Management of Patients with Septic Shock in in Intensive Care Unit: Review Article

Ayman Abdellatif Mohamed El-Sayed, Tarek Yousef Gaafar, Khaled Mohamed El-Sayed, Yasser Mohamed Nasr
Department of Anesthesia, Intensive care and pain management, Faculty of Medicine, Zagazig University
Corresponding author: Ayman Abdellatif Mohamed El-Sayed
Email: Aymanabdellatif404@gmail.com

Abstract: Early management of sepsis and septic shock is crucial for patients' prognosis. As the intensive care unit (ICU) is the place where the first medical contact for septic patients is likely to occur, emergency physicians play an essential role in the early phases of patient management, which consists of accurate initial diagnosis, resuscitation, and early antibiotic treatment. Since the issuing of the Surviving Sepsis Campaign guidelines in 2016, several studies have been published on different aspects of sepsis management, adding a substantial amount of new information on the pathophysiology and treatment of sepsis and septic shock. In light of this emerging evidence, the present narrative review provides a comprehensive account of the recent advances in septic patient management in the ICU.

Keywords: Sepsis, septic shock, ICU.

Tob Regul Sci. ™ 2023 ;9(1): 6097-6102
DOI: doi.org/10.18001/TRS.9.1.425

Introduction:

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. It affects millions of patients per year and has a high risk of mortality, which has become a major global health problem . The Global Burden of Diseases Study showed that sepsis affects at least 49 million patients each year, causing 11 million deaths and accounting for 19.7% deaths worldwide. Epidemiological data showed that over 20% of the septic patients required mechanical ventilation , which is associated with enormous costs for health care systems worldwide (1).

The main clinical goal of the b 2021 Surviving Sepsis Campaign was to optimize sepsis treatment and improve patient outcomes.Sepsis has ahigh mortality rate of 15.00%. Due to its high incidence and mortality, more effective diagnosis and treatment schemes for the disease have been explored . With the deepening of research and the development of medical technology in recent years, remarkable progress has been made in anti-infection treatment and organ support

therapy, but the fatality rate of sepsis remains high . Therefore, the effective treatment of sepsis is still a major research difficulty (2).

At present, sepsis is mostly common in intensive care unit (ICU) and usually complicated with organ dysfunction, so the treatment of the disease is difficult.Septic shock is defined by persisting hypotension requiring vasopressors to maintain a mean arterial pressure of 65 mm Hg or higher and a serum lactate level greater than 2 mmol/L (18 mg/dL) despite adequate volume resuscitation.This new 2016 definition, also called Sepsis-3, eliminates the requirement for the presence of systemic inflammatory response syndrome (SIRS) to define sepsis, and it removed the severe sepsis definition. What was previously called severe sepsis is now the new definition of sepsis (3).

Pathogenesis of sepsis

Pathogenesis is complex, with many immune and non-immune mediators involved. Four key areas are endothelial dysfunction, coagulation abnormalities, alterations in cell function and dysregulated cardiovascular responses (4)

Acomplex network of cytokines are important in mediating many of the effects of sepsis. Moreover, although initial proinflammatory pathways are important, anti-inflammatory pathways are also activated and can downregulate corrective responses later in the course of sepsis. In addition to protein and peptide mediators, there are also a plethora of other mediators involved, including prostanoids, platelet activating factor, and endogenous damage-associated molecular patterns (DAMPS) released from injured cells, such as ATP and high mobility group proteins. In an attempt to simplify this complex pathogenic pathway, four main features can be highlighted – the four horsemen of the septic apocalyp. Generalised endothelial activation increases the expression of a number of leucocyte adhesins, with increased leucocyte transmigration into tissues. The permeability of the endothelium is also increased, in the lung leading to interstitial pulmonary edema and in the gut increasing bacterial translocation, potentially exacerbating the inflammatory cascades already initiated by microbial products (5).

Altered coagulation is extremely common in sepsis. Endothelial damage removes the protective function of the natural anticoagulation protein C pathway and converts the endothelium into a prothrombotic surface. In addition, bacterial products and inflammatory cytokines activate tissue factor, the main initiator of the extrinsic pathway of blood coagulation. This prothrombotic state may lead to blockage of the microvasculature, as well as giving rise to a consumption coagulopathy (disseminated intravascular coagulation). Gram-positive products can also directly activate the contact clotting system. One of the enigmas of the field is that even in the most severe cases of lethal sepsis, autopsy studies show little evidence of cell death, despite widespread organ dysfunction. The molecular basis of this is still not clear, although a generalised reduction in energy expenditure by cells suggests some kind of hibernationlike process (6).

Concomitant with this alteration in cellular function are numerous metabolic changes, notably increased catabolism, insulin resistance and hyperglycaemia. Many studies have shown that patients with sepsis have a decreased systemic vascular resistance (SVR) with a normal or increased cardiac output, the so-called 'hyperdynamic' state of sepsis. Cardiac output is maintained at the expense of left ventricular dilation, with reduced ejection fraction and a reduced left ventricular stroke work index in response to left ventricular end diastolic volume increase. These changes can lead to the hypotension characterising septic shock. Changes in SVR are probably largely mediated by excess production of the vasodilator nitric oxide in the vasculature which can be difficult to correct with vasopressors. Poor tissue perfusion also likely underlies the increased lactate seen in septic shock, although other mechanisms are possible (7).

However, we still lack a specific molecular therapy for this condition, other than antimicrobial therapy. Certain types of sedation in septic patients can improve the condition of the patient.

Management of sepsis and septic shock

An increase in 2 points or more for a patient suspected to have infection using the Sequential Organ Failure Assessment (SOFA) best predicted in-hospital mortality.The SOFA is well known within the intensive care community, but is not so well known generally. Therefore, the task force developed a simpler clinical screening tool that performed very well in identifying adult patients with suspected infection who were likely to have poor outcomes, which they termed 'quick SOFA' (qSOFA) (table.1) (8).

Table (1): Quick Sequential Organ Failure Assessment Score

Assessment	qSOFA score
Low blood pressure (SBP≤ 100 mmHg)	1
High respiratory rate (≥22 breath per minute)	1
Altered mentation (GCS ≤14)	1

This measures three clinical parameters. A patient who fulfilled two of these criteria had similar outcomes to those who had an increase in 2 points on the full SOFA scale.A qSOFA score of 2 or more should prompt clinicians to investigate further for organ dysfunction, consider escalation of therapy, and evaluate for referral to critical care confirming infection as cause of a severe inflammatory response is the main challenge in the diagnosis of sepsis. A new developed concept called the PIRO (predisposition, infection, response, organ dysfunction) concept for an improved characterization and staging of patients with sepsis (9).

Detection of microbial nucleic acids by polymerase chain reaction (PCR) and biomarkers were named as future tools to describe the conditions infection and response within the PIRO system.Biomarkers to separate infectious from non-infectious causes of sepsis like C-reactive

(CRP), Procalcitonin (PCT), Interleukin-6 and Lipopolysaccharide (LPS)-binding protein (LBP) are important to follow up.

Initial evaluation – For patients with sepsis and septic shock, therapeutic priorities include securing the airway, correcting hypoxemia, and establishing appropriate vascular access for the early administration of fluids and antibiotics. Simultaneously obtaining the following is preferable (within 45 minutes) but should not delay the administration of fluids and antibiotics. 'Immediate evaluation):

- •Routine laboratory studies complete blood picture, liver function tests, kidney function tests and co-agulation tests.
- •Serum lactate >2 mmol/L or greater than the laboratory upper limit of normal) may indicate the severity of sepsis and is used to follow the therapeutic response
- •Arterial blood gases ABGs may reveal acidosis, hypoxemia, or hypercapnia.

Procalcitonin while the diagnostic value of procalcitonin in patients with sepsis is poorly supported by evidence, its value in de-escalating antibiotic therapy is well established in populations, in particular, those with community acquired pneumonia and respiratory tract infections; measurement of procalcitonin to guide duration of antibiotic use is appropriate in those populations with sepsis

- • Blood cultures (aerobic and anaerobic) from two distinct venipuncture sites and from all indwelling vascular access devices; it is preferable that blood cultures be drawn before the initiation of antibiotics
- • Cultures from easily accessible sites (eg, sputum, urine)
- • Imaging of suspected sources

Initial resuscitation – For patients with sepsis and septic shock, we suggest the infusion of intravenous fluids (30 mL/kg), commencing within the first hour and completed within the first three hours of presentation, rather than vasopressors, inotropes, or red blood cell transfusions :

Intravenous fluids – Fluid boluses are the preferred method of administration and should be repeated until blood pressure and tissue perfusion are acceptable, pulmonary edema ensues, or there is no further response.

Crystalloid solutions (eg, normal saline or Ringer lactate) are our preferred resuscitation fluid. Balanced crystalloid may be preferred if there is a perceived need to avoid or treat the hyperchloremia that occurs when large volumes of nonbuffered crystalloid (eg, normal saline) are administered. We recommend that a hyperoncotic starch solution **not** be administered (10).

Antibiotics – For patients with sepsis, we recommend that optimal doses of empiric broad spectrum intravenous therapy with one or more antimicrobials be administered in a prompt fashion (eg, within one hour) of presentation. Broad spectrum is defined as therapeutic agent(s)

with sufficient activity to cover a broad range of gram-negative and positive organisms, and, if suspected, against fungi and viruses.

For patients with septic shock associated with likely gram-negative sepsis, we suggest consideration of the use of two antibiotics from different classes to ensure effective treatment of resistant organisms.

Agent selection depends upon patient's history, comorbidities, immune defects, clinical context, suspected site of infection, presence of invasive devices, Gram stain data, and local prevalence and resistance patterns. The routine administration of antifungal therapy is not warranted in nonneutropenic patients.

Monitoring – For most patients with sepsis and septic shock, we recommend that fluid management be guided using clinical targets including mean arterial pressure 60 to 70 mmHg and urine output ≥0.5 mL/kg/hour.

Hemodynamics – In addition, while dynamic measures of fluid responsiveness (eg, respiratory changes in the radial artery pulse pressure) are preferred, static measures of determining adequacy of fluid administration (eg, central venous pressure 8 to 12 mmHg or central venous oxygen saturation ≥70 percent) may be more readily available.

Laboratory – Serum lactate should be followed (eg, every six hours) until there is a definitive clinical response. It is prudent that other measures of the overall response to infection also be followed (eg, routine laboratory studies, arterial blood gases, microbiology studies).

Source control – Following initial investigations and empiric antimicrobial therapy, further efforts aimed at identifying and controlling the source(s) of infection (ideally within 6 to 12 hours) should be performed in **all** patients with sepsis. In addition, for those who fail despite therapy or those who fail having initially responded to therapy, further investigations aimed at removal of devices suspected to be infected, adequacy of the antimicrobial regimen, or nosocomial super infection should be considered.

Patients who fail initial therapy – For patients with sepsis who remain hypotensive despite adequate fluid resuscitation (eg, 3 L in first three hours), we recommend vasopressors; the preferred initial agent is norepinephrine . For patients who are refractory to intravenous fluid and vasopressor therapy, additional therapies, such as glucocorticoids, inotropic therapy(epinephrine and dobutamine) (11).

For patients with distributive shock from sepsis, vasopressin may be added.

, and blood transfusions, can be administered on an individual basis. We typically reserve red blood cell transfusion for patients with a hemoglobin level <7 g/dL.

Patients who respond to therapy – For patients with sepsis who have demonstrated a response to therapy, we suggest that the rate of fluid administration should be reduced or stopped, vasopressor support weaned, and, if necessary, diuretics administered. We also recommend that

antimicrobial therapy be narrowed once pathogen identification and susceptibility data return. Antimicrobial therapy should be pathogen and susceptibility directed for a total duration of 7 to 10 days, although shorter or longer courses are appropriate for select patients.

References:

[1] Chen P, Jiang J, Zhang Y, Li G, Qiu Z, Levy MM, Hu B. Effect of Dexmedetomidine on duration of mechanical ventilation in septic patients: a systematic review and meta-analysis. BMC Pulm Med. 2020;20(1):42.

[2] Wang C, Chen Q, Wang P, Jin W, Zhong C, Ge Z, Xu K. The effect of dexmedetomidine as a sedative agent for mechanically ventilated patients with sepsis: a systematic review and meta-analysis. Front Med. 2021

[3] Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. Lancet. 2020;395(10219):200–11.

[4] Oh TK, Song IA, Lee JH. Clinical usefulness of C-reactive protein to albumin ratio in predicting 30-day mortality in critically ill patients: a retrospective analysis. Sci Rep. 2018;8:14977.

[5] Patel P, Walborn A, Rondina M, Fareed J, Hoppensteadt D. Markers of inflammation and infection in sepsis and disseminated intravascular coagulation. Clin Appl Thromb Hemost. 2019;25:1076029619843338.

[6] Kang K, Gao Y, Wang SC, et al. Dexmedetomidine protects against lipopolysaccharide-induced sepsis-associated acute kidney injury via an alpha7 nAChR-dependent pathway. Biomed Pharmacother 2018;106: 210–6.

[7] Zhou J, Yang D, Liu K, et al. Systematic review and meta-analysis of the protective effect of resveratrol on multiple organ injury induced by sepsis in animal models. Biomed Rep 2019;10:55–62.

[8] Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, McIntyre L, Ostermann M, Prescott HC, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181–247.

[9] Chi C, Buys N, Li C, et al. Effects of prebiotics on sepsis, necrotizing enterocolitis, mortality, feeding intolerance, time to full enteral feeding, length of hospital stay, and stool frequency in preterm infants: a metaanalysis. Eur J Clin Nutr 2018;

[10] Bai Y., He H., Zhang P., Liu W., Huang L."Effects of dexmedetomidine on immune function, renal function and inflammatory factors of patients undergoing percutaneous nephrolithotomy under general anesthesia". Experimental and Therapeutic Medicine 2021, no. 4: 406.

[11] Bosch NA, Cohen DM and Walkey AJ. Risk factors for new-onset atrial fibrillation in patients with sepsis: a systematic review and meta-analysis.Crit Care Med 2019;47:280–287.