Chapter

99

Sepsis in 2007

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INTRODUCTION

Sepsis is defined as suspected or proven infection plus a systemic inflammatory response syndrome (SIRS)[1]. SIRS is diagnosed by the presence of two or more of the following features: (a) oral temperature >38°C or < 36°C, (b) heart rate > 90/min, (c) respiratory rate > 20/min and (d) white blood cell count > 12,000/cumm or < 4000/cumm[2]. When accompanied by organ dysfunction characterized by features such as hypotension, hypoxemia, oliguria, metabolic acidosis, etc. the condition is referred to as severe sepsis. Severe sepsis with hypotension resistant to adequate fluid resuscitation constitutes septic shock (Fig. 1).

The management of sepsis has seen the emergence of many new innovations and treatment strategies. Not all benefit every situation. It is therefore imperative to administer therapy that is individualized to a particular situation/clinical setting. The overall treatment thus depends on the status of the patient in terms of the stage of illness and the underlying pathophysiological processes. Heroic treatment may prove counterproductive and thus the aim should be an early identification of the underlying pathophysiology, an assessment of the immunological status of the patient, the likely causative organism (s) based on the source of the infection and the stage of the illness. Though targeted therapy individualized to each patient is ideal and desired, this review discusses certain broad management guidelines that are likely to be beneficial to treating clinicians.

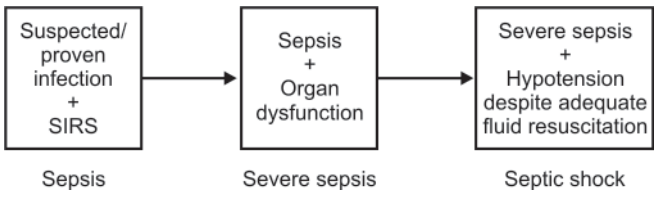

Fig. 1: Standardized terminologies in infective conditions

PATHOPHYSIOLOGY OF SEPSIS

The pathophysiolgical process involves complex interactions between a number of factors which include the type of causative organism, the immune status of the patient and the activation status of the patient's inflammatory and coagulation responses[3,4]. The outcome of the condition depends largely on the type and characteristic of the infecting organism and the nature of the patient's responses. In the setting of an inadequate host response to the infection, sepsis with organ dysfunction is very likely. A high infective load, highly virulent organisms, the presence of super-antigens, compromised host immune responses and antibiotic resistance often lead to progression of the condition[5].

Activation of the host innate immune mechanisms leads to release of pro and anti-inflammatory molecules. The resultant activation of neutrophils attempts to kill the infecting organism but in the process also inflicts vascular endothelial injury. This results in the release of mediators that increase vascular permeability resulting in tissue edema. The activated endothelial cells also release nitric oxide which is a potent vasodilator and a key mediator of septic shock. The inflammatory response of early sepsis is amplified by specific humoral and cell mediated adaptive immune responses.

Sepsis also results in an alteration of the pro and anticoagulant balance of the body. There is an increase in pro-coagulant activity mediated by the lipo-polysaccharide present in gram-negative bacteria. The

anticoagulant machinery of the body is conversely suppressed by sepsis resulting in lowered levels of anti coagulant molecules such as protein C, S and anti thrombin III[6].

Sepsis is also associated with immunosupression and apoptosis which is often the cause of late death in patients[7]. Under experimental laboratory conditions, monocytes from patients with sepsis have been seen to express lower amounts of pro-inflammatory cytokines compared to healthy individuals[8]. Apoptosis of critical immune, epithelial and endothelial cells and a shift to an anti-inflammatory status is probably responsible for the multi-organ dysfunction in sepsis. The apoptotic process is stimulated by pro-inflammatory molecules, activated T and B cells and high levels of circulating glucocorticoids common in such situations[9]. As a result of altered signaling pathways multi-organ dysfunction and tissue injury ultimately results.

CLINICAL PRESENTATION AND DIAGNOSIS OF SEPTICEMIA

The aims of clinical evaluation in cases of sepsis are essentially three: the establishment of a diagnosis, an estimation of severity and prognosis of the condition and identification of the underlying cause. It must be emphasized that the presentation is often a medical emergency requiring immediate resuscitation and empirical therapy. A full clinical assessment would be delayed in such cases.

Sepsis may not always present with classical clinical features and diagnostic investigative markers. The clinical picture is determined by a number of factors which include the site of infection, the infecting organism, the immune status of the host, the presence of coexisting illnesses among others. The clinical setting is an extremely important factor in all cases. Nosocomial infections and community acquired infections need to be distinguished to ascertain the causative organism and antibiotic sensitivity. Sepsis must always be suspected and considered in the differential diagnosis of any unexplained illness[3].

The presenting symptoms of sepsis are usually non-specific in the form of sweating, chills and rigors, nausea and vomiting, headache and breathlessness. Elderly patients may present with confusion. Severe sepsis may present as unexplained hypotension and the rapid onset may mimic myocardial infarction or a massive pulmonary embolism. In some cases, symptoms specific to the underlying infection may be present in the form of cough, dysuria or features of meningial irritation which may make the diagnosis easier. In all cases a thorough history may reveal pointers towards establishing a definitive diagnosis as well as aid the choice of empiric therapy. Such history should include history of recent surgical procedures, presence of prosthetic devices in the body, immunosuppressive medication, antibiotic therapy, recent travel, contact with animals and local disease outbreaks. Risk factors for nosocomial infection include patients on ventilators for more than 3 days, presence of catheters (intravenous and urinary), nasogastric tubes, cases of trauma, cases on stress ulcer prophylaxis and patients with prolonged stay in the hospital[10]. Intravenous lines that have not been changed for more than 4 days are a high risk source of infection. Other major sites of infection that must be suspected in critically ill patients are the abdomen which includes intra abdominal abscesses, necrotic gut, pancreatitis and acute cholecystitis, the urinary tract, heart valves, meninges, joints and bones, nasal sinuses, genitor urinary and gastrointestinal tract. In fact, any small infective focus any where in the body can lead to sepsis even in an apparently healthy individuals.

The clinical examination of cases may reveal features of SIRS with or without features of organ failure. The classic picture is that of a febrile patient who is tachypneic, tachycardic, hypotensive, has a bounding arterial pulse and warm peripheries. The patient may be disoriented and oliguric. A detailed physical examination is imperative and should include the skin, ear, nose throat, sinuses and all wounds and pressure points. Rectal and vaginal examinations are a must which are often overlooked. In already hospitalized patients all indwelling catheters must be viewed with suspicion. Fundus examination must be carried out to look for retinal lesions including *Candida endophthalmitis*. In certain cases, clinical examination may directly reveal the underlying cause of infection such as purpuric rash or peripheral gangrene of meningococcemia, peripheral emboli of endocarditis and erythematous rash of staphylococcal or streptococcal toxic shock syndrome. In hypotensive patients, myocardial infarction, pulmonary embolism, cardiac tamponade and hypovolemic/redistributive shock must be considered.

LABORATORY INVESTIGATION IN SEPTICEMIA

The initial investigations for all cases of suspected sepsis should include a full blood count and peripheral film, urinalysis, chest X-ray, cultures of blood, sputum, urine, wound discharges and IV lines. It is important to ascertain the coagulation status of the patient and a coagulation profile must be requested for Plasma lactate, arterial blood gases must be done wherever available. Plasma lactate, which is often elevated 3-5 times, relates

to the degree of tissue hypoxia and are useful in not just confirming the diagnosis but also monitoring the response to therapy. It is interesting to note that only about 10% of ICU patients with a clinical diagnosis of septic shock have positive blood culture reports[11]. The reasons for the same are the possible effects of prior antibiotic therapy, an inflammatory state that is not necessarily infected, viral/fungal infections and faulty culture methodology. Other investigations mandatory are estimation of blood glucose, serum electrolytes, renal and liver functions and ultrasound of the abdomen. Specific investigations such as CT imaging, aspiration and culture of fluid/pus collections are based on the clinical setting of each case.

TREATMENT MODALITIES FOR SEPSIS

The management of sepsis can be considered at three different levels. The first involves identification of the underlying cause and administration of specific therapeautic modalities. The second involves the general supportive care of patients and the final aims at the management of associated clinical conditions/ complications. Certain newer treatment modalities with potential for use in the near future must also be considered where appropriate.

The treatment modalities for sepsis should ideally be tailor-made for specific situations. Certain consensus guidelines for management of this condition are available[12]. Therapy is broadly decided by the stage of the illness. Emergency care is ideal for early stage of sepsis (0-6 hours) and patients in later stages require critical care. The principles of emergency care center on early goal-directed therapy,[13] lung protective ventilation[14] and broad spectrum antibiotics[15,16]. In certain situations, activated protein C can also be considered[17].

Early goal-directed therapy has been reported to reduce mortality and duration of hospitalization. The therapy mainly consists of crystalloids administration to keep CVP at 8-12 mm Hg, vasopressor if mean arterial pressure is less than 65 mm Hg. Dobutamine therapy is needed if venous oxygen saturation is below 70% even after optimizing the CVP, mean arterial pressure and a hematocrit level of 30% The mechanisms underlying the benefits of this therapy are unknown but may include reversal of tissue hypoxia and reduction of inflammation and coagulation defects[18].

Ventilatory support is usually considered once early goal-directed therapy has been initiated. Acute lung injury very often complicates sepsis and thus use of relatively low tidal volumes also known as lung-protective ventilation, forms an important part of the management of such cases. Six ml per kg ideal body weight tidal volume has been reported as beneficial when compared to 12 ml per kg ideal body weight. Such ventilation is documented to decrease mortality rates, lessen organ dysfunction and lower levels of cytokines[19]. Judicious and appropriate sedation is required for patients receiving ventilation[20]. Care must be taken to ensure that the sedation is not excessive. Neuromuscular blocking agents should be avoided with the aim of reducing the risk of prolonged neuromuscular dysfunction[21].

The causative organism and the site of infection are generally not certain in the early stages of sepsis. The expeditious use of intravenous *broad spectrum antibiotics* is therefore indicated in the interim while the culture and host immune status is ascertained. The choice of antibiotics must be judicious and appropriate to the clinical setting and likely pathogenic organisms. The possibility of antibiotic resistance in the concerned hospital must be borne in mind. The use of inappropriate/ineffective antibiotics in the early management of sepsis has a direct bearing on the outcome of sepsis and septic shock[22].

The use of *activated protein C* should be considered once the above measures have been initiated. This therapeautic modality should be offered in cases of severe sepsis in a dose of 24 μg per kg per hour for 96 hours for its anti-inflammatory, anti-apoptotic and anticoagulant actions. The indications for the same are an Acute Physiology and Chronic Health Evaluation (APACHE) II score of greater than or equal to 25 or dysfunction of two or more organs[23]. Activated protein C has been reported to decrease mortality and ameliorate organ dysfunction in severe sepsis. Its use in low-risk patients is not justified. Activated protein C therapy is contraindicated in patients with history of recent trauma or surgery (<12 hours), recent stroke, concurrent therapeutic anticoagulation and a platelet count of < 30,000/cumm to avoid serious bleeding and intracerebral bleeding.

General supportive care. This revolves largely around cardio-respiratory support, nutrition of patients, prevention of deep vein thrombosis, prevention of stress ulcers and prevention of nosocomial infections. Cardio-respiratory support is aimed at maintaining perfusion and venous oxygen saturation by means of fluids, transfusion, vasopressor agents and assisted ventilation. Enteral nutrition is safer and more effective than total parentral nutrition[24]. The latter may be required in certain cases such as patients with abdominal sepsis, surgery or trauma. The risk of deep venous thrombosis

can be addressed by use of prophylactic heparin provided the patient has no coagulopathy or active bleeding. Stress ulcer prophylaxis with H_2 receptor antagonists must be considered especially in patients on ventilatory support. The same may reduce the risk of gastrointestinal hemorrhage[25]. The efficacy of proton pump inhibitors is yet to be established. Nosocomial infections can be controlled by avoiding immunosuppression, early weaning from ventilatory support, removing catheters and use of narrow spectrum and appropriate antibiotics.

A number of clinical conditions may be associated with sepsis or may develop during the course of the management of such patients. Important among these are anemia, hyperglycemia and renal dysfunction.

Anemia is fairly common in sepsis[26] and results from a depression of erythropoiesis. The management should involve transfusion of blood. Use of erythropoietin has not been seen to increase survival and this form of treatment requires days to weeks to induce erythropoesis. If indicated, early transfusion results in marked lowering of mortality[13]. The decision of transfusion can be taken based on the hematocrit or hemoglobin value. Values of 30% for the former and 7-9 g% for the latter have been used with encouraging results as the threshold for transfusion in early sepsis[26].

Insulin resistance and hyperglycemia are invariably present in sepsis. The latter needs to be corrected since high blood sugar levels increase the risk of infection, delay wound healing, impair neutrophil function, induce apoptosis and promote blood coagulation[27,28]. Insulin therapy not only lowers the blood sugar levels but also has anti-inflammatory, anti-apoptotic and anticoagulant actions. The ideal blood sugar range and insulin dose for such patients has not been studied. In intubated surgical patients aggressive insulin therapy aimed at achieving a blood sugar level of 4.4-6.1 mmol/L can decrease the mortality rates in the ICU among patients who remain in the ICU for more than 5 days. In contrast, the same therapy increases the mortality rate among patients in the medical ICU who stay for less than 3 days while the mortality rate is lower for patients who spend more than 3 days in the medical ICU.[29] Further studies are required to address this issue.

Sepsis with acute renal failure leads to increased morbidity and mortality. Low-dose dopamine is not recommended since it does not decrease the need for renal support or improves survival. Lactic acidosis is a common complication of septic shock. The use of sodium bicarbonate in the setting of lactic acidosis has not been found useful in improving the haemodynamics or the response to vasopressor[30].

Corticosteroids in the management of sepsis. Contrary to the practice of using corticosteroids in the management of sepsis for decades, randomized controlled trials suggest that an early, short course of high dose corticosteroids does not improve survival in severe sepsis.[31] The controversy over the use of corticosteroids results from a number of factors. These include the controversial status of adrenal insufficiency in sepsis, the inconsistent finding of a decrease in the need for vasopressor support in patients of sepsis offered low dose hydrocortisone and the lack of sufficient evidence of a survival benefit of such treatment in patients with no response to a corticotrophin stimulation test.

The estimation of cortisol levels for diagnosis of adrenal insufficiency in patients with sepsis needs careful examination. Since serum total cortisol reflects both the protein bound and the free cortisol, the lowered albumin levels in septicemic patients may result in a lowering of the total cortisol values, falsely suggesting adrenal insufficiency, while the free cortisol, which is physiologically active, may be normal or increased.

Traditionally considered essential for management of persistent ARDS, corticosteroids have not proved beneficial in reducing 60-day mortality in such cases.[32] In patients with sepsis, corticosteroids can have important side effects such as hyperglycemia, neuromyopathy, immunosuppression and loss of intestinal epithelial cells by apoptosis. The immunosupression can lead to nosocomoial infections and delayed / impaired wound healing.

Vasopressin in the management of sepsis. Vasopressin deficiency is common in septic shock as is the down regulation of its receptors[33,34]. Short-term low-dose infusion of this drug has been reported to increase blood pressure, urinary output and creatinine clearance, permitting a dramatic increase in vasopressor therapy. However, intestinal ischemia, skin necrosis, lowered cardiac output and an increased risk of death are the important issues which presently do not favor its use in sepsis[35].

Emerging Treatment Modalities

Current research on newer treatment modalities for sepsis include the use of anti-TSST-I i.e. Staphylococcal toxic shock syndrome toxin 1 (superantigen), inhibitors of tissue factor to combat the procoagulant activity. Animal studies have indicated improved survival with the use of anti-apoptotic agents such as anticaspases[36]. Measures to boost the immune status of patients with interferon gamma may also prove beneficial[37]. Other measures being evaluated are the use of lipid emulsions to bind and neutralize lipopolysaccharide of infecting bacteria.

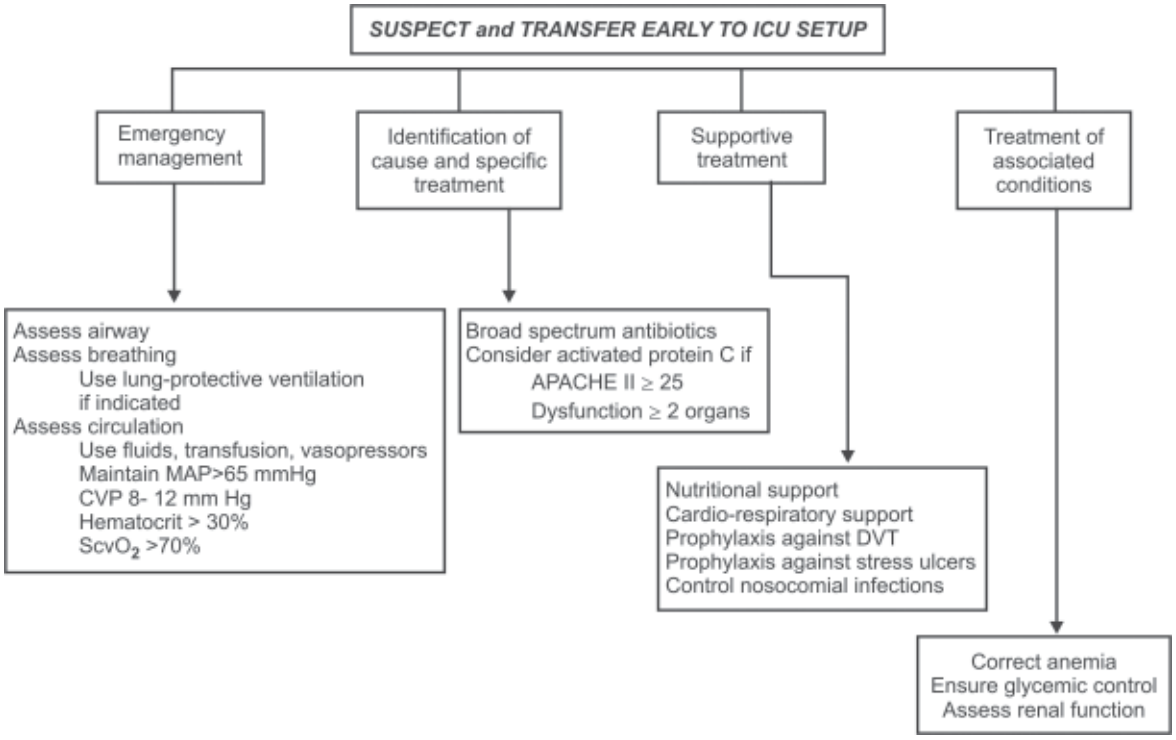

Fig. 2: Outline for management of cases of sepsis

SUMMARY AND CONCLUSION

Sepsis is a fairly common clinical condition that is often difficult to diagnose. Prompt diagnosis and management requires a high degree of suspicion and diligent clinical and investigative work-up of patients. The condition often presents as a medical emergency where the priority is on prompt resuscitation and logical empiric therapy to begin with, followed by rational investigative workup. The management of cases has to be individualized. The role of certain drugs like corticosteroids, vasopressin and insulin needs further study. Newer treatment modalities like superantigens, interferon gamma and anticaspases are being evaluated for clinical efficacy. It is recommended that certain broad guidelines as illustrated in Figure 2 be kept in mind while managing cases.

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