Int.,* **24,** 422–423.

3. Nayak, K. S., M. V. Prabhu, K. A. Sinoj, S. V. Subhramanyam, and G. Sridhar, 2009: Peritoneal dialysis in developing countries. *Contrib. Nephrol.,* **163,** 270–277.

4. Abraham, G., B. Pratap, S. Sankarasubbaiyan, P. Govindan, K. S. Nayak, R. Sheriff, and S. A. J. Naqvi, 2008: Chronic peritoneal dialysis in south Asia: challenges and future. *Perit. Dial. Int.,* **28,** 13–19.

5. Aditi, N. K., A. K. Sinoj, and M. V. Prabhu, 2010: Improving peritoneal dialysis (PD) outcomes in rural patients compared to urban by employing novel and practical initiatives. *Perit. Dial. Int.,* **30,** 65.

6. Nayak, K. S., K. A. Sinoj, S. V. Subhramanyam, B. Mary, and N. V. Rao, 2007: Our experience of home visits in city and rural areas. *Perit. Dial. Int.,* **27,** 27–31.

7. Nayak, K. S., 2007: Key success factors for a quality peritoneal dialysis program. *Perit. Dial. Int.,* **27,** 9–15.

8. Rosner, M. H., and C. Ronco, 2012: Remote monitoring for continuous peritoneal dialysis. in Peritoneal Dialysis- State of the Art 2012. *Contrib. Nephrol.,* **178,** 68-73.

9. Hailey, D., R. Roine, and A. Ohinmaa, 2002: Systematic review of evidence for the benefits of telemedicine. *J. Telemed. Telecare,* **8,** 1-7.

10. Bashshur, R. L., T. G. Reardon, and G. W. Shannon, 2000: Telemedicine: A new health care delivery system. *Ann. Rev. Pub. Health,* **21,** 613-637.

11. Karopadi, A. N., G. Mason, E. Rettore, and C. Ronco, 2013: Cost of peritoneal dialysis and haemodialysis across the world. *Nephrol. Dial. Transplant.,* **10,** 2553-2569.

12. Nayak, A., A. Karopadi, S. Antony, S. Sreepada, and K. S. Nayak, 2012: Use of a peritoneal dialysis remote monitoring system in India. *Perit. Dial. Int.,* **32,** 200-204.

13. Rygh, E., E. Arild, E. Johnsen, and M. Rumpsfeld, 2012: Choosing to live with home dialysis- patient's experiences and potential for telemedicine support: a qualitative study. *BMC Nephrol.,* **13,** 13-21.

14. Lew, S. Q., and N. Sikka, 2013: Are patients prepared to use telemedicine in home peritoneal dialysis? *Perit. Dial. Int.,* **33,** 714-715.

15. Nakamoto, H., 2007: Telemedicine system for patients on continuous ambulatory peritoneal dialysis. *Perit. Dial. Int.,* **27,** 21-27.

16. Berman, S., C. Wada, D. Minatodani, T. Halliday, R. Miyamoto, J. Lindo, and P. J. Jordan, 2011: Home-based preventative care in high-risk dialysis patients: a pilot study. *Telemed. J. E. Health,* **17,** 283-287.

17. Gallar, P., M. Gutierrez, O. Ortega, I. Rodriguez, A. Oliet, J. C. Herrero, C. Mon, M. Ortiz, A. Molina, and A. Vigil, 2006: Telemedicine and follow up of peritoneal dialysis patients. *Nefrol.,* **26,** 365-3671.

18. Struijk, D. G., 2012: e-Health: remote health care models in peritoneal dialysis. *Contrib. Nephrol.,* **178,** 74-78.

19. Schachter, M. E., J. M. Bargman, M. Copland, M. Hladunewich, K. K. Tennanore, A. Levin, M. Oliver, R. P. Pauly, J. Perl, D. Zimmerman, and C. T. Chan, 2014: Rationale for a home dialysis virtual ward: design and implementation. *BMC Nephrol.*, **15,** 33.

20. Nayak, A., A. Anthony, S. V. Subhramanyam, K. S. Nayak, 2013: Remote monitoring of peritoneal dialysis: Why? Where? How? *Hong Kong J. Nephrol.,* **15,** 6-13.

21. Cargill, A, and A. R. Watson, 2003: Telecare support for patients undergoing chronic peritoneal dialysis. *Perit. Dial. Int.,* **23,** 91-94.

Chapter 61

Cost of Peritoneal Dialysis *versus* Haemodialysis across the World and in India

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Cost of Peritoneal Dialysis *versus* Haemodialysis across the World and in India

Introduction

As of 2013, end-stage renal disease (ESRD) affected the lives of more than 3.20 million people. Of these, over 2.50 million received renal replacement therapy (RRT) in the form of dialysis, under the two broad categories of haemodialysis or HD (over 2.25 million) and peritoneal dialysis or PD (over 272,000). This is a rather steep increase from 2008 (2.31 million ESRD, 1.59 million HD and 190,000 PD) [1, 2]. A possible explanation for the nearly 40% increase in the number of dialysis patients worldwide could be the considerable progress made in developing countries like India and China over the last 5-year period.

HD which is seen as the most conventional form of renal replacement therapy in India and in the rest of the world alike has been offered to ESRD patient since the early 1960s. PD, a relatively newer form of renal replacement, was first introduced in the late 1970s. Although, initially PD was not clinically as effective as HD, recent improvements have made PD and HD at par with each other. At the current level of technology, it is not unreasonable to consider HD and PD as clinically equivalent modalities when we consider the general population of ESRD patients, with similar survival rates at 6, 12, 24, 36, 48 and 60 months.

This is confirmed by the United States renal data system (USRDS) 2012 Annual Report, which adjusted for all possible patient characteristics [3] including age, sex, race, ethnicity and primary diagnosis. The same report goes on to say that the quality of life of patients on PD is at least as good as that of patients on HD, if not better.

HD versus PD cost: Comparison in literature

There are several published articles which compare the annual per patient cost of PD with that of HD. Given the lack of consistency of these reports, it is better to state the results using the ratio between the per patient annual cost of HD to that of PD; for example an HD/PD ratio of 1.50 signifies that HD is on an average 50% more expensive than PD. This approach, which was followed by Just *et al*. [4], has numerous advantages in an economic perspective. It avoids possible bias introduced by heterogeneity in currency, eliminating the need for conversion rates. Furthermore, currency values are influenced by inflating prices; by using the HD/PD cost ratio, we overcome the difficulties implied by adjusting for inflation.

It is evident from published literature that most developed countries can provide PD at a lesser expense to the healthcare system than HD. The evidence on developing countries is more mixed, but in most cases PD can be provided at a similar cost either by local production or by low import duties on PD equipment. The following table (**Table 1**) from a publication in 2013 [4] summarises the cost data in 46

countries. This conclusion that PD is more affordable than HD in most countries is further corroborated by the fact that some cases (*i.e.*, the basic cost assessments) do not consider the hidden costs like loss of productivity of patient and his family members and cost of transportation to the centre. For this reason, any possible bias deriving from the measurement error in costs is likely to underestimate—and not overestimate—the cost advantage of PD over HD. In some developing countries like India and Bangladesh, patients receive only twice weekly HD sessions instead of thrice weekly HD sessions due to prohibitive costs. We should take this into consideration when we are looking at the relative costs.

Table 1: The Cost of Dialysis in Various Countries

No.	Country	Year	Type of study	No. of recent studies	Total No. of studies	Final HD/PD cost ratio
1	India	2013, 2012	CB, CB	2	2	1.08
2	USA	2012, 2009, 2005	CB, CB, CB	3	5	1.29
3	Brazil	2012, 2010	CB, CB	2	2	0.93
4	Argentina	2011	R	1	1	1.00
5	Spain	2011	CU	1	2	1.40
6	Austria	2011	CU	1	1	1.68
7	Nigeria	2011	B	1	1	0.70
8	France	2011, 2007	CB, CB	2	5	1.51
9	Belgium	2010	R	1	1	1.25
10	Senegal	2010	B	1	1	1.38
11	South Africa	2010	B	1	1	0.58
12	Sudan	2010	B	1	1	0.89
13	Kenya	2010	B	1	1	1.33
14	Egypt	2010	B	1	1	0.22
15	Iran	2010	B	1	1	1.08
16	Chile	2009, 2007	CB, CB	2	2	1.03
17	Mexico	2009	CB	1	2	1.53
18	Uruguay	2009	B	1	1	0.81
19	Colombia	2009	B	1	1	1.00
20	Finland	2009	CB	1	2	1.38
21	Romania	2009	CB	1	1	1.45
22	China	2009	CB	1	1	1.16
23	Thailand	2009, 2007	CB, CE	2	2	1.10
24	Singapore	2009	CB	1	1	1.38
25	Australia	2009	CU	1	1	1.44
26	UK	2008	CB	1	8	1.94
27	Greece	2008, 2006	CU, CB	2	2	1.18
28	Pakistan	2008	B	1	1	0.81
29	Sri Lanka	2008	B	1	1	0.85
30	Vietnam	2008	B	1	1	1.00
31	Turkey	2008	CB	1	2	1.16
32	Italy	2007	CB	1	9	1.81
33	Germany	2007	CI	1	1	1.00
34	Croatia	2007	CB	1	1	1.53
35	Japan	2007	CB	1	2	0.85

No.	Country	Year	Type of study	No. of recent studies	Total No. of studies	Final HD/PD cost ratio
36	Hong Kong	2007	B	1	1	2.35
37	New Zealand	2007	CB	1	1	1.58
38	Indonesia	2006	B	1	1	1.03
39	Peru	2005	B	1	1	0.82
40	Malaysia	2005, 2005	CE, B	2	3	1.07
41	Canada	2002	CB	0	1	1.90
42	Sweden	2002, 2000	CU, B	0	1	1.36
43	Switzerland	2001	B	0	1	1.41
44	The Netherlands	1998	CE	0	1	1.54
45	Denmark	1998	CI	0	1	1.34
46	Philippines	1998	CE	0	1	1.14

B- Basic Cost Analysis; R- Reimbursement Tariff; CB – Cost Benefit Analysis; CE – Cost Effectiveness Analysis; CU – Cost Utility Analysis; CI – Cost Identification

*The final estimate reported in the table accounts instead for four daily exchanges of CAPD versus thrice weekly HD sessions.

**Final HD/PD ratio was estimated by calculating the arithmetic mean of HD/PD ratios reported in studies classified as recent (we considered studies published in 2005 or newer as recent studies). In the case of a few countries (Canada, Sweden, Switzerland, the Netherlands, Denmark and Philippines), no recent data were available so the final ratio was estimated using 2002, 2002 and 2000 combined, 2001, 1998, 1998 and 1998 data, respectively.

***Studies with CU/CE/CB methodology account for all possible costs and patient characteristics, studies with CI methodology account for all costs but not patient characteristics, studies with B only account for basic treatment costs without hospitalization and complications and studies with R methodology just show the reimbursement provided for the therapy.

Again, this factor will lead to lower estimates for the overall cost ratio. The actual HD/PD ratios might be higher than reported. For these reasons, such measurement errors deriving from heterogeneous methodologies (which are quite possibly present in literature) cannot invalidate the fact that PD is overall more cost-effective than HD.

Factors that influence HD and PD costs

Despite being clinically equivalent therapies, PD and HD have very dissimilar cost compositions. Considering the underlying production factors, HD can be viewed as a labour-intensive service, while PD is more capital-intensive [5]. Most of HD costs arise from the compensation of medical personnel devoted to assisting the patients, including doctors, nurses and technicians, since this kind of treatment is usually administered in-hospital or in-centre (we will not be considering home HD in this article). PD costs on the other hand are instead mainly composed of medical

consumables such as dialysate bags, and the cycler machine in the case of automated peritoneal dialysis (APD). Bearing these considerations in mind, it is quite straightforward to assume that these costs will vary in different parts of the world depending on resource availability. For instance, the costs connected to HD will vary, among many other factors, according to the availability and price of skilled labour; in the same way, the cost of PD will depend on the price at which a health-care provider in a particular country is able to acquire the main pieces of equipment necessary for the therapy. A combination of these and other factors will presumably reflect on the relative cost of PD with respect to HD.

Previous literature has already pointed out how economic factors play a prominent role in each country's dialysis modality mix, *i.e.*, the relative utilization of PD and HD. In particular, the characteristics of a country's health-care system, such as the public–private split in health-care expenditure [6] and the structure of financing and reimbursements for providers of ESRD care [7], ultimately determine the availability, distribution and funding of dialysis services. In addition, a country's overall development level is heavily correlated with relative cost of capital and labour, which is a key factor in the balance between the provision of the two types of dialysis: namely HD (more labour-intensive) and PD (more capital-intensive).

Cost of PD relies on the cost of the dialysis bags, which must be produced under stringent standards and regulations. If not manufactured locally, such bags need to be imported from abroad. Economies of scale in the provision of PD bags can be achieved in two ways:

1. If the national market for PD is sizeable enough, a local manufacturer can serve the market at a relatively low cost; for example, the Indian market is said to have over 6,000 PD patients today which makes it possible for some companies (like Mitra Industries Pvt. Ltd.; New Delhi) to make CAPD bags available to the patient for as less as INR 250 per unit.

2. If instead the internal market is not large enough, or not yet mature, PD bags can still be acquired by health-care providers at a low cost if the government relieves restrictions on their import, effectively taking advantage of the economies of scale of another country; one such example is Thailand, which, albeit it started from a relatively small PD population (about 1200 in 2008 [8]), is able to acquire bags at the lowest cost in the world (close to 3 USD per bag) [9].

Sometimes governments adopt policies that strongly favour one of the two dialysis modalities or the country in question, to the extent that the HD/PD cost ratio is isolated from its macroeconomic determinants. Following are important examples of such policies:

1. In Hong Kong, a long-standing PD-first government policy renders HD more than twice as expensive as PD [10].

2. Mexico's PD supplies market is truly oligopolistic; competition exists between Fresenius Medical Care, Baxter International and Pisa Farmacéutica Mexicana, which can significantly reduce the overall cost of PD therapy [11].

3. In Japan, doctors are paid a substantial fee for each HD patient, creating a financial disincentive to prescribe PD [12].

4. Germany has only recently introduced reimbursement schemes that are balanced between HD and PD, while its market still feels the inertia of many years of HD domination. A fee-for-service physician reimbursement system for HD—similar to Japan's—skews the balance as well. Currently, the utilization of home therapy is on the rise, only in the case of home HD but not PD. [13].

HD versus PD: Cost Comparison in India

In India, the cost of PD consumables is more or less similar all over the country while haemodialysis cost varies from one centre to another and from one city to another city. Due to this difference in haemodialysis cost, a uniform conclusion is not very simple to make. However, we can overcome this difficulty by comparison of both the modalities within the same centre. The article by Jeloka *et al.* [14] compares between three sessions of HD a week and three exchanges of PD a day which is considered as the standard practice all over India.

The study showed that even though the apparent dialysis cost of PD is higher than HD when only dialysate cost is compared to haemodialysis procedure cost, there is actually no difference between the two modalities in terms of the total monthly cost of treatment. The higher cost of dialysate is compensated by lower cost incurred in erythropoietin and travel to the centre per month. Cost and requirement of erythropoietin is almost twice in haemodialysis as compared to peritoneal dialysis. Total monthly cost of dialysis reported was similar in both HD and PD patients (INR 29,252 ± 6859 *vs.* INR 28,763±5486, *P*= 0.85). The lower cost of haemodialysis procedure *per se* as compared to the peritoneal dialysis procedure cost (INR 14,669±1376 *vs.* INR 19,528±4072, *P*=0.000) was compensated by higher cost of erythropoietin (INR 7160±3353 *vs.* INR 3093±1889, *P*=0.002) and travel cost (INR 1654 ±1085 *vs.* INR 76±66, P< 0.0001) to equalize the monthly cost between the two groups.

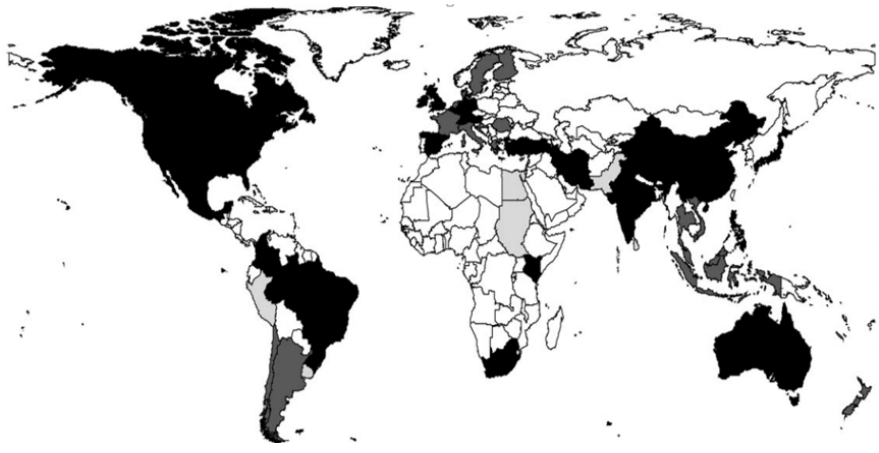

Figure 1: Economies of Scale for Production of PD Bags across the World.

**Dark Grey: Local manufacturing exists within the country*

**Light Grey: No local manufacturing exists within the country, but import duties reduced or slashed*

**Very Light Grey: No local manufacturing exists within country, regular or normal import duties apply*

**White: No data*

Conclusion

We are likely to see a further reduction in the cost of PD therapy as we continue to witness rapid strides in the field including better monitoring of PD patients due to telemedicine and extensive home visit programmes. Further, it is also possible that the cost of PD consumables will further reduce with increased uptake of the therapy. It is envisioned that a better understanding of the cost drivers and cost variables at a government policy level can lead to better decision-making which will ultimately benefit tens of thousands of patients with CKD in the country.

Nephrologists are called to make a decision on single patient treatment but also on general CKD therapeutic approach in a given population. Such decisions require department directors to consider a more holistic approach to renal replacement therapy including the choice of conservative therapy, PD, HD or transplantation. The cost of treatment should also be matched against QALYs (Quality adjusted life years—measure of QoL), survival rates, complication rates and hospitalization rates. The cost/benefit ratio should be considered in light of additional risk factors, population age and geographical issues.

The health-care system is also of great importance in the overall management strategy. Thus, we can imagine a sort of capitation in which the overall budget for the nephrologists has to be divided among all patients requiring CKD management and renal replacement therapy. Furthermore, this can be even complicated by the management of acute kidney injury with extracorporeal therapies that interferes with the management of the chronic disease. Thus, the physician is not only a care giver but also a manager in the selection of a sustainable programme for the patients with CKD.

References

1. Fresenius Medical Care, 2013: Fresenius Medical Care. ESRD Patients in 2013: a Global Perspective. Survey (http://www.vision-fmc.com/files/pdf_2/ ESRD_Patients_2013.pdf).

2. Fresenius Medical Care, 2008: ESRD Patients in 2008: a Global Perspective. Survey (http://www.vision-fmc.com/files/pdf/ESRD%20Patients%20in%202008.pdf).

3. United States Renal Data System (USRDS), 2012: Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases.

4. Nayak, K. A., G. Mason, E. Rettore, and C. Ronco, 2013: Cost of peritoneal dialysis and haemodialysis across the world. *Nephrol. Dial. Transplant.*, **28**, 2553-2569.

5. Just, P. M., M. C. Riella, E. A. Tschosik, L. L. Noe, S. K. Bhattacharyya, and F. de Charro, 2008: Economic evaluations of dialysis treatment modalities. *Health Policy*, **86**, 163-180.

6. Blake, P. G., 2004: The complex economics of modality selection. *Perit. Dial. Int.*, **24**, 509-511.

7. De Vecchi, A. F., M. Dratwa and M. E. Wiedemann, 1999: Healthcare systems and end-stage renal disease (ESRD) therapies—an international review: costs and reimbursement/funding of ESRD therapies. *Nephrol. Dial. Transplant.*, **14,** 31-41.

8. Jain, A. K., P. Blake, P. Cordy, and A. X. Garg, 2012: Global trends in rates of peritoneal dialysis. *J. Am. Soc. Nephrol*., **23**, 533-544.

9. Lo W. K., 2009: Peritoneal dialysis in the fareast—an astonishing situation in 2008: *Perit. Dial. Int.*, **29,** 227-229.

10. Yu A. W., K. F. Chau, Y. W. Ho, and P. K. Li, 2007: Development of the 'peritoneal dialysis first' model in Hong Kong. *Perit. Dial. Int.*, **27,** 53-55.

11. Cueto-Manzano, A. M., and E. Rojas-Campos, 2007: Status of renal replacement therapy and peritoneal dialysis in Mexico. *Perit. Dial. Int.*, **27**, 142-148.

12. Li, P. K., andK. M. Chow, 2001: The cost barrier to peritoneal dialysis in the developing world—an Asian perspective. *Perit. Dial. Int.*, **21**, 307-313.

13. Lameire, N., P. Peeters, R. Vanholder and W. Van Biesen, 2005: Peritoneal dialysis in Europe: an analysis of its rise and fall. *Blood Purif*., **24**, 104-114.

14. Jeloka, T. K., S. Upase, and S. Chitikeshi, 2012: Monthly cost of three exchanges a day peritoneal dialysis is same as of thrice a week hemodialysis in self-paying Indian patients. *Indian J. Nephrol.*, **22**, 39–41.

Chapter 62

Disposal of Peritoneal Dialysis Waste

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Disposal of Peritoneal Dialysis Waste

Peritoneal Dialysis (PD) procedure is a boon to the patients with end stage renal disease (ESRD). However, it generates awful lot of waste, which is left over after each treatment. This is a part of bio medical waste (BMW). BMW is defined as any waste generated during diagnosis, treatment or immunization of human beings or animals or in research activity. This waste produced in the course of healthcare activities has great potential and possibility for causing injury and infection than from any other types of waste.

Patients on continuous ambulatory/automated PD (CAP/APD) constitute unique problem for waste disposal planners. Each patient generates on an average 6-10 liters of fluid per day translating into about 3500 liters of waste fluid per patient per year which can be potentially recycled and reused for industrial purposes. They also generate 0.8-1 kilograms of plastic waste per day by means of bags and tubings amounting to 350kgs per patient per year. This plastic is usually disposed by land filling which is hazardous and leaves a large carbon footprint. To avoid this, plastic can be shredded and recycled for purposes like laying roads and creating objects, which should be the way forward.

Peritoneal Dialysis waste is potentially infectious

In the majority of instances, these patients are not infected except during episodes of peritonitis or those who have HIV, HBsAg and HCV infections. HIV antigen[1] and HBV antigen[2] have been detected in peritoneal dialysate of AIDS and HBV patients undergoing PD. However, the exact prevalence is not known. The BMW generated during PD can be categorized into three components for segregation at the source.

1. Dialysate;

2. Used dialysis bags and tubings; and

3. Sharps like needles used for IP medications.

Each of these three categories requires separate disposal system. Also, the disposal of PD waste in hospital setting and at home needs a separate system except for the disposal of dialysate which is the same at these two places. These are discussed below under two headings.

Disposal of PD waste in the hospital

The solid PD waste generated in the hospital is dealt with as per the standard guidelines issued by BMW management rules, 2016 issued by Govt. of India, Ministry of environment forest and climate change; however, there are no national

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guidelines for the disposal of spent dialysate either in the hospital or community [3].

1. Spent dialysate is drained into the toilet. A cupful of bleach (10%) should be poured into the toilet and the bag drained into it using gloves and facemask. The toilet should be flushed after 5 minutes, which would allow any particles to be killed before they reach the sewerage system.

2. Emptied PD bags and tubings should be placed in a plastic bag to which bleach/disinfectant is added wrapped and discarded into red coloured bags placed in the PD/renal unit in the hospital.

3. Sharp wastes such as needles are collected in puncture proof/ leak proof translucent containers.

Skilled workers taking universal precautions transport this to the common storage area of the hospital from where the BMW is transported to the final treatment and disposal site.

Disposal of PD waste at home/community

As there are no universal guidelines for the PD waste disposal at home each renal unit is advised to train the patient and care givers all the instructions regarding the disposal of dialysate fluid, bags and tubings during the initial training period before they get discharged from the hospital.

1. Spent dialysate is disposed similar to what is done to it at the hospital as described in the previous section.
2. Emptied PD bags and tubings are to be placed into separate plastic bag to which household bleach is added, wrapped and disposed of as household garbage. This holds well in those areas, which have a proper existing waste segregation management and disposal system in the community/municipality.
3. Sharp waste has to be kept in a translucent container, which can be secured from the renal unit. The patient has to be instructed to hand over this to the concerned authority/renal/PD nurse when he/she visits the care facility/hospital for the monthly follow-up. Community sharps should never be disposed of into council recycling or waste services.

References

1. Breyer, J. A., and M. A. Harbison, 1993: Isolation of Human Immunodeficiency Virus from Peritoneal Dialysate. *Am. J. Kid. Dis.,* **21,** 23-25.

2. Salo, R. J., A. A. Salo, W. J. Fahlberg, and J. T. Ellzey, 1980: Hepatitis B surface antigen (HBsAg) in peritoneal fluid of HBsAg carriers undergoing peritoneal dialysis. *J. Med. Virol.,* **6,** 29–35.

3. Government of India ministry of Environment, Forest and Climate change, Notification dated 28th March, 2016, New Delhi, pp.1-37. *Published in the Gazette of India, Extraordinary*, Part II, Section 3, Sub-section (i) (http://www.iwma.in/BMW%20Rules,%202016.pdf)

4. Bailie, G. R., S. F. Kowalsky, G. Eisele, and M. S. Schwartzman, 1991: Disposal of CAPD waste in the community. *Perit. Dial. Int.,* **11,** 72-75.

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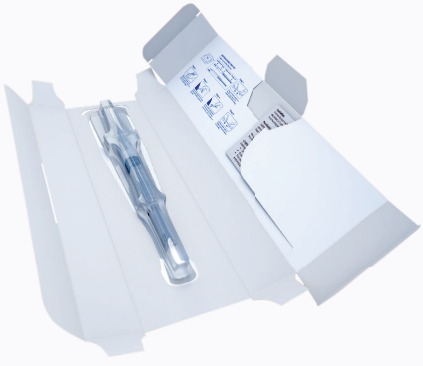

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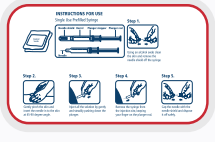

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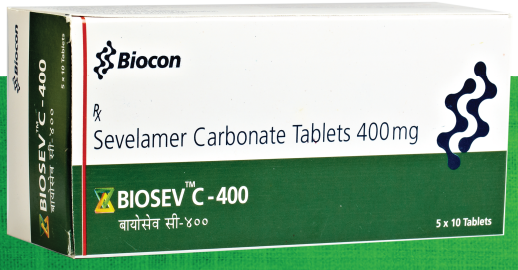

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1. Spaia, S. Phosphate binders: Sevelamer in the prevention and treatment of hyperphosphataemia in chronic renal failure. Hippokratia (2011). Available at: https://www.ncbi.nlm .nih.gov/pmc/articles/PMC3139674/.
2. Abraham, G. et al. Sevelamer carbonate experience in Indian end stage renal disease patients. Indian Journal of Nephrology (2012). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3459522/.

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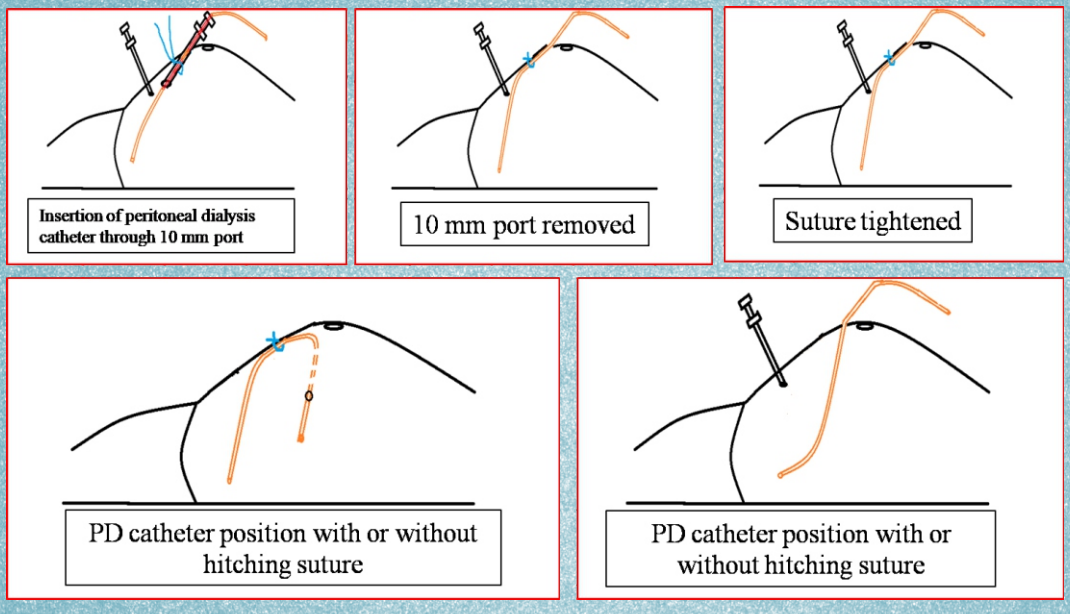
Composition:Each Prefilled syringe of 1ml contains: Recombinant Human Erythropoietin Alfa: 4000, 5000, 6000 and 10000 IU/ml and Human Serum Albumin as Stabilizer:2.5 mg/ml.INDICATIONS AND USAGE: Recombinant Human Erythropoietin is indicated for the treatment of anemia associated with CRF, including patients on dialysis (ESRD) and patients not on dialysis. CONTRAINDICATIONS: Erythropoietin is contrain dicated in patients with: 1. Uncontrolled hypertension. 2. Known hypersensitivity to mammalian cell-derived products. 3. Known hypersensitivity to Albumin (Human). PRECAUTIONS: The parenteral administration of any biologic product should be attended by appropriate precautions in case allergic or other untoward reactions occur in clinical trials, while transient rashes were occasionally observed concurrently with Erythropoietin therapy, no serious allergic or anaphylactic reactions were reported.The safety and efficacy of Erythropoietin therapy have not been established in patients with a known history of a seizure disorder or underlying hematologic disease (eg, sickle cell anemia, myelodysplastic syndromes, or hypercoagu lable disorders). In some female patients, menses have resumed following Erythropoietin therapy; the possibility of pregnancy should be discussed and the need for contraception evaluated. Pregnancy Category C:There are no adequate and well-controlled studies in pregnant women. Erythropoietin should be used during pregnancy only if potential benefit justifies the potential risk to the fetus. Nursing Mothers:It is not known whether Erythropoietin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Erythropoietin is administered to a nursing woman. ADVERSE EFFECTS: Erythropoietin is generally well tolerated. In a multicentric phase III open label prospective study conducted on Indian patients to evaluate the efficacy and safety of rHuEPO (Eryprо) in patients either on dialysis or non dialysis for management of anemia in CKD a total 154 adverse events were reported in the study with hypotension, headache, muscle cramps, fever, vomiting and cough in the descending order of frequency. All these events occurred in greater than five percent subjects in the study.Though the rHuEPO is known to increase the blood pressure or cause hypertension when used in CKD patients, the same occurred in less than five percent study subjects. This was also corroborated by the baseline and end of study blood pressure values which remained near their original values at the end of the study . Most of the adverse events reported i.e, 93% of them were mild in severity with 86% being reported as very unlikely to be related to the study drug, while only 2% of them were reported to be probably related to rHuEPO. All the events were managed by established standard of care defined in the medical literature.DOSAGE AND ADMINISTRATION: Chronic Renal Failure patients Adults/Subcutaneous Initial dose: 50 to 100 units/kg 3 times/wk. Maintenance: Individually titrate. Children/Subcutaneous 50 units/kg 3 times/wk. Please read the full prescribing information before usage.

Abridged Prescribing Information for Biosev C™:
Composition: BIOSEVTM C-400: Each film coated tablet contains Sevelamer Carbonate 400 mg, Excipients q.s., Colour: Tartrazine Yellow lake, Brilliant Blue lake and Titanium Dioxide IP. BIOSEVTM C-800: Each film coated tablet contains Sevelamer Carbonate 800 mg, Excipients q.s., Colour: Ponceau 4R and Titanium Dioxide IP. Indications: To control serum phosphorus in patients with chronic kidney disease (CKD) on hemodialysis or peritoneal dialysis and patients with CKD not on dialysis, with serum phosphate levels > 5.5 mg/kg. Dosage and Administration: Initial recommended dose of sevelamer (in g, taken over 3 times a day) is 2.4, 3.6 to 4.8, and 4.8, when serum phosphate level (mg/dL)observed is 5.5 to ≤7.5, 7.5 to ≥9 and ≥9 respectively. Not recommended for use in patients with serum phosphorus <1.78 mmol/L and in children <18 years. Tablets should be swallowed intact and should not be crushed, chewed, or broken. Contraindications: bowel obstruction and hypophosphatemia. Warnings and Precautions: Caution should be taken when sevelamer is used in following patients: dysphagia; swallowing disorder; severe gastrointestinal motility disorder including untreated or severe gastroparesis, retention of gastric contents and abnormal or irregular bowel motion; active inflammatory bowel disease and major gastrointestinal tract surgery. Treatment with sevelamer should be re-evaluated in patients who develop severe constipation or other severe gastrointestinal symptoms. Serum vitamin A, D, E, K, folic acid, calcium status should be assessed regularly; vitamin supplements and elemental calcium should be given, if necessary. Monitoring serum levels of calcium, bicarbonate and chloride are recommended in patients with CKD, as the patients are predisposed to metabolic acidosis. Patients on peritoneal dialysis should be closely monitored for symptoms of peritonitis to ensure the correct use of appropriate aseptic technique. In patients with secondary hyperparathyroidism, use within the context of a multiple therapeutic approach. Pregnancy and Lactation: Category C, sevelamer should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is unknown whether sevelamer is excreted in human breast milk. A decision on intake of the drug in lactating women is based on potential risk-benefit analysis. Drug Interactions: Ciprofloxacin, ciclosporin, mycophenolate mofetil, tacrolimus, levothyroxine, anti-arrhythmic, anti seizure drugs. Undesirable Effects: Diarrhoea, dyspepsia, flatulence, abdominal pain, nausea, vomiting, upper abdominal pain, constipation, headache, infection, hypertension, hypotension, thrombosis, cough, pruritus, rash, intestinal obstruction, ileus/subileus, and intestinal. Presentation: BIOSEVTM C-400/ BIOSEVTM C-800: Each carton contains 5 blister pack of 10 tablets each. Marketed By: Biocon Limited, 20th K.M., Hosur Road, Electronics City, Bangalore - 560100, India.

Abridged Prescribing Information Bionesp™:
COMPOSITION: Each prefilled syringe contains: Darbepoetin Alfa (DNA origin) and excipients viz. sodium phosphate monobasic monohydrate, polysorbate 80, sodium chloride, sodium phosphate dibasic anhydrous and water for stability. INDICATIONS AND USAGE: Darbepoetin Alfa is indicated for the treatment of anemia with CRF including patients on dialysis and not on dialysis. CONTRAINDICATIONS: Darbepoetin Alfa is contraindicated in patients with 1. Uncontrolled hypertension. 2. Known hypersensitivity to active substance or any of the excipients. 3. Pure red cell aplasia (PRCA) that begins after treatment with Darbepoetin Alfa or other ESA's. PRECAUTIONS: 1. Increased Mortality, Serious Cardiovascular Events, Thromboembolic Events, and Stroke: Patients with chronic renal failure comparing higher Hemoglobin targets (13 - 14 g/dL) to lower targets (9 - 11.3 g/dL), Darbepoetin Alfa and other ESAs increased the risk of death, myocardial infarction, stroke, congestive heart failure, thrombosis of hemodialysis vascular access, and other thromboembolic events in the higher target groups. Hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit. Use caution in patients with co-existent cardiovascular disease and stroke. Darbepoetin Alfa and other ESAs increased the risks for death and serious cardiovascular events in controlled clinical trials of patients with cancer. These events included myocardial infarction and stroke (Hemoglobin rise of > 1 g/dL over 2 weeks may contribute to these risks). ESAs increased the risk of death in patients undergoing CABG and the risk of DVT in patients undergoing orthopaedic procedures. 2. Hypertension: Darbepoetin Alfa is contraindicated in patients with uncontrolled hypertension. In Darbepoetin Alfa, approximately 40% of patients with CKD required initiation or intensification of antihypertensive therapy during the early phase of treatment. Hypertensive encephalopathy and seizures have been reported in patients with CKD receiving Darbepoetin Alfa. Advise patients of the importance of compliance with antihypertensive therapy and dietary restrictions. 3. Seizures: Risk of seizures has been reported in patients with chronic renal failure when treated with Darbepoetin Alfa. During the first several months of therapy, blood pressure and the presence of premonitory neurologic symptoms should be monitored closely. 4. Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) and of severe anemia, with or without other cytopenias, associated with neutralizing antibodies to erythropoietin have been reported in patients treated with Darbepoetin Alfa. Any patient who develops a sudden loss of response to Darbepoetin Alfa, accompanied by severe anemia and low reticulocyte count, should be evaluated for the presence of neutralizing antibodies to erythropoietin. Permanently discontinue Darbepoetin Alfa in patients who develop PRCA following treatment with Darbepoetin Alfa or other erythropoietin protein drugs. Do not switch patients to other ESAs. 5. Lack or Loss of Response to Darbepoetin Alfa: Deficiencies of infections, inflammation and bleeding should be suspected. 6. Allergic Reactions: Potential serious allergic reactions, including anaphylactic reactions, angioedema, skin rash and urticaria, associated have been reported. 6. Dialysis Management: Patients receiving Darbepoetin Alfa may require increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis. Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Darbepoetin Alfa should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Because many drugs are excreted in human milk, caution should be exercised when Darbepoetin Alfa is administered to a nursing woman. ADVERSE EFFECTS: Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism, Hypertension, Seizures, PRCA, Serious allergic reactions which are mentioned in detail in precautions. DOSAGE AND ADMINSTRATION: Correction of anemia: The initial dose by subcutaneous administration is 0.45 mcg/kg body weight, as a single injection once weekly. Alternatively, in patients not receiving dialysis, an initial dose of 0.75 mcg/kg may be administered subcutaneously as a single injection once every 2 weeks or 1.5 mcg/kg once monthly. Maintenance: Individually titrate to target Hemoglobin levels within the range of 10 to 12 g/dL. Conversion from Epoetin Alfa to Darbepoetin Alfa and dose
To report adverse events and/or product complaints visit our website www.biocon.com or call Toll Free No.: 1800 102 9465 or e-mail : drugsafety@biocon.com
For further information please refer to Full prescribing information. For use of a Registered Medical Practitioner or Hospital or Lab use only.

www.biocon.com



Insertion Technique for Prevention of Catheter Tip Migration

Radhakrishna K, Sandeep P, Chakarpani U, Venkata Rami Reddy V, Ram R, Siva Kumar V. Insertion technique for prevention of peritoneal dialysis catheter tip migration. Int Uro Nephrol. 2014;46 (9):1867-8.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