# Sepsis and Septic Shock: An Update

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## Abstract

**Objective:** To conduct a review of the literature about sepsis and septic shock in adults.

**Methodology:** An extensive literature search using multiple databases (Medline, Embase, Scopus, and Science Direct) was used to identify articles from 2013 to 2019 that evaluated the sepsis and septic shock. The keywords "sepsis" and "septic shock" were used. Approximately 1,200 abstracts were identified initially and of these, 35 articles were selected.

**Results:** Sepsis is a major cause of death, disability, and cost to the health care system. The new definition of sepsis is "life-threatening organ dysfunction caused by a dysregulated host response to infection" the current management of sepsis primarily involves early resuscitation (Administer intravenous fluid, mean arterial pressure ≥ 65 mmHg, normalize lactate, use vasopressors), and infection control (The current guidelines recommend initiation of intravenous antimicrobials within 1 hour of recognition of sepsis and septic shock).

**Conclusion:** Sepsis and septic shock should be diagnosed and treated effectively to reduce morbidity and mortality in intensive care units and emergency departments.

**Keywords:** Sepsis; Septic Shock; Dysfunction

## Introduction

In 2016, the definitions of sepsis were updated with the emphasis on organ dysfunction being triggered by a dysregulated host response to infection. Septic shock was redefined as a subset of sepsis carrying a worse prognosis. Sepsis is a common illness and is recognized in the recent World Health Organization resolution as a global health priority [1]. Sepsis is a major cause of death, disability, and cost to the health care system. For more than 2 decades, the sepsis classification framework has been based on identifying infection accompanied by the systemic inflammatory response syndrome (SIRS), and then looking for organ dysfunction (severe sepsis) or refractory hypotension (septic shock). The new definition of sepsis is "life-threatening organ dysfunction caused by a dysregulated host response to infection" [2]. The new sepsis definitions also propose Quick SOFA (qSOFA) criteria (two or more of hypotension, tachypnea, and/or altered mental status) for efficient bedside screening to identify potentially infected patients at risk for poor outcomes in out-of-hospital, emergency department, and general hospital ward settings [3].

### *Sepsis*

Life-threatening organ dysfunction caused by dysregulated host response to infection.

***Septic shock***

Subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality [2,3].

## Methodology

Literature search strategy: An extensive literature search using multiple databases (Medline, Embase, Scopus, and Science Direct) was used to identify articles from 2013 to 2019 that evaluated the sepsis and septic shock. The keywords "Sepsis" and "Septic Shock" were used. The literature searches attempted to be exhaustive, and every effort was made to identify all of the articles pertaining to each of the categories reviewed. Approximately 1,200 abstracts were identified initially and of these, 35 articles were selected.

## Epidemiology

International data demonstrate that sepsis contributes to more than 5 million deaths annually and represents a significant financial burden to patients and society. Since 2005 to 2015, the sepsis incidence was 437 cases per 100,000 person-year, with an incidence of severe sepsis from 270 per 100,000 person-year. Furthermore, a significant proportion of these patients are treated in intensive care units (ICU), with estimates ranging from 10% to 20% of all ICU admissions being specifically for severe sepsis or septic shock [4]. The quantification of the global burden of sepsis is patchy and incomplete, especially in low- and middle-income countries, where sepsis is concentrated and delivery of health care is generally suboptimal. Despite this uncertainty, sepsis is conservatively estimated to claim over 8 million lives annually [5]. The actual epidemiology of sepsis is currently unknown and extremely variable. Recently, these definitions have changed, with many controversies and we do not have any study that evaluated their impact on incidence [6]. An important epidemiological data is to know the origin of sepsis, which it is community in most cases, around 60-70% of whole cases, followed by hospital-acquired outside ICU in 20-30%, while cases of in ICU origin were the least frequent, around 5%-9% [7].

## Pathophysiology

Sepsis is an nonlinear pathophysiologic process involving the activation and dysregulation of pro inflammatory and anti-inflammatory responses of the innate immune system, complement and coagulation systems, metabolic changes, hormonal alterations, cytopathic hypoxia, and epithelial and microcirculatory dysfunction. Although in sepsis, bacterial products initiate this series of events, shock induced hypo perfusion and cellular hypoxia and products released by host cell injury accelerate the cascade [8]. Organ dysfunction in sepsis is now recognized to be more than just the consequence of decreased tissue oxygen delivery and instead involves multiple responses to inflammation, including endothelial and micro vascular dysfunction, immune and autonomic dysregulation, and cellular metabolic reprogramming [9]. Sepsis is characterized by destructive "endothelial response" of the host, leading to endotheliopathy and its molecular dysfunction. Complement activation generates membrane attack complex and this provokes endotheliopathy, which activates two independent molecular pathways: inflammatory and micro thrombotic [10]. An integral feature of septic shock is hypotension. Although cardiac dysfunction and hypovolemia contribute to the hypotension, loss of vascular smooth muscle reactivity causing peripheral vasodilation is the major mechanism. Vasodilation in sepsis is mediated mainly by two mechanisms: increased nitric oxide (NO) and prostacyclin synthesis. A calcium-independent NO synthase is induced by endotoxin interaction with vascular endothelial cells, leading to increased levels of NO. Prostacyclin is released by endothelial cells in response to both endotoxin and inflammatory cytokines [11].

### *Diagnostic*

**Clinical presentation:** The clinical presentation of sepsis depends on the site of the infection. Arterial hypotension can be present, but its absence does not exclude sepsis or provide reassurance about the severity of the syndrome, as organ perfusion can already be impaired even in the context of normal blood pressure. Patients often present to the emergency department with general malaise and non-specific signs, such as fever, hypothermia, tachycardia, tachypnea, or altered mental status [12].

**Microbiological assessment:** Samples for microbiologic cultures should be collected before administering antibiotics in patients with suspected sepsis or septic shock because the antimicrobial therapy can alter the results of cultures. Samples from each suspected foci of infection should be collected for microbiologic tests in patients with sepsis and septic shock: blood, cerebrospinal fluid, urine, wounds, respiratory secretions, and other body fluids. Standard culture-based microbiology techniques often yield results within 48–96 h. Therefore, in patients with suspected sepsis or septic shock, microbiological analysis should be started as soon as possible, within the first 45 min, to avoid delay in the initiation of antimicrobial therapy [13].

**Procalcitonin:** Procalcitonin (PCT) is a precursor of calcitonin released by parenchymal cells in response to bacterial toxins. Sepsis and systemic inflammation can be excluded if PCT plasma concentration is 0.2 ng/mL while plasma levels of 0.5 ng/mL suggest sepsis. PCT secretion starts within the first 2–4 h after the onset of sepsis, peak levels are reached at 24–48 h. Monitoring procalcitonin levels in septic patients may provide also other information, such as the appropriateness of deescalating the antimicrobial therapy [14]. Rising levels correlate with bacteremia and poor outcomes and are more reliable than considering a single value. Elevated levels may also be seen in Addisonian crisis, certain paraneoplastic syndromes and in patients receiving treatment with certain immunoglobulin or monoclonal antibodies, perhaps the best role for procalcitonin may be as a tool to distinguish infectious from noninfectious conditions, thereby facilitating the decision to de-escalate antibiotic therapy [15,16].

**Lactate:** Lactic acid, which is a by-product of anaerobic metabolism. In adults with severe sepsis, an increased lactate level (>4 mmol/L) is a negative prognostic indicator [17]. Lactate elevation reflects the pathophysiological changes of sepsis (hypotension, tissue hypoperfusion and organ dysfunction); it defines the diagnosis and prognosis of septic patients. Moreover, monitoring this parameter has been shown to improve the outcome of critically ill patients [18].

**C-Reactive protein:** C-reactive protein (CRP) is an acute phase reactant synthesized in the liver and it detects the presence of inflammatory or infectious processes but its specificity for the diagnosis of sepsis is low. CRP is not considered to be an ideal marker of sepsis [19].

### *Treatment*

In the firsts 3 hours of the presentation of septic shock it measurement of lactate level, obtaining blood cultures before antibiotics, administration of broad spectrum antibiotics and crystalloid 30 ml/kg for hypotension or lactate ≥ 4 mmol/L. The second part, contains all therapeutic steps to be performed within 6 h of the presentation with septic shock: application of vasopressors (for hypotension not responding to initial fluid replacement) in order to maintain a mean arterial pressure (MAP) ≥ 65 mmHg, measurement of central venous pressure (CVP) and venous oxyhemoglobin saturation (ScvO2) when hypotension persists despite volumen replacement [20]. The current management of sepsis primarily involves early resuscitation, and infection control.

*Early resuscitation*

**Mean arterial pressure:** Recent guidelines recommend initially targeting a MAP level of more than 65 mm Hg and a higher MAP in septic patients with a history of hypertension who respond to a higher blood pressure. The results of the SEPSISPAM (Sepsis and Mean Arterial Pressure) study suggest that a MAP target of 65 to 75 mm Hg is usually sufficient in patients with septic shock, but a higher MAP (around 75 to 85 mm Hg) may be preferable in patients with chronic arterial hypertension [21].

**Lactate:** Hyperlactatemia has been confirmed to be a marker of illness severity, is a strong predictor of mortality in sepsis and the current Surviving Sepsis Guidelines recommend guiding resuscitation to normalize lactate in patients with elevated lactate levels. Lactate "clearance" was popularized in 2004 when the patients with severe sepsis and septic shock with a higher percentage decrease in lactate levels after 6 hours of emergency department intervention had improved mortality, and presumed that lactate normalization was a marker for resolution of global tissue hypoxia [22,23].

**Administer intravenous fluid:** The administration of intravenous fluids to improve circulation, perfusion, and oxygen delivery is a fundamental principle in sepsis management. However, the potential benefits of administering fluid must be balanced against the potential for harm due to the accumulation of fluid, such as, tissue edema, pulmonary edema and compartment syndrome. The fundamental reasoning for administering fluid is to improve tissue perfusion by increasing cardiac output [24]. Early effective fluid resuscitation is obligatory for the stabilization of sepsis-induced tissue hypo perfusion or septic shock. The guidelines recommend this should comprise a minimum of 30 ml/kg of intravenous crystalloid fluid within the first 3 h [25].

**Vasopressors:** Vasopressor agents are used to counteract the sepsis-induced decrease in vascular tone with the aim of restoring tissue perfusion pressure. If hypotension is severe or if it persists despite initial fluid administration, the use of vasopressors is indicated. Achieving a mean systemic arterial pressure of 65–70 mmHg is a good initial goal. Adrenergic agonists are the first-line vasopressors, norepinephrine being the first-choice agent. In cases of refractory septic shock, adding another vasopressor with a different mechanism of action (non-adrenergic) could be considered. Vasopressin has been shown to be a valuable alternative agent [26,27].

**Red blood cell transfusion:** Studies no longer argue for a 10 g/dL (30% hematocrit) transfusion threshold during the early phase of septic shock. Similarly, most septic patients can be managed with a restrictive transfusion strategy using a 7 g/dL hemoglobin threshold. A more liberal transfusion strategy should be adopted if patients are not stabilized or for patients at risk of bleeding, with myocardial ischemia, or oncohematologic patients with potential hemostasis disorders [28].

**Corticosteroids:** Clinicians and researchers have postulated that the immunosuppressive effects of corticosteroids may mitigate the inflammatory reaction of the septic patient resulting in improved mortality. Hydrocortisone is the ideal corticosteroid of choice as it features equal glucocorticoid and mineralocorticoid properties and is an exogenous analog to cortisol. Corticosteroids act through two mechanisms: immune modulation and cardiovascular modulation. Currently, the Surviving Sepsis Campaign guidelines recommend against the use of low□dose corticosteroids if fluid resuscitation and vasopressor therapy are adequate in restoring hemodynamic stability. If hemodynamic instability persists despite adequate fluid resuscitation and vasopressor therapy, intravenous hydrocortisone can be added at a dose of 200 mg per day [29,30].

**Infection control:** Delays in appropriate antimicrobial therapy have been associated

with higher mortality rates, and quality improvement initiatives that encouraged earlier prescribing have reported substantial decreases in mortality [31]. Infection control is a cornerstone of sepsis treatment, empiric antibiotic therapy selection should, therefore, be guided by a patient's risk for bacterial and fungal pathogens, and be broad enough to include all potential pathogens. Combination therapy, defined as the use of 2 or more antimicrobial agents from different classes of drugs, is recommended for patients with septic shock. It is prudent to de-escalate antibiotics based on culture results and daily assessment and potentially, the use of procalcitonin. The current guidelines recommend initiation of intravenous antimicrobials within 1 hour of recognition of sepsis and septic shock [32]. Nonetheless, it may be difficult to provide an appropriate empiric regimen to every patient, given the wide variety of infections that may be present. General guidance is that the regimen should be chosen on the basis of the suspected organism(s) according to the drug susceptibility patterns [33].

**Mechanical vent:** Target a tidal volume of 6 mL/kg of predicted body weight and a plateau pressure of 30 cm H2O. Application of an upper limit goal for plateau pressures of 30 cm H2O over higher plateau pressures in adult patients with sepsis-induced severe ARDS. Ventilation strategy of prone over supine position in adult patients with sepsis-induced ARDS and a PaO2/FIO2 ratio <150 [34,35].

## Conclusion

Sepsis and septic shock should be diagnosed and treated effectively to reduce morbidity and mortality in intensive care units and emergency departments.

## Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that be construed as a potential conflict of interest.

## References

1. Shankar-Hari M, Singer M. Caring for sepsis patients: An update. Crit Care Clinics 2018; 34: 13-15.
2. Rhee C, Klompas M. New sepsis and septic shock definitions: clinical implications and controversies. Infect Dis Clin North Am 2017; 31: 397-413.
3. Marshall JC. Sepsis definitions: A work in progress. Crit Care Clinics 2018; 34: 1-14.
4. Tillmann B, Wunsch H. Epidemiology and outcomes. Crit Care Clinics 2018; 34: 15-27.
5. Dugani S, Laxminarayan R; Kissoon N. The quadruple burden of sepsis. CMAJ 2017; 189: E1128-E1129.
6. Bracht H, Hafner S, Weiß M. Sepsis-Update: Definition und Epidemiologie. Anästhesiol Intensivmed Notfallmed Schmerzther 2019; 54: 10-20.
7. Candel FJ, Borges Sá M, Belda S, Bou G, Del Pozo JL, et al. Current aspects in sepsis approach. Turning things around. Rev Espde Quimioter 2018; 31: 298-315.
8. Armstrong BA, Betzold RD, May AK. Sepsis and septic shock strategies. Surg Clin

North Am 2017; 97: 1339-1379.

9. Pool R, Gomez H, Kellum JA. Mechanisms of organ dysfunction in sepsis. Crit Care Clinics 2018; 34: 63-80.
10. Chang JC. Sepsis and septic shock: endothelial molecular pathogenesis associated with vascular microthrombotic disease. Thromb J 2019; 17: 1-19.
11. Russell JA, Rush B, Boyd J. Pathophysiology of Septic Shock. Crit Care Clin 2018; 34: 43–61.
12. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet 2018; 392: 75-87.
13. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017; 43: 304–377.
14. Esposito S, De Simone G, Boccia G, De Caro F, Pagliano P, et al. Sepsis and septic shock: New definitions, new diagnostic and therapeutic approaches. J Glob Antimicrob Resist 2017; 10: 204-212.
15. Graber ML Patel M, Claypool S. Sepsis as a model for improving diagnosis. Diagnosis 2018; 5: 3-10.
16. Rowland T, Hilliard H, Barlow G. Procalcitonin: potential role in diagnosis and management of sepsis. Adv Clin Chem 2015; 68: 71–86.
17. Maloney PJ. Sepsis and septic shock. Emerg Med Clin North Am 2013; 31: 583-600.
18. Zaccone V, Tosoni A, Passaro G, Vallone CV, Impagnatiello M, et al. Sepsis in Internal Medicine wards: Current knowledge, uncertainties and new approaches for management optimization. Ann Med 2017; 49: 582-592.
19. Henriquez-Camacho C, Losa J. Biomarkers for sepsis. Biomed Res Int 2014; 2014: 547818.
20. Rello J, Valenzuela-Sánchez F, Ruiz-Rodriguez M, Moyano S. Sepsis: A review of advances in management. Adv Ther 2017; 34: 2393-2411.
21. Leone M, Asfar P, Radermacher P, Vincent JL, Martin C. Optimizing mean arterial pressure in septic shock: A critical reappraisal of the literature. Crit Care, 2015; 19: 101.
22. Casserly B, Phillips GS, Schorr C, Dellinger RP, Townsend SR, et al. Lactate measurements in sepsis-induced tissue hypoperfusion: results from the Surviving Sepsis Campaign database. Crit Care Med, 2015; 43: 567-573.
23. Arnold RC, Shapiro NI, Jones AE, Schorr C, Pope J, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock 2009; 32: 35-39.
24. Coopersmith CM, De Backer D, Deutschman CS, Ferrer R, Lat I, et al. Surviving sepsis campaign: Research priorities for sepsis and septic shock. Crit Care Med 2018; 44: 1334-1356.
25. Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 update. Crit Care Medicine 2018; 46: 997-1000.
26. Ortiz JA, De Backer D. Vasopressors in Sepsis. In: Handbook of Sepsis. Springer, Cham, 2018: 127-138.

27. Colling KP, Banton KL, Beilman GJ. Vasopressors in sepsis. Surg Infect, 2018; 19: 202-207.

28. Dupuis C, Sonneville R, Neuville M, Vinclair C, Abid S, et al. Transfusion for patients With Sepsis in 2018. Clin Pulmonary Med 2018; 25: 138-143.

29. Thompson K, Venkatesh B, Finfer S. Sepsis and septic shock: Current approaches to management. Int Med J 2019; 49: 160-170.

30. Schurr JW, Mclaughlin KC, Szumita PM. Defining the role of corticosteroids in Sepsis: Adjunctive therapy for shock reversal. Crit Care Med 2019; 47: e157-e158.

31. Klompas M, Calandra T, Singer M. Antibiotics for sepsis: Finding the equilibrium. JAMA, 2018; 320: 1433-1434.

32. Jain S. Sepsis: An update on current practices in diagnosis and management. Am J Med Sci 2018; 356: 277-286.

33. Buckman SA, Turnbull, IR, Mazuski JE. Empiric antibiotics for sepsis. Surg Infect 2018; 19: 147-154.

34. Scala R, Schultz M, Bos LDJ, Artigas A. New Surviving Sepsis Campaign Guidelines: Back to the art of medicine. Eur Respir J 2018; 52: 1701818.

35. Howell MD, Davis AM. Management of sepsis and septic shock. JAMA 2017; 317: 847-848.