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Knowledge, management, and complications of sepsis and septic shock: A significant therapeutic challenge in the intensive care unit

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ABSTRACT

Sepsis and septic shock are life-threatening conditions that are globally responsible for almost 20% of mortality, especially in low and middle-income countries. This review was conducted on PubMed and Google Scholar databases with keywords sepsis, septic shock, sepsis management, and sepsis complications. Articles published up to July 2023 in English were included. Diagnosis and management should be carried out without unnecessary delay. Cooperation between various medical specialties including intensive care doctors, neurologists, hepatologists, cardiologists, and pediatric doctors is needed if a child is affected. New strategies have to be implemented in low and middle-income countries to decrease the sepsis incidence and reduce mortality in the population.

KEYWORDS: Sepsis; Septic shock; Management; Complications; Diagnosis; Review

1. Introduction

Sepsis and septic shock are pathological conditions characterized by a heightened immune response to an infection, which causes tissue damage and significant organ dysfunction. According to an estimation of the global burden of sepsis in 2017, the global incidence of sepsis was almost 50 million cases, with approximately 11 million sepsis-related fatalities. Almost half of these cases (around 20 million) and nearly three million deaths were observed among children under the age of 5. This data suggests that sepsis accounts for nearly 20% of all global deaths, which is a serious and urgent problem, especially in low- and middle-income countries[1]. In intensive care units, multi-organ failure in the course of sepsis and septic shock stands as the primary cause of lethality among adult patients[2].

Sepsis primarily arises from bacterial infections and it can also be caused by viral or fungal infections. Gram-negative pathogens are more common (62.2%) than gram-positive microbes (46.8%) among patients with positive bacterial blood culture results. One out of every six sepsis patients is infected with *Escherichia coli*[3]. Due to the increased use of antibiotics, the prevalence of Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), has recently increased. The lungs are usually the primary site of infection, with pneumonia accounting for 38% to 39% of all bacterial sepsis cases. Additionally, significant proportions of sepsis cases are also abdominal, urinary tract, and wound-related[4]. When patients in the Intensive Care Unit develop sepsis within the hospital, the disease tends to be more severe than sepsis diagnosed at the time of hospital admission. This difference is also reflected in the types of microorganisms causing the infection. Hospital-acquired sepsis is mainly caused by opportunistic microorganisms that are resistant to various first-line antibiotics. Notably, a substantial proportion of hospital-acquired sepsis cases are attributed to drug-resistant *Pseudomonas* species, while other bacteria such as *Escherichia coli*, *Klebsiella*, and *Enterobacter*

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can also be frequently identified[5,6]. In contrast to community-acquired sepsis, which is primarily linked to pathogenic Gram-negative bacteria, hospital-acquired sepsis is usually caused by a heterogeneous mixture of causative microorganisms, which, apart from the above-mentioned microorganisms, most often includes Gram-positive *Staphylococcus* species, especially methicillin-resistant *Staphylococcus aureus* (MRSA). Pathomechanism of sepsis is similar to other infections of bacterial species. Bacterial surface toxins, such as lipopolysaccharides and other pathogen-associated molecular patterns, cause host cell toll-like receptors and other cell-surface receptors stimulation. Intracellular signaling pathways are then activated, resulting in the induction of pro-inflammatory cascades and the recruitment of inflammatory cells[3].

The pro-inflammatory mechanisms underlying viral sepsis are very comparable to bacterial sepsis. Viral sepsis is uncommon and accounts for less than 5% of all documented adult sepsis[3]. Among the susceptible groups vulnerable to viral sepsis, such as children and the elderly, common pro-inflammatory pathways are implicated, despite differences in causative pathogens. Respiratory syncytial virus (RSV) is a major cause of systemic viral infection in these susceptible populations. RSV, like other sepsis-related pathogens, primarily causes death through secondary infections due to impaired immunity. Pre-existing immunocompromised states and insufficient medical care are major risk factors for RSV-related fatalities[7,8].

Fungal sepsis also has similar mechanisms to bacterial sepsis. It is frequently associated with a higher lethality rate and a faster clinical progression. *Candida* species cause approximately 17% of fungal sepsis cases, while an additional 2% to 3% are caused by *Aspergillus*[3]. Fungi can be commonly found in the normal flora of various parts of the body, particularly in the digestive system. Nonetheless, in invasive conditions, fungal sepsis may have a mortality rate ranging from 40% to 60%[5].

Since sepsis and septic shock are very common worldwide and have high fatalities, accurate and timely diagnosis is very important. Moreover, cooperation between various clinician specialties is needed to properly treat complications in the course of sepsis.

2. Novelties in sepsis and septic shock diagnostic criteria

Researchers and scientists have tried to establish universal sepsis and septic shock criteria since sepsis-1 recommendations were released in 1991. They were updated in 2001 in sepsis-2 guidelines and have become outdated currently due to the advancements in diagnostic methods. In 2016 sepsis-3 criteria were released which nowadays remain in effect[9].

Sepsis is currently defined as a potentially fatal condition characterized by a dysregulated host response to infection that results in organ dysfunction. The clinical identification of organ dysfunction is based on a Sequential (sepsis-related) Organ Assessment Score (SOFA) (Table 1). Systemic inflammatory response syndrome (SIRS) criteria are no longer required for sepsis diagnosis. In comparison to Sepsis-2 guidelines, the term severe sepsis has been removed, emphasizing that all cases of sepsis should be considered severe disease. Septic shock is defined as a subset of sepsis characterized by severe cellular, circulatory, and metabolic abnormalities that are associated with a higher mortality risk. In the absence of hypovolemia, diagnostic criteria for septic shock include the demand for vasopressor therapy to maintain a mean arterial pressure greater than 65 mmHg and a serum lactate level greater than 2 mmol/L[10].

In addition, a simplified version of SOFA known as a quick SOFA (qSOFA) has been recommended as a bedside tool to quickly identify adult patients with a high likelihood of poor outcomes. qSOFA is a screening tool for critically ill patients and serves as an alarm to initiate timely interventions when the patient meets at least two of the following clinical criteria: respiratory rate of 22/min or

Table 1. SOFA score summary[10].

Organ system	SOFA 0	SOFA 1	SOFA 2	SOFA 3	SOFA 4
Respiratory (pO_2 / FiO_2)	≥400	<400	<300	<200 with mechanical ventilation	<100 with mechanical ventilation
Cardiovascular	MAP >70 mmHg	MAP <70 mmHg	Dopamine <5 mg/kg/min or dobutamine any dose	Dopamine 5.1-15 mg/kg/min or adrenaline/noradrenaline ≤0.1 mg/kg/min	Dopamine >15 mg/kg/min or adrenaline/noradrenaline >0.1 mg/kg/min
Neurologic (GCS)	15	13-14	10-12	6-9	3-6
Blood (Pallalets, /mL)	≥150 000	<150 000	<100 000	<50 000	<20 000
Renal (Creatinine serum or diuresis)	Creatinine ≤1.2 mg/dL	Creatinine 1.2-1.9 mg/dL	Creatinine 2-3.4 mg/dL	Creatinine 3.5-4.9 mg/dL or <500 mL of diuresis	Creatinine >5 mg/dL or <200 mL of diuresis
Hepatic (Bilirubin serum, mg/dL)	1.2	1.2-1.9	2-5.9	6-11.9	>12

GCS- Glasgow Coma Scale.

higher, Glasgow Coma Scale score of less than 15, or systolic blood pressure of 100 mmHg or lower[11].

Various investigators define septic shock differently, but most focus on SIRS criteria, systolic blood pressure values, mean arterial pressure (MAP), decrease in systolic blood pressure values, vasopressor use, and hypoperfusion abnormalities. Bone *et al*.[12] define septic shock as sepsis-induced hypotension that persists despite sufficient resuscitation measures or while receiving vasopressors or inotropes, in combination with the presence of perfusion abnormalities. Another definition established by Levy *et al*.[13] considers septic shock as a condition of acute circulatory failure that can be characterized by sustained arterial hypotension even though adequate resuscitation is performed. Moreover, other possible causative factors have to be ruled out (Table 2).

There are some other septic shock definitions based on the aforementioned criteria. Surviving Sepsis Campaign[14] defines it as sepsis-induced hypotension that endures despite appropriate fluid resuscitation while Worldwide Evaluation in Severe Sepsis Study Group[15] describes septic shock as a cardiovascular dysfunction, characterized by persistent hypotension despite sufficient resuscitation efforts, or necessitating the use of vasopressors (Table 3).

In summary, based on surveys, systematic reviews, and cohort studies, septic shock can be defined as a distinct subgroup within sepsis, wherein underlying circulatory, cellular, and metabolic disturbances can lead to a higher mortality risk. Clinical criteria, such as the presence of hypotension requiring vasopressor administration to maintain a mean blood pressure of 65 mmHg or higher and the persistence of serum lactate levels exceeding 2 mmol/L even after adequate fluid resuscitation, can be utilized to identify adult patients with septic shock[16].

3. Sepsis management

The early detection and treatment of sepsis and septic shock are critical, including precise initial diagnosis, prompt resuscitation, and timely antibiotic therapy initiation[17].

3.1. Anti–microbial therapy

Antimicrobial therapy, in conjunction with fluid resuscitation, is the fundamental basis for the therapeutic management of septic patients[18]. Appropriate routine microbiological culturing should be conducted to identify the causative pathogen, as long as this does not cause significant treatment delays. According to established guidelines, two sets of blood cultures should be obtained, one for aerobic and one for anaerobic assessment[19,20].

The 2016 Surviving Sepsis Campaign (SSC) guidelines recommend initiating intravenous antibiotic therapy within one hour after the diagnosis of sepsis or septic shock[21]. The guidelines recommend starting treatment with a broad-spectrum carbapenem such as imipenem/meropenem or an extended-range penicillin with beta-lactamase inhibitor like piperacillin/tazobactam and adding third- or higher-generation cephalosporins if necessary. Besides, the SSC guidelines suggest combining multiple antimicrobials to improve broad-spectrum coverage[22]. To increase the likelihood of at least one effective antibiotic in critically ill patients who are at high

Table 2. Definition criteria of septic shock.

Items	Bone *et al*.[12]	Levy *et al*.[13]
SIRS criteria no.	2	One or more of 24 variables from an extended variable list consisting of general (n=7), inflammatory (n=5), hemodynamic (n=3), organ dysfunction (n=7), and tissue perfusion (n=2)
SBP	<90 mmHg	<90 mmHg
Decrease in SBP	>40 mmHg	>40 mmHg
MAP	Not included	<60 mmHg
Vasopressor use	Yes, but not as an absolute requirement	Yes (CVS SOFA score)
Hypoperfusion abnormalities	Lactit acidosis, low GCS, oliguria	Serum lactate >1 mmol/L or delayed capillary refill

SIRS: Systemic Inflammatory Response Syndrome; SBP: systolic blood pressure; MAP: mean arterial pressure; CVS SOFA – cardiovascular Sequential Organ Failure Assessment.

Table 3. Other definition criteria of septic shock.

Items	Surviving sepsis campaign	PROWESS
SIRS criteria no.	2	3
SBP	<90 mmHg	<90 mmHg
Decrease in SBP	>40 mmHg	NA<70 mmHg
MAP	<70 mmHg	Hypotension which lasts more than 1 h after resuscitation
Vasopressor use	Yes, but not as an absolute requirement	Yes, but not as an absolute requirement
Hypoperfusion abnormalities	Oliguria or >4 mmol/L of serum lactate and infection-induced hypotension	Not included

risk of infection from multidrug-resistant pathogens, the addition of a supplementary gram-negative agent like fluoroquinolone or aminoglycoside is recommended. Similarly, vancomycin, teicoplanin, or another anti-MRSA agent should be used in cases of suspected MRSA-related sepsis, according to the guidelines. Furthermore, for patients at high risk of invasive *Candida* infection, the application of an echinocandin such as anidulafungin or caspofungin is considered a reasonable approach[21,23].

3.2. Fluid therapy

As aforementioned, together with antibiotics fluid administration serves as a primary therapeutic approach for septic patients[24]. The objective of this treatment is to manage hypovolemia by increasing blood volume, which leads to an increase in venous return and cardiac preload and is expected to increase cardiac output and oxygen delivery. It is worth noting, however, that after the initial stages of resuscitation, roughly half of the patients will eventually transition to a non-fluid responsive state. Administering a fluid bolus in this condition may result in fluid accumulation, impaired oxygen delivery, and compromised venous return, exacerbating the organ perfusion pressure. Nonetheless, it is critical to emphasize that all septic shock patients should be presumed fluid-responsive upon admission to the emergency department and promptly treated with a fluid bolus[25]. According to the guidelines, the crystalloid dose should amount to 30 mL/kg. Fluid administration is recommended within the first 3 hours of sepsis diagnosis[21].

3.3. Vasopressors

Norepinephrine (NE) is utilized as the primary vasoactive agent in treatment of patients with septic shock[21]. Its vasoconstrictive effects primarily concentrate on the stimulation of α1-adrenergic receptors, with little impact on heart rate. Once NE administration is started, the dosage should be chosen to achieve a mean arterial pressure (MAP) of 65 mmHg. However, it remains uncertain whether higher MAP values should be targeted[26,27].

The Surviving Sepsis Campaign (SSC) guidelines from 2016 recommend the addition of vasopressin to NE in cases of refractory shock. The goal of this combination is to reduce reliance on adrenergic tone while increasing vasoconstriction by activating different receptors. Epinephrine is another secondary vasopressor agent recommended by the 2016 SSC guidelines. Its application should be considered in situations involving concurrent cardiac dysfunction[21].

3.4. Adjunctive therapies

Steroids enhance cardiovascular function *via* two main pathways. First, mineralocorticoid activity is thought to contribute to blood volume restoration. Secondly, steroids may increase systemic vascular resistance through the mediation of glucocorticoid receptors. According to the 2016 SSC guidelines, low-dose corticosteroids, specifically hydrocortisone at 200 mg intravenously once daily, are only recommended for patients experiencing severe shock who are unresponsive to fluid resuscitation and vasopressor therapy[21].

Ascorbic acid and thiamine have emerged as potential therapeutic agents in the management of septic patients, as proposed by Marik *et al*. in a retrospective study[28]. The intravenous administration of ascorbic acid in combination with thiamine and hydrocortisone reduces both fatality rates and organ failure occurrences among septic and septic shock patients[28]. This improvement may be attributed to synergistic and overlapping effects on host immune response to infection, such as the restoration of dysregulated immune system processes[29].

4. Sepsis and septic shock complications

In the course of sepsis, multiple systems failure occurs. In this review, we include hepatic complications, coagulopathy, encephalopathy, and cardiomyopathy.

4.1. Liver dysfunction

Bilirubin concentration greater than 2 mg/dL combined with an international normalized ratio greater than 1.5 is used to diagnose liver dysfunction during sepsis. However, due to a lack of specificity and inability to distinguish between acute liver failure and pre-existing liver dysfunction, bilirubin is unsuitable as a single indicator to comprehensively reflect the complex liver function[30,31].

The clinical manifestations of liver dysfunction associated with sepsis involve sepsis-induced cholestasis, hypoxic hepatitis, and impairment of protein synthesis, which may manifest as edema and coagulopathies. Additionally, detoxification deficiencies of the liver may also lead to hepatic encephalopathy and elevated serum ammonia concentrations. However, these conditions are often camouflaged because of the administration of analgesics and sedatives in the intensive care unit[30].

The concept of "shock liver" can be used to identify liver dysfunction in critically ill patients. This complicated syndrome is characterized by a series of cellular, hemodynamic, immunological, and molecular changes that result in severe liver hypoxia followed by organ failure[32].

Regrettably, current clinical practice lacks a standardized diagnostic panel to detect acute liver dysfunction early and definitively. Furthermore, therapeutic panels for complete restoration of

impaired liver function are also lacking. As a result, managing sepsis-associated liver dysfunction remains difficult, necessitating additional research and development of effective diagnostic and therapeutic approaches[30,32].

4.2. Coagulopathy

Disseminated intravascular coagulation (DIC) is a fatal complication in septic patients. The host's response to infection involves the activation of coagulation, inflammation, and other pathways, which are necessary for infection control but can also cause tissue and organs injury. Recently, there have been some advances in understanding thrombus formation in infection control. The characteristic of DIC is the formation of blood clots in the microvasculature which is not visible in the macro scale. Hence, diagnosing sepsis-induced DIC relies on laboratory tests and the clinical context[33]. Simplified criteria have recently been introduced to aid in diagnosis. Distinguishing DIC from other similar conditions, such as thrombotic microangiopathy and heparin-induced thrombocytopenia, remains critical[34].

Managing DIC requires addressing the underlying cause, which is an important aspect of treatment. In addition, several adjunct therapies, such as thrombomodulin, antithrombin, and heparins, have demonstrated potential benefits in the treatment of DIC[34].

4.3. Encephalopathy

Sepsis-associated encephalopathy (SAE) is a common complication in septic conditions, resulting in increased mortality and poor outcomes in affected patients. SAE is caused by uncontrolled neuroinflammation and ischemic injury, which are primarily caused by immune dysregulation and disruption of neuroendocrine-immune networks such as the hypothalamic-pituitary-adrenal axis, the cholinergic anti-inflammatory pathway and the sympathetic nervous system[35]. The malfunctioning of these critical neuromodulatory mechanisms caused by SAE has a significant impact on systemic immune responses, including neutrophils, macrophages, dendritic cells, and T lymphocytes, resulting in a negative feedback loop between brain injury and progressively abnormal immune activity[36].

4.4. Cardiomyopathy

Cardiac dysfunction is a well-known complication associated with sepsis and septic shock. Sepsis-related cardiac impairment can be characterized by decreased ejection fraction, ventricular dilatation, and decreased contractile function[37]. Initially, cardiac dysfunction was thought to manifest only during the hypodynamic phase of shock. However, current research shows that it can happen very early in sepsis, even during the hyperdynamic phase of septic shock[38]. Advances in diagnostic techniques have improved the sensitivity of detecting myocardial abnormalities, which creates a need for new therapeutic strategies cardiomyopathy management concentrates on restoring tissue perfusion, and a better understanding of the progression and implications can help optimize interventions and improve clinical outcomes[39].

Sepsis and septic shock are complex conditions requiring cooperation between various medical professionals. Effective sepsis management requires early diagnosis and quick treatment without unnecessary delays. Globally different strategies should be implemented, especially in low and middle-income countries to decrease sepsis incidence and lower mortality.

Conflict of interest statement

The authors report no conflict of interest.

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Authors' contributions

JM: concept, literature search, data acquisition, manuscript editing and manuscript review, guarantor. AB: concept, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. JP: design, definition of intellectual content, manuscript preparation, manuscript editing, and manuscript review. KM: design, literature search, data acquisition, manuscript preparation, manuscript editing, and manuscript review. UG: concept, definition of intellectual content, data analysis, statistical analysis, guarantor.

References

[1] Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: Analysis for the Global Burden of Disease Study. *Lancet* 2020; **395**(10219): 200-211. DOI:10.1016/S0140-6736(19)32989-7.

[2] Rello J, Valenzuela-Sánchez F, Ruiz-Rodriguez M, Moyano S. Sepsis: A review of advances in management. *Adv Ther* 2017; **34**: 2393. DOI:10.1007/S12325-017-0622-8.

[3] Dolin HH, Papadimos TJ, Chen X, Pan ZK. Characterization of pathogenic sepsis etiologies and patient: A novel approach to triage

and treatment. *Microbiol Insights* 2019; **12**: 117863611882508. DOI:10.1177/1178636118825081.

[4] Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. *Virulence* 2014; **5**: 4. DOI:10.4161/VIRU.27372.

[5] Palavutitotai N, Jitmuang A, Tongsai S, Kiratisin P, Angkasekwinai N. Epidemiology and risk factors of extensively drug-resistant *Pseudomonas aeruginosa* infections. *PLoS One* 2018; 13. DOI:10.1371/JOURNAL.PONE.0193431.

[6] Thaden JT, Li Y, Ruffin F, Maskarinec SA, Hill-Rorie JM, Wanda LC, et al. Increased costs associated with bloodstream infections caused by multidrug-resistant gram-negative bacteria are due primarily to patients with hospital-acquired infections. *Antimicrob Agents Chemother* 2017; **61**. DOI:10.1128/AAC.01709-16.

[7] Koch RM, Kox M, De Jonge MI, Van Der Hoeven JG, Ferwerda G, Pickkers P. Patterns in bacterial- and viral-induced immunosuppression and secondary infections in the ICU. *Shock* 2017; **47**: 5-12. DOI:10.1097/SHK.0000000000000731.

[8] Caballero MT, Polack FP. Respiratory syncytial virus is an "opportunistic" killer. *Pediatr Pulmonol* 2018; **53**: 664-667. DOI:10.1002/PPUL.23963.

[9] Singer M, Deutschman CS, Seymour C, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; **315**: 801. DOI:10.1001/JAMA.2016.0287.

[10]Salomão R, Ferreira BL, Salomão MC, Santos SS, Azevedo LC, Brunialti MK. Sepsis: Evolving concepts and challenges. *Brazilian J Med Biol Res* 2019; **52**. DOI:10.1590/1414-431X20198595.

[11]Machado FR, De Assunção MSC, Cavalcanti AB, Japiassú AM, De Azevedo LC, Oliveira MC. Getting a consensus: Advantages and disadvantages of sepsis 3 in the context of middle-income settings. *Rev Bras Ter Intensiva* 2016; **28**: 361. DOI:10.5935/0103-507X.20160068.

[12]Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest* 1992; **101**: 1644-1655. DOI:10.1378/CHEST.101.6.1644.

[13]Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med* 2003; **31**: 1250-1256. DOI:10.1097/01.CCM.0000050454.01978.3B.

[14]Dellinger RP, Levy M, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; **41**: 580-637. DOI:10.1097/CCM.0B013E31827E83AF.

[15]Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF, Lopez-Rodriguez A, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001; **344**: 699-709. DOI:10.1056/NEJM200103083441001.

[16]Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, et al. Developing a new definition and assessing new clinical criteria for septic shock: For the third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016; **315**: 775. DOI:10.1001/JAMA.2016.0289.

[17]Gavelli F, Castello LM, Avanzi GC. Management of sepsis and septic shock in the emergency department. *Intern Emerg Med* 2021; **16**: 1649. DOI:10.1007/S11739-021-02735-7.

[18]Levy MM, Evans LE, Rhodes A. The surviving sepsis campaign bundle: 2018 Update. *Crit Care Med* 2018; **46**: 997-1000. DOI:10.1097/CCM.0000000000003119.

[19]Kumar A, Roberts D, Wood KE, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; **34**: 1589-1596. DOI:10.1097/01.CCM.0000217961.75225.E9.

[20]Funk DJ, Kumar A. Antimicrobial therapy for life-threatening infections: Speed is life. *Crit Care Clin* 2011; **27**: 53-76. DOI:10.1016/J.CCC.2010.09.008.

[21]Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. *Crit Care Med* 2017; **45**: 486-552. DOI:10.1097/CCM.0000000000002255.

[22]Kalil AC, Gilbert DN, Winslow DL, Masur H, Klompas M. Infectious Diseases Society of America (IDSA) Position Statement: Why IDSA did not endorse the surviving sepsis campaign guidelines. *Clin Infect Dis* 2018; **66**: 1631. DOI:10.1093/CID/CIX997.

[23]Pappas PG, Kauffman CA, Andes D, Benjamin DK, Calandra TF, Edwards JE, et al. Clinical practice guidelines for the management of candidiasis: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009; **48**: 503. DOI:10.1086/596757.

[24]Rochwerg B, Alhazzani W, Sindi A, Heels-Ansdell D, Thabane L, Fox-Robichaud A, et al. Fluid resuscitation in sepsis: A systematic review and network meta-analysis. *Ann Intern Med* 2014; **161**: 347-355. DOI:10.7326/M14-0178.

[25]Monnet X, Teboul JL. Prediction of fluid responsiveness in spontaneously breathing patients. *Ann Transl Med* 2020; **8**: 790-790. DOI:10.21037/ATM-2020-HDM-18.

[26]Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C. et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock 2021. *Crit Care Med* 2021; **49**: E1063-E1143. DOI:10.1097/CCM.0000000000005337.

[27]De Backer D, Creteur J, Silva E, Vincent JL. Effects of dopamine, norepinephrine, and epinephrine on the splanchnic circulation in septic shock: Which is best? *Crit Care Med* 2003; **31**: 1659-1667. DOI:10.1097/01.CCM.0000063045.77339.B6.

[28]Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock: A retrospective before-after study. *Chest* 2017; **151**: 1229-1238. DOI:10.1016/J.CHEST.2016.11.036.

[29]Moskowitz A, Andersen LW, Huang DT, Berg KM, Grossestreuer AV, Marik PE, et al. Ascorbic acid, corticosteroids, and thiamine in sepsis: A review of the biologic rationale and the present state of clinical evaluation. *Crit Care* 2018; 22. DOI:10.1186/S13054-018-2217-4.

[30]Woznica EA, Inglot M, Woznica RK, Lysenko L. Liver dysfunction in sepsis. *Adv Clin Exp Med* 2018; **27**: 547-551. DOI:10.17219/ACEM/68363.

[31]Chand N, Sanyal AJ. Sepsis-induced cholestasis. *Hepatology* 2007; **45**: 230-241. DOI:10.1002/HEP.21480.

[32]Kobashi H, Toshimori J, Yamamoto K. Sepsis-associated liver injury: Incidence, classification and the clinical significance. *Hepatol Res* 2013; **43**: 255-266. DOI:10.1111/J.1872-034X.2012.01069.X.

[33]Taylor J, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation: On behalf of the scientific subcommittee on disseminated intravascular coagulation (DIC) of the International Society on Thrombosis and Haematostasis (ISTH). *Thromb Haemost* 2001; **86**: 1327-1330. DOI:10.1055/S-0037-1616068/BIB.

[34]Iba T, Levi M, Levy JH. Sepsis-induced coagulopathy and disseminated intravascular coagulation. *Semin Thromb Hemost* 2020; **46**: 89-95. DOI:10.1055/S-0039-1694995.

[35]Dimopoulou I, Tsagarakis S, Kouyialis AT, Roussou P, Assithianakis G, Christoforaki M, et al. Hypothalamic-pituitary-adrenal axis dysfunction in critically ill patients with traumatic brain injury: Incidence, pathophysiology, and relationship to vasopressor dependence and peripheral interleukin-6 levels. *Crit Care Med* 2004; **32**: 404-408. DOI:10.1097/01.CCM.0000108885.37811.CA.

[36]Ren C, Yao RQ, Zhang H, Feng YW, Yao YM. Sepsis-associated encephalopathy: A vicious cycle of immunosuppression. *J Neuroinflammation* 2020; **17**. DOI:10.1186/S12974-020-1701-3.

[37]Levy RJ, Deutschman CS. Evaluating myocardial depression in sepsis. *Shock* 2004; **22**: 1-10. DOI:10.1097/01.SHK.0000129198.53836.15.

[38]Flynn A, Chokkalingam Mani B, Mather PJ. Sepsis-induced cardiomyopathy: A review of pathophysiologic mechanisms. *Heart Fail Rev* 2010; **15**: 605-611. DOI:10.1007/S10741-010-9176-4.

[39]Hollenberg SM, Singer M. Pathophysiology of sepsis-induced cardiomyopathy. *Nat Rev Cardiol* 2021; **18**: 424-434. DOI:10.1038/S41569-020-00492-2.

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