Management of severe sepsis

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Sepsis is a clinical syndrome characterised by systemic inflammation and widespread tissue injury due to infection. There is a continuum of illness severity ranging from sepsis to severe sepsis and septic shock. Sepsis remains a critical problem with significant morbidity and mortality even in the modern era of critical care management.

Nomenclature of sepsis

Sepsis is defined as a suspected or proven infection with a systemic inflammatory response syndrome (SIRS). The clinical features considered as a part of SIRS are

Body temperature of >38.5°C or <35.0°C

Heart rate >90/min

Respiratory rate >20/min

WCC >12000 or <4000/mm^3 or immature forms >10%

Severe sepsis is defined as a state of sepsis with evidence of organ dysfunction. The clinical features of evidence of organ dysfunction are hypotension, hypoxaemia, oliguria, metabolic acidosis, thrombocytopaenia and obtundation.

Septic shock is defined as a state of severe sepsis with hypotension despite adequate fluid resuscitation[1].

Pathophysiology

Multiple derangements exist in sepsis involving several different organs and systems, although controversies exists over their individual contribution to the disease process. At this point in time, the literature richly illustrates that no single mediator, system, pathway, or pathogen drives the pathophysiology of sepsis. Three important key pathological processes are identified. They are inflammation, procoagulation and immunosuppression.

The initial phase of pathogenesis involves the innate immune system. Antigen recognition, intracellular signaling, and the transcription of proinflammatory molecules like TNFα, IL-1 and proinflammatory cytokines like IL-10 are the initial steps in inflammation. These mediators lead to increased production of adhesion molecules in polymorphonuclear leucocytes as well as endothelial cells. This in turn leads to endothelial damage and increased production of vasodilatory mediator nitric oxide. The collective effect of these is the vascular damage and leakage. In later phases of inflammation humoral and cell mediated immunity are activated. B-cells secrete immunoglobulins and Th-1 cell subset of CD4 cells secrete proinflammatory cytokines. Th-2 subset secretes anti-inflammatory cytokines.

Procoagulation is an important aspect of severe sepsis. Lipopolysaccharides (LPS) of bacterial origin stimulate endothelial cells to up-regulate tissue factor and activate coagulation. Fibrinogen is converted to fibrin leading to micro vascular thrombi formation. Sepsis lowers anticoagulant factors protein C, protein S, antithrombin III, and tissue factor pathway inhibitors. LPS and TNFα impair activation of protein C.

Immunosuppression is also an important factor to be considered in late sepsis as evidenced by lymphopenia and reduced level of proinflammatory mediators in late sepsis[1].

Treatment of sepsis in early stages

Treatment of sepsis needs emergency care in the early stages. Following important treatment aspects are to be considered in early stages – early goal related therapy, lung protective ventilation, broad spectrum antibiotics, and possibly activated protein C.

Early goal related therapy

This is considered to be the cornerstone in the initial management of sepsis. Most effective if the goal is achieved within 6 hours. It prevents organ dysfunction and death. Establishing a central venous line is the key since most of the treatment targets rely on information gained from central venous line. The target CVP to be achieved is greater than 8 mmHg, the target mean arterial pressure is 65 mmHg or greater, and the central venous oxygen saturation is to be maintained at ≥70%[2]. These targets are to be

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achieved with fluids, vasopressors, inotropes, RBC transfusion and mechanical ventilation[3].

Fluid therapy

Several randomized trials have shown that the type of fluid did not have any influence in the outcome. Trials of crystalloids vs albumin and crystalloids vs synthetic colloids did not show any difference in mortality or organ dysfunction. Fluid challenges are repeated until the cardiac output increases by 10% or until CVP increases by 3mmHg.

Vasopressors

Vasopressors are indicated when the hypotension persists even after adequate fluid resuscitation. Dobutamine was the inotrope used in large trials in evaluating the initial goal related therapy when CV saturation was <70% after optimizing CVP, blood pressure and haematocrit. Controversy regarding the optimum choice of vasopressor in the management of patients with septic shock continues. Currently dopamine or norepinephrine is recommended as the initial vasopressor of choice for patients with septic shock[3]. Eventhough results are awaiting regarding combination therapy, it is rational to advocate combination therapy in those when the targets are not achieved[4].

Erythrocytes

Erythrocytes are transfused to keep the haematocrit at >30%.

Ventilation

Acute lung injury or ARDS often complicates severe sepsis, and lung protective ventilation is an important treatment option in managing severe sepsis. Lung protective ventilation involves mechanical ventilation with a low tidal volume. The tidal volume is to be maintained between 6-7 ml/kg as opposed to the usual practice of 10-15 ml/kg. It may be kept as low as 4 ml/kg if the ventilatory pressure exceeds 30 mmHg. Eventhough positive end expiratory pressure ventilation (PEEP) reduces the oxygen requirement it has been shown that it does not have an impact on outcome[1].

Sedation

Sedation is often overlooked in the management of septic patients, especially those who are on ventilators. Sedation should be appropriate but not excessive. It increases the risk of prolonged ventilation and nosocomial pneumonia. Titrating sedation and interrupting sedation daily are shown to be effective. Neuromuscular blocking drugs should be avoided in septic patients who are ventilated[1].

Broad spectrum antibiotics

In septic patients the site of primary infection and the type of organism are usually obscure. Samples for cultures should be obtained without any delay and the antibiotics should be administered expeditiously. Organisms to be considered are gram positive bacteria, highly resistant gram negatives, MRSA, vancomycin resistant enterococci and penicillin resistant pneumococci. Local antibiotic resistant pattern should be considered in selecting initial antibiotic therapy. The outcome is worse when the initial antibiotic is resistant[1].

Empirical antibiotic therapy in severe sepsis

If pseudomonas is an unlikely pathogen vancomycin is commenced with one of the following class of antibiotics[5].

1) Cephalosporin 3rd/4th generation – ceftriaxone, cefotaxime or cefepime.
2) Betalactam – ticarcillin + clavulanate or ampicillin+salbactam
3) Carbapenam – meropenam or imipenam.

If pseudomonas is a likely pathogen vancomycin is commenced with one of the following antipsudomonal antibiotics[5].

1) Ceftazidime or cefepime
2) Carbapenam – meropenam
3) Aminoglycoside – amikacin or netilmycin
4) Floroquinolones – ciprofloxacin
5) Monobactam – aztreonam

Anticoagulant therapy

Activated protein C is the most commonly employed anticoagulant. Its effect does not depend on the site of infection or type of organism. The benefits of activated protein C include improvement of haemodynamics, reduction of duration of shock, improvement of organ dysfunction and reduction of mortality.

The mechanism of its action is not fully understood but it's probably due to its anti-inflammatory, anti-apoptotic and anticoagulant effects. It increases protein C levels and reduces the levels of thrombin markers like D-dimers.

Indications for activated protein C include severe sepsis (two or more organ dysfunction), one new (<48H) organ dysfunction, shock not responding to steroids and shock not meeting the criteria for steroid therapy. The dosage is 24 µg/kg/min for 96 hours.

Exclusion criteria for activated protein C are recent trauma or surgery, active haemorrhage, concurrent therapeutic anticoagulation, platelet count of <30000/ mm^3.

Therapy with activated protein C is not beneficial in low risk patients. There is an increased risk of serious bleeding especially intra cranial haemorrhage. The risk is high in patients with meningitis and patients with thrombocytopenia.

Corticosteroids in sepsis

Early high dose steroid therapy is ineffective in severe sepsis.

Indications for steroid therapy are refractory septic shock with a basal cortisol concentration of <150µg/l and a cortisol response to ACTH of <90µg/l (adrenal insufficiency).

Values should be interpreted with caution in patients with hypoalbuminaemia which is a common finding in sepsis; in such cases free cortisol assay is more reliable. Effects of steroids on septic patients include improvement in haemodynamics, and reduction in mortality, duration of shock, organ dysfunction and systemic inflammation. The recommended dose is 200-300 mg daily in 4 divided doses and oral fludrocortisone 50µ/day may be added.

Vasopressin

Low dose vasopressin is recommended in patients with severe sepsis. The recommended dose is 0.03-0.04 units/min. Probable mechanisms of action are increase in blood pressure, urine output and creatinine clearance, improving haemodynamics, reducing duration of shock and increased vasopressor effect.

The adverse effects of vasopressin include risk of developing intestinal ischaemia, reduction in cardiac output, skin necrosis and myocardial ischaemia[3].

Treatment of hyperglycaemia

Adverse effects of hyperglycaemia in septic patients include promotion of coagulation, induction of apoptosis, impairment in neutrophil function, increased risk of infection and defective wound healing. Insulin can counteract all these effects. Intensive insulin therapy has been shown to be beneficial in surgical patients with sepsis[3].

Treatment of anaemia

Anaemia is a common finding in septic patients. Erythropoietin gene expression is affected in septic patients but erythropoietin treatment is ineffective as it takes time to act. Evidence suggests transfusion is worthwhile if needed during the emergency stage of sepsis. The target of treatment is to achieve a haematocrit of >30% or haemoglobin of 7-9 g/dl.

Renal dysfunction and dialysis

Continuous renal replacement therapy decreases the adverse biomarkers but has little effect on outcome. Daily intermittent dialysis is better than alternate day dialysis.

Low dose (2-4 µg/kg/min) dopamine neither decreases the need for renal support nor improves survival and is not recommended.

Lactic acidosis is common in severe sepsis but sodium bicarbonate is not recommended as it has not shown to be of any benefit in this situation.

Supportive care

Prophylaxis of deep vein thrombosis should be considered in all patients. Heparin can be combined with activated protein C. Enteral nutrition is preferred to parenteral as it is safer and effective. Stress ulcer prophylaxis is given in the form of antihistamines and proton pump inhibitors. Sedation, neuromuscular blockers and steroids should be minimized. They can exacerbate septic encephalopathy, polyneuropathy and myopathy. Immune support may be considered in certain instances, for example – granulocyte colony stimulating factor in neutropenia.

The future

Various treatment options are under evaluation with promising results. Blockade of complement cascade, inhibition of tissue factor, inhibition of apoptosis, inhibition of lipopolysaccharides. strategies to boost immunity, inhibition of late proinflammatory mediators, inhibition of NO synthesis, blockade of endothelin receptors, vagal nerve stimulation and inhibition of poly-ADP-ribose synthase are some of them.

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