Review Article

Management of Sepsis and Septic Shock

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Abstract

Management of sepsis and septic shock has been greatly evolved since the initial publications of Surviving Sepsis Campaign (SSC) guidelines in 2004. But still these conditions are associated with high mortality in patients admitted to the hospital as well as to the intensive care unit. From time to time experts have gathered information and new evidences for the betterment of care of these patients as well as to decrease the high rate of mortality associated with sepsis and septic shock. The guidelines have been revised in 2008 and 2012. The recent guideline, which is published in 2016 have taken into consideration of the best available evidences for the management of sepsis and septic shock till date. While they have incorporated few evidence based recommendation, definitions and newer modalities of assessment for the management of sepsis and septic shock; at the same time they have revised the previous recommendations based on the recently published evidences against these recommendations. Overall these guidelines will greatly help all the physicians involved in the care of sepsis and septic shock patients and will help in improving the outcome of these patients. Till new evidences are available, these recommendations will guide physicians taking their best clinical decision for the management of sepsis and septic shock.

Key Words: Sepsis, septic shock, Sequential Organ Failure Assessment (SOFA) score, resuscitation, screening, antimicrobial therapy, fluid therapy.

Review

Despite remarkable advancement in the understanding of sepsis patho-biology, it still remains as one of the leading cause of inhospital mortality. Its management has evolved greatly since the initial publications of Surviving Sepsis Campaign (SSC) guidelines in 2004[1]. The guidelines are revised in 2008, 2012 and 2016.Here is the latest recommendation for the management of severe sepsis and septic shock, which is based on the 2016 SSC guidelines[2].

The recent definition of sepsis as defined by The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) has defined sepsis as change in Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score (≥2) or presence of two of the three criterion qSOFA (Quick SOFA; Altered mental status, RR >22/min, SBP <100mmHg) score in the background of infection.[3] The task force has also defined septic shock as sepsis with persistent hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) of ≥ 65mmHg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation. It will enable clinicians to immediately start the management of patients with sepsis even before admission to the intensive care unit (ICU).

Initial Resuscitation

Once a patient is identified with severe sepsis the guidelines recommend initiation of the treatment and resuscitation as it is a medical emergency; and it should not be delayed pending the ICU admission. Over the last one decade these measures were based on the early goal-directed therapy (EGDT) protocol, whose credibility has been questioned in view of recently published 3 trials namely ProCESS trial, ARISE trial and ProMISE trial[4-7]. These trials have failed to show any significant mortality benefit associated with protocolized goal directed therapy compared to the standard of care protocol. But these findings could be attributed to the significant improvement in the standard of care practices which have practically incorporated the elements of EGDT over the last decade in the management of severe sepsis patient due to better sensitization. During the first 3 hours, atleast 30ml/kg of IV crystalloid fluid should be given for hypo perfusion due to sepsis and additional fluid administration should be guided based on repeated assessment of hemodynamic status. During further evaluation of shock, cardiac function should be evaluated and if available dynamic hemodynamic variables should be used to assess fluid responsiveness. The guideline strongly recommends maintaining a MAP of 65mmHg in patients with septic shock requiring vasopressors. The resuscitation should be guided with the measurement of serum lactate level as it is a marker for tissue perfusion.

Screening for Sepsis and diagnosis

A hospital performance improvement program for sepsis should be in place. It will help in screening and early identification of high risk patients. Early identification of sepsis focus will lead to early institution of treatment protocol and will improve the patient outcome[8]. The time gap between sepsis identification

and initiation of treatment is vital to the patient survival[9]. With widespread use of ultrasound by the Emergency medicine department and ICU, it is a valuable tool for the immediate screening of the patient with severe sepsis. It will be a useful tool for initial noninvasive evaluation of sepsis focus identification. For the identification of the causative organisms, at least two sets of blood cultures (both aerobic and anaerobic bottles) should be obtained before starting antimicrobial therapy. Of the two samples, at least one should be drawn percutaneously and the other one from the vascular access device, unless the device was recently (< 48 hours) inserted. The volume of blood drawn with the culture tube should be ≥ 10 mL[10]. Samples can be refrigerated or frozen if processing cannot be performed immediately. For identification of systemic fungal infection rapid diagnostic methods such as the use of 1, 3 β-d-glucan assays, mannan and anti-mannan antibody assays will be helpful.

Antimicrobial Therapy

Effective antimicrobials should be administered within 1 hour of sepsis identification. Each hour of delay in septic shock patient is associated with significantly increased mortality. Most studies support giving antibiotics to septic shock patient without any delay[8, 11]. The empiric antibiotics will include one or more drugs that have broad spectrum activity covering suspected pathogens. Also they should able to achieve adequate therapeutic concentration at presumed site of suspected infection. Empiric antifungal therapy should be considered where invasive fungal infection is suspected. The choice of antibiotic should be guided by the local prevalence patterns of bacterial pathogens and susceptibility data. Daily reassessment of the antibiotic regimen should be done by the clinician and due consideration should be given for potential de-escalation of the drug, once the causative organism is identified or if there is failure of any response to the treatment regimen. The empiric coverage should be narrowed once the causative pathogen is identified or if there is adequate clinical recovery. It will prevent development of resistance as well as reduce both toxicity and cost. Bio marker such as low procalcitonin level may be used to assist the clinician in making the decision regarding the discontinuation of the empiric antibiotics in patients who have no subsequent evidence of infection[12, 13]. The guideline recommends against the use of prophylactic antimicrobial therapy in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury). Appropriate antibiotic dosage should be used according to both pharmacokinetic and pharmacodynamics of the drug.

Combination empiric antibiotic should used only for patients with septic shock aiming at the most likely pathogen. It strongly recommends against the use of combination therapy for the routine treatment of patients with neutropenic sepsis or bacteremia. An infectious disease consultation should be taken wherever multidrug resistance pathogen is suspected. Combination antimicrobial therapy should be used for streptococcal toxic shock syndrome with penicillin and clindamycin. For Pseudomonas aeruginosa bacteremia associated with respiratory failure and septic shock, a combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is necessary[14,15]. Similarly, for Streptococcus pneumonia infections a more complex combination of beta-lactam and a macrolide is required. However the combination therapy should not be given for more than 3 to 5 days. The duration of antibiotic therapy should not be more than 7 to 10 days unless clinically indicated. Longer duration of treatment is required in patients with slow response, those with undrainable foci of infection, bacteremia with Staphylococcus aureus; some fungal and viral infections, or immunologic deficiencies, including neutropenia. Those patiets who have suspected associated viral infection empiric antiviral treatment should be initiated.

Source Control and infection prevention

Emergent source control should be done with specific anatomical diagnosis of infection like necrotizing soft tissue infection, peritonitis, cholangitis andintestinal infarction. An intervention should be undertaken for source control within the first 12 hours after the diagnosis, except in case of infected peri-pancreatic necrosis. For infected peri-pancreatic necrosis the definitive intervention should be delayed until an adequate demarcation of viable and nonviable tissues has occurred[16]. For the purpose of source control the least invasive physical insult will be preferred[17]. If any intravascular access device is suspected as the source of infection then it should be removed promptly after establishing other site for vascular acess[18, 19].

Selective oral decontamination (SOD) and selective digestive decontamination (SDD) should be used to reduce the incidence of ventilator-associated pneumonia (VAP). Also oral chlorhexidine gluconate (CHG) should be used for oropharyngeal decontamination to reduce the risk of VAP in ICU patients with severe sepsis.

Fluid Therapy

A fluid challenge technique should be always used where fluid administration continues. The fluid resuscitation of severe sepsis and septic shock should be done with crystalloid. Either balanced crystalloids or saline can be used for this purpose. When patients requires substantial amount of crystalloids, then albumin can be added with crystalloids for fluid resuscitation. Hydroxyethyl starches(HES) must be best avoided for fluid resuscitation of severe sepsis and septic Shock. This recommendation is based on the findings of the results of the VISEP, CRYSTMAS, 6S, and CHEST trials[20-23]. Those who require substantial amounts of crystalloids should be resuscitated with the use of albumin, as albumin administration is safe and equally effective as 0.9% saline[24]. Patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia should be given an initial fluid challenge to achieve a minimum of 30 mL/kg of crystalloids. It has suggested the use of crystalloids over gelatins while resuscitating patients with sepsis or septic shock. During ongoing fluid administration hemodynamic improvement should be assessed using dynamic parameters of fluid responsiveness. These techniques include passive leg raises, fluid challenges against stroke volume measurements, systolic pressure variation,

and stroke volume variation. Echocardiography also can be used as bed side tool to assess the volume status and fluid responsiveness.

Vasoactive medications

Vasopressors to be started early to maintain a MAP of 65 mmHg and norepinephrine is recommended as the first-choice of vasopressor[25]. Norepinephrine is more potent as well as more effective at reversing hypotension in patientswith septic shock as compared to dopamine. Dopamine causes more tachycardia and is also more arrhythmogenic than norepinephrine[26]. When an additional agent is required to maintain the target MAP then either vasopressin (up to 0.03 U/min) or epinephrine should be added to norepinephrine. Vasopressin levels have been found to be low in patients with septic shock[27]. Vasopressin (up to 0.03 U/min) can be added to norepinephrine to raise the MAP or to decrease the norepinephrine dosage. However, low-dose vasopressin is not recommended as the single initial vasopressor for the treatment of sepsis-induced hypotension[28]. Use of dopamine as an alternative vasopressor agent to norepinephrine is reserved only for highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia). Phenylephrine is not recommended for the treatment of patients with septic shock. Also low dose dopamine should not be used for renal protection[29,30]. All patients who require vasopressor therapy should be placed with an arterial catheter, as estimation of BP using cuff will be mostly inaccurate during shock. Patients with myocardial dysfunction as evidenced by low cardiac output or with ongoing signs of hypoperfusion, despite adequate intravascular fluid loading and adequate use of vasopressor agents, should be given trial with dobutamine infusion. Any predetermined cardiac output goal should not be targeted during its use.

Corticosteroids

The guideline recommends against the use of intravenous hydrocortisone for the treatment of adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If patient has persistent hypotension despite all the measures then add intravenous hydrocortisone alone at a dose of 200 mg per day[31]. A continuous infusion is preferred over its bolus administration to avoid hyperglycemia and hypernatremia. Clinicians should taper the patient from steroid therapy when vasopressors are no longer required. The guidelines recommended against the use of corticosteroids in the treatment of sepsis when there is no shock.

Blood and blood products

Red blood cell should be transfused only when the hemoglobin concentration decreases to < 7.0 g/dLin adults except in patients with myocardial ischemia, severe hypoxemia or acute hemorrhage[32]. Erythropoietin should not be used for the treatment of anemia associated with severe sepsis. Fresh frozen plasma should not be used to correct laboratory clotting abnormalities in the absence of bleeding[33, 34]. It can be transfused prior to any planned invasive procedures. For platelets, it should be administered prophylactically when counts are ≤ 10,000/mm3 (10 × 10^9/L) in the absence of apparent bleeding. If the patient has a significant risk of bleeding then platelet should be transfused when counts are ≤ 20,000/mm^3 (20 × 10^9/L). Higher platelet counts (≥ 50,000/mm3 [50 × 10^9/L]) are required for active bleeding, surgery, or invasive procedures. Intravenous immunoglobulins should not be used in adult patients with sepsis or septic shock.

Anticoagulants and blood purification

While the guidelines recommends against the administration of antithrombin; there is no recommendation for the use of thrombomodulin or heparin for the treatment of sepsis or septic shock. The guideline made no recommendation for the use of blood purification techniques such as high-volume hemofiltration and hemoadsorption (or hemoperfusion).

Mechanical Ventilation

Clinicians should use lung protective ventilation strategy with a target tidal volume of 6 mL/kg predicted body weight in patients with sepsis induced acute respiratory distress syndrome (ARDS). Plateau pressures should be measured in these patients and the initial upper limit goal should be ≤ 30 cm H2O[35, 36]. PEEP should be applied to avoid alveolar collapse at end expiration. Strategies based on higher levels of PEEP should be used for patients with sepsis-induced moderate to severe ARDS[37]. Recruitment maneuvers should be used in sepsis patients with severe refractory hypoxemia due to ARDS. Ventilation strategy with positioning should be considered in sepsis-induced ARDS patients with a PaO_2/FiO_2 ratio ≤ 100 mm Hg wherever feasible[38]. The guideline strongly recommends against the use of high-frequency oscillatory ventilation (HFOV) in adult patients with sepsis-induced ARDS.

Patients who are on mechanical ventilation should be be maintained with the head of the bed elevated between 30 and 45 degrees to limit aspiration risk and to prevent the development of VAP[39]. A specific weaning protocol should be in place for patients on mechanical ventilation. Patients will undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation and if the spontaneous breathing trial is successful, extubation should be considered. Guidelines recommended against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS[40,41]. A conservative fluid strategy is recommended for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion. In the absence of bronchospasm, β2-agonists should not be used for the treatment of patients with sepsis-induced ARDS[42, 43]. The guideline made no recommendation regarding the use of NIV for patients with sepsis induced ARDS.

Sedation, Analgesia, and Neuromuscular Blockade in Sepsis

Sedation should be minimized in mechanically ventilated sepsis patients, targeting specific titration end points, so as to reduce the duration of mechanical ventilation and ICU and hospital lengths of stay[44-46]. Neuromuscular blocking agents (NMBAs) must be avoided if possible in septic patients without ARDS due to the risk of prolonged neuromuscular blockade following their discontinuation. If NMBAs must be used then depth of blockade should be monitored using train-of-four. A short course of an NMBA (≤ 48 hours) can be used for patients with early, sepsis-induced ARDS and PaO_2/FiO_2< 150 mm Hg.

Glucose Control

Guideline recommends a protocolized approach to blood glucose management in ICU patients with severe sepsis. Insulin should be started when two consecutive blood glucose levels are > 180 mg/dL[47,48]. Blood glucose values should be monitored every 1 to 2 hrs until glucose values and insulin infusion rates are stable, after that it should be monitored every 4 hours. The point-of care capillary blood glucose testing should be interpreted with caution, as it may not accurately estimate arterial blood or plasma glucose values[49]. If patient has arterial catheter than arterial blood should be used for point of care testing of blood glucose. The target upper blood glucose level should be ≤180 mg/dL and hypoglycemia should be avoided[47].

Renal Replacement Therapy (RRT) and bicarbonate therapy

Both continuous renal replacement therapy (CRRT) and intermittent HD are equivalent in achieving short term survival rate in patients with severe sepsis and AKI[50]. Those patients who are hemodynamically unstable, CRRT will facilitate management of fluid balance. RRT should not be used without absolute indication for dialysis. Sodium bicarbonate therapy should not be used to improve hemodynamics or reducing vasopressor requirements in patients who has hypoperfusion-induced lactic acidemia with pH ≥ 7.15[51, 52]. Bicarbonate will lead to sodium and fluid overload, an increase in lactate and PCO_2, and a decrease in the serum ionized calcium.

Deep Vein Thrombosis Prophylaxis

Patients admitted to the ICU have significant risk for developing deep vein thrombosis (DVT)[53]. Patients with severe sepsis should receive daily pharmaco-prophylaxis against venous thromboembolism (VTE). This should be done with daily subcutaneous low-molecular weight heparin (LMWH). If the creatinine clearance of the patient is < 30 mL/min, then dalteparin or UFH should be used. Patients with severe sepsis should be treated with combined pharmacologic therapy and intermittent pneumatic compression devices[54, 55]. Those patients who have contraindication to heparin use (eg, thrombocytopenia, severe coagulopathy, active bleeding, and recent intracerebral hemorrhage) should not receive pharmaco-prophylaxis. They should receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices unless contraindicated[56-58].

Stress Ulcer Prophylaxis

The risk factor for GI bleeding includes coagulopathy, mechanical ventilation for at least 48 hours and possibly hypotension. Stress ulcer prophylaxis should be given with either proton pump inhibitor or Histamine-2 receptor antagonists (H2RAs)to patients with severe sepsis/septic shock who have bleeding risk factors[59-61]. Those patients who do not have any risk factors should not receive any stress ulcer prophylaxis.

Nutrition

Nutrition should be started within the first 48 hours after a diagnosis of severe sepsis/septic shock. Oral or enteral feedings should be started rather than either complete fasting or administration of only intravenous glucose. Mandatory full caloric feeding should be avoided in the first week of illness, rather a low-dose feeding (eg, up to 500 kcal per day), should be started and advanced gradually as tolerated by the patient[62, 63]. Intravenous glucose and enteral nutrition should be started rather than total parenteral nutrition (TPN) alone or parenteral nutrition in conjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis/septic shock. The guideline suggests the use of either early trophic/hypocaloric; which can be increased according to patient tolerance or early full enteral feeding in critically ill patients with sepsis or septic shock. While the guideline suggested against the routine monitoring of gastric residual volumes, the same can be measured in patients with feeding intolerance and those patients who are at high risk for aspiration. For patients with feeding intolerance prokinetic agents should be used. Also post-pyloric feeding tube should be placed for patients with feeding intolerance and those who are at high risk for aspiration.

No specific immune modulating supplementation should be added to the nutrition[64]. It has recommended against the use of omega-3 fatty acids as an immune supplement to the feed.The guideline strongly recommended against the use of IV selenium and glutamine, while suggested against the use of arginine to treat sepsis and septic shock. The guideline has no recommendation for the use of carnitine for sepsis and septic shock.

Setting Goals of Care

The goals of care and prognosis of the patient should be discussed with patients and families. Appropriate palliative care principles and end-of-life care planning should be considered where applicable. These goals of care should be addressed within 72 hours of ICU admission.

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