Editorial:

Sepsis and related syndromes: lessons learnt, the challenges ahead

Sepsis begins with a microbial invasion and leads to a dysregulated host response with dangerous consequences of organ dysfunction, hypotension and tissue hypoxia. For a practicing clinician, sepsis is an increasingly familiar challenge, and right understanding and intervention in this dangerous scenario will save several lives. In recent times, sepsis has emerged as the fourth major cause of mortality all over the world. Further, 30% of this subset of hospitalized patients develop multiple organ dysfunction syndrome (MODS), and the severest form of sepsis which is septic shock carries a mortality of up to 60%.[1] There is evidence to show that with the better understanding of its pathophysiology the prognosis in sepsis is improving over the years.[2]

The documentation of data regarding sepsis has been somewhat difficult given that broad definitions tend to lump simpler conditions as sepsis and precise definitions may miss many patients. As per the Third International Consensus Definitions for Sepsis and Septic Shock,[3] *sepsis* is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection; organ dysfunction is represented by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or more; and septic shock is defined as a subset of sepsis where profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Septic shock can be clinically detected by a vasopressor requirement to maintain a mean arterial pressure of ≥ 65 mm Hg and serum lactate level > 18 mg/dL in the absence of hypovolaemia. Thus, our current understanding provides better clarity regarding the degrees of severity of sepsis and relatd syndromes emphasizing the need for urgent intervention in sicker patients.

Our approach to sepsis has changed with the better understanding of the pathophysiology. The key issues to contend with in sepsis are the host response triad of dysregulated inflammation, coagulation, fibrinolysis and the development of septic shock in addition presents cellular, and biological abnormalities which contribute to mortality.[4]

The untoward consequence is the damage to the microcirculation causing organ dysfunction, and each organ involved increases the mortality by 15%-20%.[5] Mycoardial depression and excessive nitric oxide (NO) synthesis causing widespread vasodilatation lead to septic shock,which severely compromises tissue oxygenation.

Given the fact that reversibility of sepsis is possible only in the earlier phases of this dysregulated immune response ,early recognition and treatment is probably life saving in sepsis. Time is literally life, as prognosis depends on how early appropriate treatment is instituted. Hence various criteria and scoring systems have evolved to identify the patients at high risk, needing early intervention in sepsis.[6]

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Early recognition of septic shock is based on two reliable parameters: requirement of vasopressors to maintain mean arterial pressure of > 65 mm of Hg and serum lactate levels of >18 mg/dL in the absence of hypovolemia. These criteria point to profound cellular and metabolic abnormalities and carry an increased mortality of up to 40%. In the emergency room, to triage patients according to severity, a quick SOFA score (qSOFA) has been applied to advantage. This takes into account cardiorespiratory parameters of blood pressure < 100 mm of Hg, respiratory rate > 22 and altered mentation[7]. Since no investigations are involved in this score, this has the advantage of application even in resource poor settings for emergency management.

The treatment of sepsis has evolved over the years. In septic shock, the 2016 Surviving Sepsis Campaign 2016 (SSC 2016) guidelines[8] are clear that initial fluid resuscitation must be with intravenous crystalloid (upto 30 mL/kg) administered in the first crucial 3 hours. This is to restore the blood volume, tissue perfusion and alleviate tissue hypoxia which can aggravate organ dysfunction.[9] Further fluid requirements must be reassessed based on response, and patient's age and clinical profile. The need to maintain mean arterial pressure > 65 mm Hg and normalizing initially elevated lactate levels is well accepted by all guidelines. The vasopressor of choice according to the 2016 SSC guidelines[8] is noradrenaline, followed if needed by vasopressin as the second ionotrope choice. Dopamine is not recommended except in select patients who have no tachycardia.

Drawing blood cultures and instituting appropriate antimicrobial therapy is probably the most important life saving intervention. The choice of antibiotic must be empirical ,aimed at the particular infection and source suspected, and broad based in the beginning, being narrowed down to precision after cultures are available. Currently Gram-negative sepsis is much more common than Gram-positive bacteraemia, but antibiotic choices need to be targeted to source of infection. The antibiotic should be continued for a period of 7-10 days, again based on response and host factors. Drainage of abscesses and removal of lines or catheters which are deemed sources of infection must be done early enough to shorten the course of illness.[8] It must be mentioned that culture positive sepsis is seen only in 30%-40% of patients and in the rest the antibiotic is based on intelligent guesswork by clinician based on prevailing data of infections especially in hospital based sepsis.

Corticosteroids have fallen out of favour in the current SSC 2016 guidelines and are not recommended for hypotension. Component therapy with red blood cells (RBCs) is recommended for haemoglobin < 7 g/dL and platelet count <10,000/mm^3 or 20,000/mm^3 with bleeding.[10] Higher platelet counts up to 50,000/mm^3, require platelet transfusion only if there is a significant bleeding risk in patients or surgical interventions are needed. The blood glucose levels need to be held under 180 mg/dL to avoid hypoglycaemia with insulin infusions if needed.

Mechanical ventilation in patients with sepsis with acute respiratory distress syndrome (ARDS) must follow the current guidelines of using low tidal volumes to avoid volutrauma , and early weaning trials must be instituted as patient shows improvement. Supportive measures such as prophylaxis against venous thromboembolism and ulcer prophylaxis must be implemented. Early enteral nutrition is advised strongly to maintain nutritional needs of these critically ill patients and avoid gut microbial translocation. Several new approaches have been tried in managing sepsis including anti endotoxin treatment, cytokine antibodies, glucocorticoid receptor antibodies levasemindon,[11] hyperbaric oxygen and fibrates, but none of these has been found to be very useful.

The understanding of the pathophysioslogy of sepsis at the cellular and cytokine level is still a challenge. The future may open up more possibilities for stopping the unregulated damage of tissues. Till then, good clinical sense, simple laboratory parameters and sensible targets will still continue to save lives.

Sudha Vidyasagar
Department of Medicine
Kasturba Medical College
Manipal
e-mail: *vsagar33@yahoo.com*

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