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A Narrative Review of Guideline-Based Recommendations for the Treatment of Sepsis and Sepsis-Related Conditions

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Abstract

Sepsis and septic shock are feared diagnoses in intensive care units and emergency departments all over the world due to the high morbidity and mortality rate of both. Sepsis and septic shock require different treatment approaches as well as careful consideration of the demographic characteristics of the patient. Following evidence-based guideline recommendations for treatment of both conditions is highly encouraged. This narrative review article provides definitions of sepsis/septic shock, basic epidemiological trends noticed among U.S. sepsis patients, and summarizes some of the strongest treatment recommendations from evidence-based sepsis guidelines for bacterial sepsis, COVID-19 viral sepsis, sepsis in neonates/infants/children, sepsis in cancer patients, and meningococcal sepsis. Brief suggestions for nutrition therapy in sepsis patients are also provided.

Keywords: *Sepsis; Sepsis Treatment Guidelines; ARDS; NRDS; Sepsis Management*

Abbreviations

US: United States; SOFA: Sequential Organ Failure Assessment; POC: Person/People of Color; LOS : Length of Stay; HIV+: Human Immunodeficiency Virus Positive; HSV: Herpes Simplex Virus; HPeVs: Human Parechoviruses; IV: Intravenous; GI: Gastrointestinal; COVID-19: Coronavirus Disease 2019; GRADE: Grades of Recommendation, Assessment, Development and Evaluation; GBS: Group B *Streptococci*; ECMO: Extracorporeal Membrane Oxygenation; PRDS: Pediatric Respiratory Distress Syndrome; UK: United Kingdom; RCTs: Randomized Controlled Trials; ICU: Intensive Care Unit

Introduction

Sepsis is a life-threatening condition that can, in turn, further induce several other life-threatening conditions in a patient. Improving mortality rates in affected patients is an important goal for many physicians. Guidelines for sepsis treatment have summarized as well as created many recommendations based on various levels of evidence, ranging from individual physician suggestions to conclusions based on data from large-scale randomized controlled trials (RCTS). This review summarizes the current accepted definitions of sepsis and various significant sepsis-related conditions, identifies some common demographic trends among sepsis-afflicted patients, and provides a summary of the strongest treatment recommendations from various international and United States (U.S.) sepsis treatment guidelines. General nutrition therapy recommendations for sepsis patients are also included.

Materials and Methods

To gather articles for review, Google Scholar and PubMed were used. Key search terms included: "sepsis epidemiology", "sepsis epidemiology united states", "sepsis treatment guidelines", "sepsis guidelines united states", and "sepsis guidelines". Evidence-based na-

tional and international consensus guidelines were considered for review regarding treatment recommendations; individual studies, case reports, and review articles were excluded whenever possible. Preference was given to U.S. clinical guidelines released between 2015 - 2020, but both international and U.S. clinical guidelines published ahead of this timeframe were included due to the low number of existing sepsis guidelines. Epidemiological information on sepsis was gathered from the U.S. population and is meant to represent trends seen in the U.S. only. For epidemiological information on sepsis, large scale retrospective studies were included for review.

Results and Discussion

Definitions of sepsis, septic shock, and severe sepsis

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) article, written in 2016, provides updated definitions of sepsis and septic shock that are approved by 19 experts and supported by many professional societies around the world [1]. *Sepsis* is defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection" [1]. *Septic shock* is defined as a "subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality" [1]. Some examples of the underlying cellular/metabolic abnormalities associated with septic shock include an elevated serum lactate level (> 2 mmol/L) and hypotension that will not resolve unless vasopressors are given in addition to fluids to keep mean arterial pressure ≥ 65 mm Hg [1].

Term	Definition
Sepsis	Life-threatening organ dysfunction caused by a dysregulated host response to infection.[1]
Septic Shock	Subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.[1]
Severe Sepsis	Redundant when compared with definition of "sepsis".[1]

Table 1*: Summary of Guideline-Based Definitions of Sepsis, Septic Shock, and Severe Sepsis.*

Severe sepsis was previously used to describe "sepsis complicated by organ dysfunction", but the 2016 task force decided that this term was redundant when compared with the definition of sepsis [1]. However, *severe sepsis* is still frequently used in the literature under the traditional definition. As such, whenever severe sepsis is mentioned in this review article, it should be considered under its traditional definition. Regarding quantifying the extent of organ dysfunction in relation to severe sepsis, the SOFA score is used; a score ≥ 2 that occurs acutely in the context of development of sepsis is considered indicative of organ dysfunction [1]. The SOFA score is built off of a criterion of respiratory rate ≥ 22 breaths/min, systolic blood pressure ≤ 100 mmHg, and changes in mental status [1]. A normal SOFA score is 0 [1].

Epidemiology of sepsis

Martin., *et al* [2] noted that between 1979 - 1987, gram-negative bacteria were the most common organisms that caused sepsis. After 1987, gram-positive bacteria became the most common organisms, with fungi also increasing in causality rate [2]. In general, the incidence rate of sepsis is increasing but the mortality rate is decreasing; the highest increase in incidence rate is seen in women [2]. However, sepsis is more common in men (average relative risk = 1.28) and POC (average relative risk = 1.90); it also develops at a younger age in men [2]. Black men have the highest incidence rate, highest mortality rate, and youngest onset age when compared with other demographic groups [2]. Although the incidence rate and prevalence vary by gender, the mortality rate from sepsis remains relatively equal between men and women [2].

According to Whittaker., *et.al* [3], patients that were older, had pre-existing comorbidities, had cancer, or had elevated serum lactate levels on admission (≥ 4 mmol/L), were significantly more likely to experience an adverse outcome from sepsis. This study found no significant relationship between the original site of infection on the patient and an adverse outcome [3]. In a study conducted by Paoli., *et al* [4], out of 2,566,689 cases of sepsis, sepsis without organ dysfunction was the most commonly occurring with 1,346,824 cases, followed by septic shock with 518, 010 cases, and severe sepsis with 412, 736 cases. As expected, the greater the severity of sepsis, the worse the mortality rate and the longer the length of hospital stay [4]. Septic shock had a mortality rate of 34.3% and average LOS of 12.6 days as compared with sepsis without organ dysfunction, which only had a mortality rate of 5.4% and average LOS of 7.7 days [4].

In terms of severe sepsis, Mayr., *et al* [5] noted that it is more common in men, black, or older individuals. Risk factors for severe sepsis include being black, having cancer, HIV+ status, being male, being a low-birth weight neonate, malnourishment, immunosuppressant use, prosthetics use, living in a long-term care facility, and being obese [5].

Watson., *et al* [6] noted that in children with severe sepsis, almost half of the children had underlying conditions, most commonly neuromuscular issues (12.4%). Female children were more likely to have an underlying condition if they developed severe sepsis but male children had a higher incidence rate in general [6]. Infants had the highest incidence rate of severe sepsis [6]. Male infants were more likely to present with severe sepsis and, if also considered low birth weight, had a higher mortality rate [6]. In neonates, primary bacteremia was more prevalent and in children, respiratory infection was more prevalent as the cause of severe sepsis [6]. Schrag., *et al* [7] found that in neonates, the most common cause of invasive early-onset sepsis was *Group B Streptococcus*, followed by *Escherichia coli*. Low birth weight infants or premature infants were more likely to develop sepsis with either pathogen [7]. Premature black infants had the highest incidence rate of invasive early-onset sepsis (10.2 out of 1000 live births) [7].

In terms of viral sepsis, HSV and enteroviruses most commonly cause neonatal viral sepsis [8,9]. In young children, human parechoviruses (HPeVs) and enteroviruses most commonly cause viral sepsis [8,9].

Guideline-based recommendations for various sepsis/sepsis-related conditions

Some of the strongest recommendations from various guidelines have been listed below for different subcategories of sepsis.

Bacterial sepsis

Blood transfusions should be done in patients with *septic shock* when the hemoglobin level is < 7 g/dL [10]; if there is evidence of acute hemorrhage, severe hypoxemia, or myocardial ischemia, do not conduct [11]. The source of infection should be controlled as quickly as possible in intraperitoneal sepsis cases [10]. For both sepsis and septic shock, IV antibiotics should be given by the first hour post-admission [11]. For sepsis cases caused by Gram negative bacilli, avoid using combination medication therapy [10]. In cases of either sepsis or septic shock, crystalloids are recommended for initial fluid resuscitation and for maintaining intravascular volume [11]. 30 mL/kg of IV crystalloid fluid should be administered within 3 hours after resuscitation [11]. Noradrenaline [10] or norepinephrine [11] are the first-line vasopressor for septic shock patients who do not respond to initial fluid resuscitation. If there is sepsis-induced anemia, do not use erythropoietin to correct [11]. Do not administer antithrombin, low-dose dopamine, or hydroxyethyl starches for treatment of hypotension, renal failure, or hypoperfusion [11]. Reduce blood glucose levels to ≤ 180 mg/dL using insulin if two consecutive readings are above 180 mg/dL [11]. In patients who are at risk of developing GI bleeds, prophylaxis for stress ulcers should be started [11].

Sepsis in COVID-19 patients

For treating adults with COVID-19 viral sepsis, the Surviving Sepsis Campaign recently provided some recommendations [12]. Strong recommendations and best practice statements were determined using the GRADE approach [12]. In situations of acute resuscitation of patients in septic shock, do not use hydroxyethyl starches, dopamine, or colloids [12]. Preferred treatments in this situation are norepi-

nephrine and crystalloids [12]. COVID-19 can cause a cytokine storm syndrome that is very similar to sepsis, but more evidence of successful treatments for this condition are needed before general treatment recommendations can be created [12].

Sepsis in neonates/infants

To treat early-onset neonatal sepsis, it is recommended to use combination therapy with both ampicillin and an aminoglycoside [13-15]. In infants with positive Group B *Streptococci* blood cultures (GBS is often the cause of either early-onset neonatal sepsis or late-onset sepsis in infants), give IV penicillin G or ampicillin for 10 days for bacteremia without focus [16].

In order to acutely treat septic shock in neonates, make sure that the airway is intact first [17]. Then, begin antibiotics, fluids, and correct any hypocalcemia/hypoglycemia [17]. Next, use vasopressors to elevate blood pressure if the neonate is not responsive to fluids [17]. Evaluate if the neonate is in cold or warm shock, check heart function, and proceed accordingly [17]. Finally, if all else fails, use ECMO [17].

In order to acutely treat septic shock in infants, give high flow oxygen first [17]. Then, begin antibiotics, fluids, and correct any hypocalcemia/hypoglycemia [17]. Next, use vasopressors to elevate blood pressure if the infant is not responsive to fluids [17]. Evaluate if the infant is in cold or warm shock, check blood pressure, and proceed accordingly [17]. Finally, if all else fails, use ECMO [17].

Sepsis in children

In children with septic shock, antibiotics should be started within 1-hour post-admission [18]. Any intravascular devices that are suspected of being the source of infection should be removed [18]. For children experiencing sepsis-induced PRDS, do not give inhaled nitric oxide [18]. In children with septic shock and/or organ dysfunction, do not give starches to resuscitate [18]. Insulin should not be given to children to lower blood glucose levels, but blood glucose should ideally be kept ≤ 180 mg/dL [18].

In order to acutely treat septic shock in children, give high flow oxygen first [17]. Then, begin antibiotics, fluids, and correct any hypocalcemia/hypoglycemia [17]. Next, use vasopressors to elevate blood pressure if the child is not responsive to fluids [17]. Evaluate if the child is in cold or warm shock, check blood pressure, and proceed accordingly [17]. Finally, if all else fails, use ECMO [17].

Sepsis in cancer patients

Experts in Germany released a set of guidelines for treatment of sepsis in neutropenic cancer patients [19]. Many treatment options are the same as those mentioned in the 2016 Surviving Sepsis Campaign guidelines when treating neutropenic cancer patients with either sepsis or septic shock; for example, there are no significant differences in terms of fluid therapy, blood products, mechanical ventilation, nutrition, analgesia, and vasopressor medication choices [19]. This guideline recommends immediately giving anti-pseudomonal broad-spectrum antibiotics and doing source control as rapidly as possible [19]. Intravascular devices should also be taken out if possible [19]. Balanced IV crystalloids are the fluid of choice in these patients [19]. Do not give combination therapy to treat sepsis in neutropenic patients [11].

Meningococcal sepsis

Experts in the U.K. released a set of guidelines with recommendations for managing meningococcal sepsis in immunocompetent adults [20]. 1B recommendations were the highest level provided for meningococcal sepsis treatment and were based off of low-quality RCTs or high-quality observational studies [20]. Euvolemia should be established using crystalloids before correcting blood pressure [20]. Norepinephrine is the recommended vasopressor for correcting hypotension and mean arterial pressure should be maintained at ≥ 65 mmHg [20]. In all patients with meningococcal sepsis, 2 grams IV ceftriaxone every 12 hours or 3 grams IV cefotaxime every 6 hours should be

given [20]. For patients older than 60 years of age or in those who are immunocompromised, 2 grams IV ampicillin/amoxicillin every 4 hours should also be added [20].

Demographic Group/Sepsis Condition	Recommendations
Bacterial Sepsis	• Give blood transfusions in patients with septic shock when hemoglobin level is < 7 g/dL[10] if no hemorrhage, myocardial ischemia, or severe hypoxemia[11] • Prioritize source control of infection[10] • Give IV antibiotics within 1 hour post-admission[11] • Give 30 mL/kg IV crystalloid within 3 hours after resuscitation[11] • Give noradrenaline[10] or NE[11] if septic shock patient is unresponsive to fluids • Do not use EPO for sepsis-induced anemia[11] • Do not give hydroxyethyl starches, dopamine, or antithrombin treatments[11] • Use insulin to maintain blood glucose ≤ 180 mg/mL[11] • Give medications to prevent stress ulcers in patients who risk GI bleeds[11]
Viral Sepsis (COVID-19)	• Use NE and crystalloids for acute fluid resuscitation in septic shock cases over dopamine, hydroxyethyl starches, and colloids[12]
Sepsis in Neonates/Infants	• Early-onset neonatal sepsis: give ampicillin and aminoglycoside[13,14,15] • GBS + cultures: give ampicillin or IV penicillin G for 10 days for bacteremia w/o focus[16] • Septic shock: airway first, then fluid resuscitation, then vasopressors for BP, ECMO is last resort[17]
Sepsis in Children	• Remove all intravascular devices if able[18] • Do not give starches, insulin, or inhaled NO[18] • Septic shock: give antibiotics w/in 1 hour of admission[18] • Septic shock: airway first, then fluid resuscitation, then vasopressors for BP, ECMO is last resort[17]

Sepsis in Cancer Patients	• Immediately give anti-pseudomonal broad-spectrum antibiotics[19] • Prioritize source control of infection[19] • Balanced crystalloids are fluid of choice[19] • Remove all intravascular devices if able[19] • Follow regular sepsis guideline recommendations for most other aspects of treatment[19]
Meningococcal Sepsis	• establish euvolemia using crystalloids before blood pressure management[20] • NE is vasopressor of choice[20] • Goal MAP ≥ 65 mmHg[20] • 2 grams IV ceftriaxone every 12 hours or 3 grams IV cefotaxime every 6 hours[20] • Add 2 grams IV ampicillin/amoxicillin every 4 hours in those > 60 years old/immunocompromised[20]

Table 2: *Summary of Best Guideline-Based Treatment Recommendations for Sepsis and Sepsis-Related Conditions in Various Demographic Groups.*

Nutrition therapy for sepsis

Wischmeyer., *et al* [21] recommend giving 1.0 g/kg/day of protein and 15 kcal/kg/day of calories during the first 4 days of illness, known as the acute phase of sepsis. 1.2 - 2.0 g/kg/day of protein and 25 - 30 kcal/kg/day of calories can be given once the patient enters the chronic phase, where they are more stable [21]. Once the patient is deemed in recovery from sepsis, they still need large continuous caloric intake (> 3,000 kcal/day) to replace any lost lean body mass [21]. Proteins should also still be given during the recovery period from sepsis (> 1.5 g/kg/day) [21].

In general, upon admission to the ICU, 200 mg of thiamine should be given for 1 week to septic patients [21]. In all septic shock patients, Vitamin D levels should be checked upon admission and every week during the recovery [21]. A patient is considered to be deficient when levels are < 30 ng/mL [21]. Vitamin D deficient patients should be given 100,000 units of Vitamin D2 or D3 for 5 days out of the first week of illness and then 1-2 times during every subsequent week in the ICU [21]. Enteral nutrient delivery should be chosen over intravenous delivery whenever possible and should be started within 48 hours of the patient being unable to eat [10].

Conclusion

Evidence-based guidelines are a valuable resource for many scientists, physicians, and other healthcare professionals to reference when determining how to approach treatment for certain conditions. One such condition, sepsis, requires multiple nuanced recommendations based on patient demographical characteristics, the type of sepsis or sepsis-related condition, and other variables. Due to the high morbidity and mortality rate, following evidence-based guidelines is recommended when treating sepsis/sepsis-related conditions to provide the best possible outcome for patients.

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Conflict of Interest

All authors declare that there are no conflicts of interest. All authors declare that no financial support or sponsorship was offered or accepted.

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