

REVIEW ARTICLE

SEPSIS AND SEPTIC SHOCK: UPDATES

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ABSTRACT

Sepsis, severe sepsis and septic shock are a spectrum which occurs in response to an infection. They are associated with a high degree of morbidity and mortality. This article reviews the definitions, pathophysiology and management of sepsis. In particular, measures to achieve adequate tissue perfusion and oxygenation, as outlined by the updated 2012 Surviving Sepsis Campaign, are discussed.

INTRODUCTION:

Sepsis is a common disease condition. It occurs when an infection causes a generalized inflammatory response in the host. Sepsis is potentially fatal and should be treated as a medical emergency. It is one of the leading causes of death across the world. It is estimated that 750,000 cases of sepsis occur in the United States annually and that about 1/3rd to 1/2 of these die^{1,2}. Despite advances in medical care, its incidence continues to rise.

Developing countries, like Pakistan, especially suffer due to sepsis. An estimated 60-80% of deaths in these countries occur due to sepsis³. Poor hygiene, low standards of living, malnutrition and a paucity of healthcare facilities and resources contribute to the disproportionately high morbidity and mortality from sepsis in these nations⁴.

Early, aggressive therapy of sepsis improves the chance of survival⁵. This article reviews the pathophysiology and management of sepsis.

DEFINITIONS:

The systemic inflammatory response syndrome (SIRS) is a deleterious reaction of the immune system to a variety of clinical insults. (See Table I). When SIRS occurs in the setting of an infection, the overall syndrome is referred to as sepsis. Severe sepsis occurs when there is evidence of acute end organ dysfunction in the setting of sepsis, whereas septic shock refers to sepsis associated with arterial hypotension that is refractory to adequate fluid resuscitation⁶.

Sepsis-induced tissue hypoperfusion is defined as infection-induced hypotension, elevated lactate, or oliguria⁶.

PATHOPHYSIOLOGY OF SEPSIS:

Bacteremia or infection at any site of the body, by any microorganism – bacteria, fungi, parasites or viruses – can lead to sepsis. Microbial molecules (e.g. bacterial cell wall components – lipopolysaccharide A, endotoxin for Gram negatives, peptidoglycans, exotoxins for Gram positive organisms – bacterial DNA, viral RNA) trigger the inflammatory cascade, via trans-membrane receptors, e.g. toll-like Receptors or T-cell antigen receptors. Pro-inflammatory cytokines, TNF alpha and IL-1, are released via signal transduction molecules (nuclear factor kappa B) and are part of a complex metabolic milieu in which, besides the inflammatory cascade (comprising prostaglandins, leukotrienes platelet activating factor, phospholipase A₂, adhesion molecules), the complement and coagulation systems, along with anti-inflammatory cytokines (IL-10), also play a role.

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The final common pathway of sepsis results ultimately in end organ damage via endothelial dysfunction, capillary micro-thrombosis, vasodilation (due to release of nitric oxide by activated neutrophils), cardiovascular insufficiency, tissue hypoxia and apoptosis⁷. In severe cases, death can ensue⁸. (Refer to figure 1)

EARLY GOAL DIRECTED THERAPY AND WHY IS IT IMPORTANT

The transition from SIRS (Systemic inflammatory response syndrome) to severe sepsis and septic shock occurs during the early critical hours. Clinical evidence indicates that early recognition and focused intervention in a septic patient has a major favorable impact on overall survival⁵.

As soon as sepsis induced tissue hypoperfusion is identified (hypotension, oliguria or blood lactate level > or equal to 4 mmol/L), protocolized quantitative resuscitation should be initiated. The most significant interventions in this early period are control of the source of infection (within 12 hours), initiation of antibiotics as soon as possible (within the first, or so called “golden”, hour), and achievement of adequate tissue perfusion via fluid resuscitation, and, if necessary, vasopressors and inotropes⁵.

MANAGEMENT OF SEPSIS:

The fundamentals of sepsis management are rapid control of source of infection, and achievement and maintenance of adequate tissue perfusion and oxygenation. Current strategies to achieve adequate tissue perfusion/oxygenation include fluid resuscitation, use of vasopressors and inotropes for refractory hypotension, and packed red blood cell transfusion in appropriate patients.

Initial investigations

Suggested initial investigations include cultures (2 sets of blood cultures, urine and sputum cultures), routine laboratory tests (complete blood count, electrolytes, blood urea nitrogen and creatinine, liver function tests, coagulation profile, lactate level, central venous oxygen saturation, arterial blood gas) and imaging to identify the source of infection (chest x-ray, and, if indicated by clinical suspicion, abdominal imaging). Other tests to consider would include lumbar puncture with cerebrospinal fluid analysis (if there is suspicion of meningitis), and, if available, 1,3 beta-D-glucan assay, galactomannan and anti-mannan antibody assays if invasive candidiasis is a possible cause of infection⁶.

Control of Infection

Antibiotics

Appropriate antibiotics should be administered to all patients with suspected sepsis as early as possible, ideally within the first hour of recognition of sepsis⁹. Broad-spectrum antibiotics (or anti-viral –especially in cases where human/avian/swine influenza is suspected - or anti-fungal therapy, if these microorganisms are suspected), that are able to penetrate the tissues at the

presumed site of infection, should be started without delay ⁹ (See Table II) Mortality rates increase exponentially with each extra hour before antimicrobial administration ^{6, 10, 11}. Antibiotics should be reassessed daily, based on the results of the cultures, for potential de-escalation to a single agent (except in situations where multi-drug resistant organisms like *P. Aeruginosa* or *Acinetobacter* spp or in selected forms of endocarditis - where combination of antibiotics may be preferred ⁶); at least two sets of blood cultures should be drawn prior to starting antibiotics. Cultures from other body sites – urine, chest, affected joint, cerebrospinal fluid, etc. – should be obtained if these are thought to be the source of infection. Biomarkers may assume an important role in the decision to de-escalate antimicrobial therapy in the future. In particular, serum pro-calcitonin appears to show promise in identifying cases where antibiotic therapy may be reduced ¹²⁻¹⁵.

Source Control

Physicians should aim to identify the anatomical site of infection as early as possible in patients with sepsis. Imaging studies, such as chest X-ray or CT, abdominal ultrasound or CT, based on clinical suspicion should be performed and appropriate intervention for source control should be carried out (e.g. thoracotomy and decortication for empyema, laparotomy for abdominal abscess) within the first 12 hours after diagnosis if indicated ¹⁶.

Fluid Resuscitation

Intravenous fluid should be given to all patients with sepsis to achieve and maintain adequate tissue perfusion. In patients with sepsis induced hypo perfusion, fluid administration should be protocolized quantitatively, i.e. physiological parameters (central venous pressure, arterial blood pressure, lactate level, mixed venous oxygen saturation) should be monitored and set targets achieved within 6 hours. Evidence of sepsis induced hypo perfusion includes hypotension despite an initial fluid challenge, elevated lactate level (> 4mmol/L) or oliguria.

Intravenous fluid should be administered at 30 cc/kg to achieve a central venous pressure of 8-12 cm H₂O (12-16 in ventilated patients), mean arterial pressure of 65 mmHg or above, lactate level < 4mmol/L (when available), urine output > 0.5 cc/kg/hour, and mixed venous saturation of > 65% (or >70% for superior vena cava oxygen saturation) ⁵. Crystalloids are the preferred fluid. Colloids confer no significant advantage and may cause harm (especially hydroxyethyl starches); albumin can, however, be used in cases where large quantities of crystalloids are being infused ¹⁷⁻²⁰.

Initial fluid resuscitation can be performed through two large bore peripheral IV cannulas. However, physicians should place a central venous catheter early in the course of severe sepsis as this allows the measurement of CVP and central venous oxygen saturation ⁶.

Vasopressors and Inotropes:

Patients with life-threatening hypotension and hypo perfusion benefit from vasopressor therapy. Ideally, vasopressors should be started after correcting hypervolemia; however, in severely ill patients with extremely low perfusion pressures, vasopressor treatment can be started in conjunction with initial fluid resuscitation ^{21, 22}.

Vasopressors should be titrated to achieve a combination of physiological endpoints: adequate arterial pressures (MAP of 65 mmHg is traditionally targeted– although in chronically

hypertensive patients or in normotensive young adults, this figure may be too low to too high respectively), clear mentation, adequate urine output, good capillary refill or low serum lactate levels⁵.

Norepinephrine is the agent of choice for septic shock⁶. Epinephrine and vasopressin can be used as second line agents; dopamine should be used as an alternative in selected patients only (those at low risk for cardiac tachy-arrhythmias or those with bradycardia)²³. Phenylephrine should also be reserved for special cases only: patients with high cardiac output yet low blood pressures who cannot tolerate norepinephrine due to serious arrhythmias^{24,25}.

Inotropes: In cases where evidence of tissue hypoperfusion persists (i.e. low mixed venous oxygen saturation or high lactate levels), despite volume resuscitation and adequate mean arterial pressures, an additional inotropic agent, dobutamine (up to 20 micrograms/kg/min), should be started⁵. Dobutamine can also be initiated if there is a low cardiac output or elevated cardiac filling pressure on recommended vasopressor therapy⁶. Mean arterial pressures generally dip when dobutamine infusion is started (due to the peripheral vasodilation caused via beta receptor activation by dobutamine); this can be overcome by increasing the dose of dobutamine to increase cardiac contractility and cardiac output (which offsets peripheral vasodilation)^{26,27}.

Blood Product Transfusion:

Packed red cells may be transfused, up to a hemoglobin level of 10 g/dL, during the initial resuscitation phase if tissue hypoperfusion persists despite the use of the above measures – aggressive fluid resuscitation, vasopressor and inotrope use⁵. However, after achieving adequate tissue oxygenation, blood transfusion should only be performed if hemoglobin drops below 7 g/dL, as per the general recommendation for critically ill patients; range of hemoglobin to be targeted is between 7-9 g/dL²⁸. Critically ill patients with a history of coronary artery disease, severe hypoxia or ongoing massive hemorrhage are exempt from this restrictive transfusion strategy, as higher target hematocrit is deemed safer for them^{6,29}.

Thrombocytopenia and coagulopathy occur commonly in sepsis. Platelets and fresh frozen plasma (FFPs) should be transfused as per the usual recommendations for critically ill patients. In general, FFPs should be transfused only for signs of overt bleeding or prior to an invasive procedure (if coagulation parameters are deranged, e.g. with International normalized ratio (INR) > 1.5). The decision to administer platelets is dependent on the clinical scenario; e.g. platelet transfusion is indicated at $< 10,000/\text{mm}^3$ [$10 \times 10^9/\text{L}$] if there are no signs of bleeding, but at $< 20,000/\text{mm}^3$ [$20 \times 10^9/\text{L}$] in cases where there is a significant risk of bleed, but a higher threshold ($< 50,000/\text{mm}^3$ [$50 \times 10^9/\text{L}$]) is used if there is ongoing bleeding or a plan for surgery or invasive procedure⁶.

Corticosteroids:

There has been a paradigm shift with regards to steroid use in septic patients. Previously, steroids were frequently used in septic shock, esp. with abnormal ACTH stimulation test [30]. The most recent large scale randomized controlled trial (CORTICUS) addressing steroid use in septic shock, however, failed to show a mortality benefit³¹. Although, some authorities have expressed concern about the methodology of the CORTICUS trial, routine ACTH stimulation testing or steroid usage is no longer recommended.

Currently, guidelines suggest that steroid use can be considered in septic shock that is refractory to fluids and vasopressors (weak recommendation)⁶. In this scenario, hydrocortisone at a dose of 200 mg/day intravenously can be used (ideally as a continuous infusion); steroids should be tapered off (typically over 5-7 days) once vasopressor therapy has been weaned off. Corticosteroids should not be administered for the treatment of sepsis in the absence of shock⁶.

Supportive Care:

The standard of care ICU practices should be followed with regards to general supportive measures. Patients should be on DVT and stress ulcer prophylaxis, and should receive enteral feeding (starting with low-dose feeding of up to 500 kcal/day and advancing slowly over a week as tolerated) if no contraindications exist to any of these measures⁶. Target range of blood glucose should be 150 to 180 mg/dL (or with no specific lower target other than hypoglycemia)^{6, 32}, sedative and analgesics should be used as sparingly as necessary to achieve an agitation free state; paralytics should be avoided unless absolutely necessary (e.g. in patients with severe Acute Respiratory Distress Syndrome); renal replacement therapy (continuous renal replacement therapy is preferred to standard hemodialysis in the setting of hemodynamic instability) should be used if necessary for acute renal failure⁶. Ventilatory support, either with BPAP (Bi-level Positive Airway Pressure) or invasive mechanical ventilation, may be necessary in patients with increased work of breathing due to SIRS or metabolic acidosis. In the presence of sepsis induced ARDS, lung protective ventilatory strategy, with low tidal volumes of 6 cc/kg of ideal body weight to achieve plateau pressures ≤ 30 cm H₂O, should be used; prone positioning (which appears to confer a survival benefit in severe ARDS) and alveolar recruitment maneuvers may be necessary with severe hypoxemia^{6, 33, 34}.

In addition, routine use of pulmonary artery catheter, bicarbonate therapy (unless pH < 7.15, in which case it may be considered), immunoglobulins, beta agonists, activated protein C, selenium, and immunomodulating nutrition is not recommended⁶.

Lastly, physicians should initiate a dialogue with patients and families with regards to prognosis, expected outcomes, expected time frame for achieving goals of care, and decisions about end of life planning, where appropriate. This dialogue should be initiated early in the course of the ICU stay⁶.

CONCLUSION:

Sepsis is a major source of morbidity and mortality across the world. It occurs when an infection causes a severe inflammatory response in the body; when severe it can progress to shock and death. Management involves rapid correction of tissue hypoperfusion and hypoxemia and early control of infection.

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Table I: Definitions

<p>SIRS Systemic inflammatory response manifests as two or more of :</p> <ol style="list-style-type: none"> 1. Temperature $>38^{\circ}$ or $<36^{\circ}$ C ($>100^{\circ}$ or $<96.8^{\circ}$ F) 2. - HR >90 beats per minute 3. Respiratory rate >20 /min or PaCo₂ <32mmHg 4. Wbc $>12,000$ or <4000 or 10% immature cells <p>SEPSIS Presence (probable or documented) of infection + SIRS</p>	<p>SEVERE SEPSIS Sepsis associated with acute organ dysfunction or tissue hypoperfusion, evidenced by one or more of:</p> <ul style="list-style-type: none"> • Sepsis induced hypotension • Altered mental status • Elevated lactate levels • Urine output <0.5 cc /kg/hour x 2 hours despite adequate fluid resuscitation- • Acute Lung Injury with PaO₂/FIO₂ <ul style="list-style-type: none"> • < 250 (no pneumonia) • < 200 (pneumonia present) • Acute kidney injury with creatinine >2 mg/dL • Bilirubin >2mg/dL • Platelet count < 100K • Coagulopathy (INR >1.5) 	<p>SEPTIC SHOCK Subset of severe sepsis with persistent hypotension despite adequate fluid resuscitation</p> <p>Systolic BP < 90 mm Hg, Mean arterial pressure < 70 mm Hg, or an SBP decrease > 40 mm Hg in adults or less than two standard deviation below normal for age</p> <p>REFRACTORY SEPTIC SHOCK Septic shock that persists despite vasopressor therapy and adequate fluid resuscitation</p>
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Table II: Suggested initial empiric antibiotic therapy for sepsis ³⁵⁻³⁷

Source of infection	Common Microorganisms	Suggested Initial Antibiotic
Community acquired pneumonia (CAP)	<i>S. pneumonia</i> , <i>H. influenzae</i> , <i>L. pneumophila</i> , <i>M. pneumoniae</i>	Ceftriaxone + azithromycin OR Levofloxacin (respiratory fluoroquinolone)
Hospital acquired pneumonia (early: < 5 days)	CAP organisms, non-resistant Gram negative bacilli	Ceftriaxone or respiratory fluoroquinolone or ampicillin-sulbactam or ertapenem
Hospital acquired pneumonia (late: ≥ day 5)	Resistant <i>S. aureus</i> (MRSA) and resistant Gram negatives (<i>P. aeruginosa</i> , <i>Klebsiella</i> & <i>Acinetobacter</i> spp.)	Imipenem/Meropenem OR Piperacillin-Tazobactam OR Ceftazidime/Cefepime + aminoglycoside OR ciprofloxacin/levofloxacin + Vancomycin OR linezolid
Abdominal infection	Enterobacteriaceae and anaerobes	Cefepime/ceftazidime/ciprofloxacin + metronidazole OR pip/tazo OR imipenem
Urinary tract infection	<i>Enterococcus</i> spp., Gram negative bacilli	Ampicillin or vancomycin if enterococcus; ceftriaxone or aztreonam +/- aminoglycoside

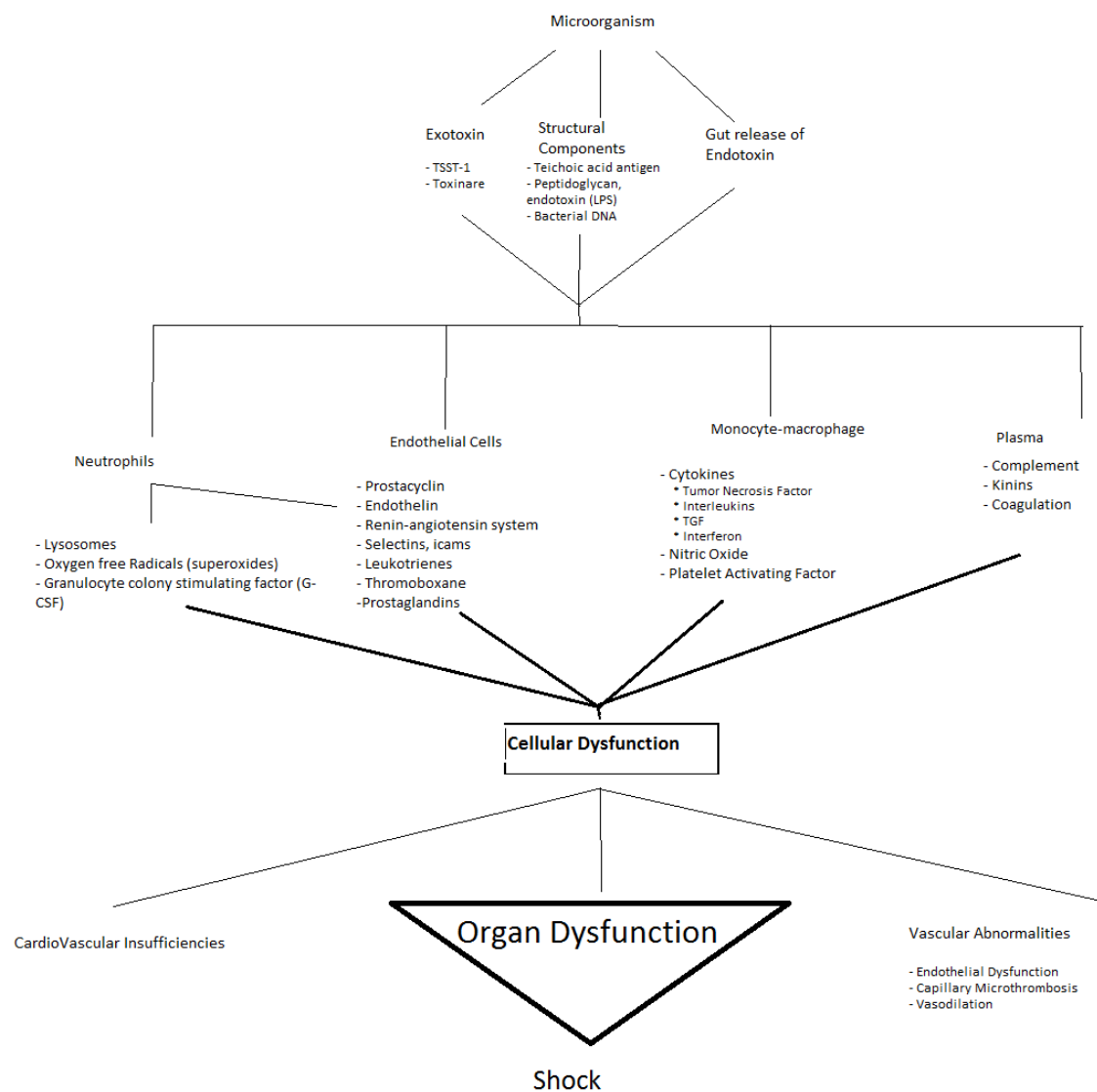


Figure I: Pathophysiology of sepsis and septic shock

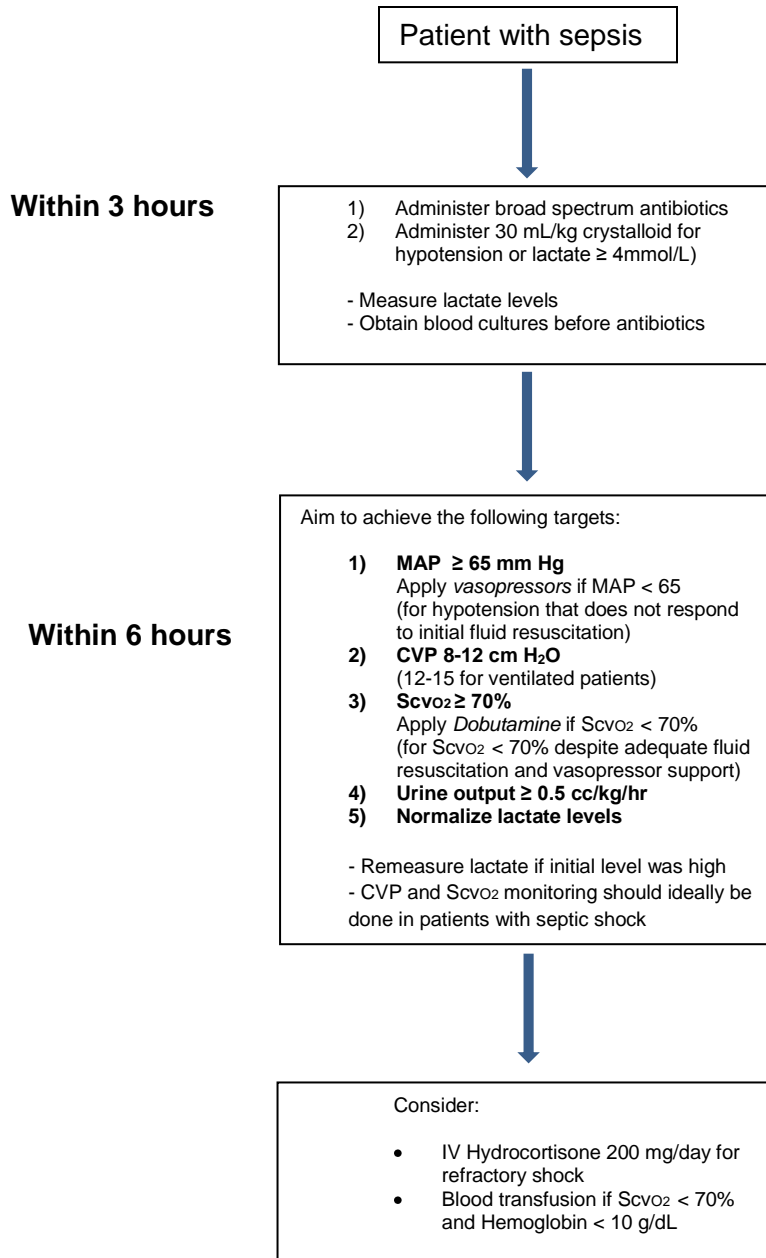


Figure II: Management of Sepsis and Septic Shock (Adapted from Surviving Sepsis Campaign 2012)