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Sepsis: An Overview of Current Therapies and Future Research

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ABSTRACT

Sepsis is a global health concern and a medical emergency, defined as the systemic immunological response of the body to an infection, which can lead to severe organ dysfunction and death. This understanding has evolved partly due to advancements in our knowledge of its pathophysiology. The aim of this review is to examine recent advancements in sepsis treatment. Accordingly, the authors reviewed the current literature on sepsis, analyzing advancements in its definitions, treatment guidelines, and management strategies. Sepsis can severely impair immune system functionality, leading to distinct subphenotypes of immunosuppression that increase patients' susceptibility to infections. These subphenotypes exhibit varying clinical features and responses to treatment, underscoring the necessity of understanding immunosuppression for the advancement of personalized treatment strategies. A transformative shift in sepsis management includes the early recognition of at-risk cases and the prompt, effective use of antibiotics, hemodynamic management, source control, and appropriate supportive care. Although current Surviving Sepsis Campaign guidelines recommend early fluid resuscitation, prompt antibiotic therapy, and monitoring lactate clearance, the authors discuss the objections raised by the Infectious Diseases Society of America regarding these recommendations. In conclusion, initial resuscitation is a critical component of managing sepsis and septic shock, significantly impacting patient outcomes. As our understanding of sepsis continues to evolve, ongoing research and discussions surrounding these guidelines remain essential for improving treatment protocols and enhancing patient care. Given the crucial role of the immune response in sepsis pathophysiology, future research on sepsis management will likely focus on anti-inflammatory mechanisms.

Keywords: Definitions, management, sepsis, septic shock, subphenotypes.

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INTRODUCTION

Sepsis is a life-threatening syndrome characterized by an abnormal response to infection, leading to organ dysfunction. Although the underlying pathophysiology of this clinical condition has become better understood over the years, and advancements in hemodynamic monitoring and resuscitation measures have been made, sepsis is still one of the leading causes of mortality and morbidity among critically ill patients.[1] According to data from the 2012 Surviving Sepsis Campaign, mortality rates

from sepsis varied significantly by region, with approximately 41% in Europe compared to around 28.3% in the United States.[2] Globally, sepsis continues to be a critical healthcare challenge.

A study investigating the epidemiology of sepsis in intensive care units across Türkiye reported that 15.8% of patients had an infection without Systemic Inflammatory Response Syndrome (SIRS), while 10.8% had an infection with SIRS. Additionally, 17.3% of patients had severe sepsis without shock, and 13.5% presented with septic shock. According to the SEPSIS-III criteria, 6.9% of patients had septic shock, with this group experiencing a mortality rate of 75.9%.[3] In another study conducted in Türkiye, Gram-negative bacteria were detected in 48% of cases, Gram-positive bacteria in 15%, and fungi in 8%, while no culture positivity was observed in 29% of patients. The mortality rate among hospitalized patients in this study was reported to be 51%.[4]

In a study comparing patients diagnosed with severe sepsis or septic shock in elderly and non-elderly groups, it was found that risk factors such as smoking, medication use, hyperglycemia, and multiple organ failure significantly increased the risk of sepsis in elderly patients. In contrast, chronic renal failure, hematologic malignancy, and leukopenia were identified as more prominent risk factors in non-elderly patients. The absence of a significant difference in 28-day mortality rates between elderly and non-elderly patients raises an important discussion regarding how differences in sepsis management between age groups impact mortality outcomes.[5]

Sepsis triggers immune system dysfunction, often leading to a state of immunosuppression. This condition increases the risk of secondary infections in septic patients, consequently elevating mortality rates. The identification of specific subphenotypes, which exhibit diverse clinical profiles and treatment responses, underscores the importance of understanding immunosuppression and the necessity for tailored therapeutic approaches.[6,7]

The aim of this narrative review is to explore the evolving definitions of sepsis and septic shock while highlighting current advancements, treatment guidelines, and future research strategies in sepsis management.

For the preparation of this article, the databases PubMed, Web of Science, and Google Scholar were searched using the terms "sepsis,""septic shock,""adult,""management,""subphenotypes," and "therapy" for studies published between November 2021 and October 2024. November 2021 was chosen as the start date because it marks the publication of the latest sepsis guidelines.[8] Additionally, we manually searched the references of included studies and previous reviews to ensure comprehensive coverage.

CLINICAL AND RESEARCH CONSEQUENCES

Definition

Over the years, our understanding of the complex pathophysiology of sepsis has advanced, along with our ability to define the condition more accurately. The term "sepsis" originates from a Greek word meaning "decomposition" or "putrefaction." The earliest recorded mentions of this concept appear in the works of Homer approximately 2,700 years ago, with further references found in the writings of notable figures such as Hippocrates and Galen in subsequent centuries.[9]

The definition of sepsis has evolved over time, with the SIRS criteria, introduced by Roger Bone and his team at the 1991 Society of Critical Care Medicine-American College of Chest Physicians (SCCM-ACCP) conference, serving as the foundation for sepsis diagnosis until 2016.[10] Over the years, advancements in biochemistry, histology, immunology, blood circulation, and organ function have played a crucial role in refining the definition of sepsis. The evolution of sepsis definitions from 1991 to 2016 is summarized in Table 1.[11–13]

Subphenotypes

The biological variability among patients with sepsis can significantly influence their responses to treatment. Therefore, categorizing sepsis patients into more homogenous subphenotypes may enhance treatment effectiveness. To achieve this, multiple classification systems have been developed, utilizing clinical data, inflammatory biomarker profiles, and gene expression analysis. Notable classification models include the Sepsis Network for the Classification of Acute Illness (SENECA) system, which relies on clinical data; the Acute Respiratory Distress Syndrome (ARDS) classification, based on biomarker profiles; and the Molecular Assessment of Sepsis (MARS) and Sepsis Response System (SRS) strategies, which utilize gene expression analysis. These classification systems help elucidate the biological and clinical characteristics of sepsis patients and contribute to the development of personalized treatment strategies.[6]

By identifying subphenotypes of sepsis, healthcare professionals can develop more targeted treatment strategies. For instance, the ARDS classification divides patients into two groups: hyperinflammatory and hypoinflammatory, with the hyperinflammatory group generally associated with severe organ failure and a high risk of death.[6] Classification models such as the MARS and SRS enhance clinical decision-making by differentiating patients based on their biological responses at the gene expression level. These subphenotype classifications, which integrate various biomarkers and gene expression profiles, hold promise for fostering more effective, individualized approaches to sepsis treatment. Additionally, the application of machine learning techniques is expected to accelerate this evolution.[6,14]

Table 1. Definitions of sepsis

SEPSIS-1 (1991)	Sepsis-2 (2001)	Sepsis-3 (2016)	
Systemic Inflammatory Response Syndrome (SIRS): Temperature >38°C or <36°C Heart Rate >90 beats/min Respiratory Rate >20 breaths/min White blood cell (WBC) count >12,000/cu mm or <4,000/cu mm or >10% immature forms (bands) Severe Sepsis: Sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria, or acute mental status changes. Septic Shock: Sepsis-induced hypotension persisting despite adequate fluid resuscitation, along with perfusion abnormalities such as lactic acidosis, oliguria, or acute mental status changes. Patients requiring inotropic or vasopressor agents may not initially present with hypotension at the time of assessment.	Infection (documented or suspected) with some of the following: **General parameters:** Fever (core temperature >38.3°C); Hypothermia; Heart rate (90 beats per minute or >2 standard deviations (SD) above normal for age; Tachypnea (respiratory rate >30 breaths per minute); Altered mental status; Significant edema or positive fluid balance (>20 mL/kg over 24 hours); Hyperglycemia (plasma glucose >110 mg/dL or 7.7 mM/L) in the absence of diabetes. **Inflammatory parameters:** Leukocytosis (WBC>12,000/µL); Leukopenia (WBC<4,000/µL); WBC with >10% immature forms; Plasma C-reactive protein >2 SD above the normal value; Plasma procalcitonin >2 SD above the normal value. **Hemodynamic parameters:** Arterial hypotension (systolic blood pressure 40 mmHg in adults or 70%; Cardiac index >3.5 L/min/m^2). Organ Dysfunction Parameters: Arterial hypoxemia (PaO_2/FiO_2) 1.5 or activated partial thromboplastin time >60 sec); Ileus (absent bowel sounds); Thrombocytopenia (platelet count 4 mg/dL or 70 mmol/L). Tissue Perfusion Parameters: Hyperlactatemia (>3 mmol/L); Decreased capillary refill or mottling.	**Definition:** Quick Sepsis-Related Organ Failure Assessment (qSOFA) ≥2. Sepsis: Life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic Shock: A state with high mortality risk due to profound circulatory, cellular, and metabolic abnormalities.	**Clinical criteria:** qSOFA, based on: Altered mental status (Glasgow Coma Scale [GCS]<15); Systolic blood pressure (BP) <100 mmHg; Respiratory rate >22 breaths/minute. Suspected or documented infection with a Sequential Organ Failure Assessment (SOFA) score increase of ≥2. Vasopressor requirement to maintain MAP ≥65 mmHg with lactate >2 mmol/L despite fluid resuscitation.

WBC: White blood cell count; qSOFA: Quick sepsis-related organ failure assessment; GCS: Glasgow Coma Scale; BP: Blood pressure; MAP: Mean arterial pressure; PaO_2: Partial pressure of oxygen; FIO_2: Fraction of inspired oxygen.

Komorowski et al.[14] suggest that employing machine learning algorithms to identify sepsis subphenotypes is a promising approach. These algorithms facilitate quicker and more precise assessments of sepsis severity and treatment responses, increasing the potential for personalized therapies based on subphenotype categorization. They criticized the limitations of traditional biomarkers in sepsis and advocated for incorporating machine learning techniques to enable more precise analysis of molecular data. This approach aims to refine patient risk classification, improve treatment efficacy, and reduce sepsis-related mortality rates.[14] For example, while ARDS subtypes are classified into hyperinflammatory and hypoinflammatory categories, gene expression-based classifications such as MARS and SRS assess biological responses at the molecular level. This approach offers the potential for improved treatment outcomes for complications such as sepsis and associated acute kidney injury (AKI).[6,14]

The exploration of novel treatment modalities for sepsis-related AKI may focus on preserving renal microcirculation, mitigating inflammation and oxidative stress, and supporting mitochondrial function. Recognizing sepsis subphenotypes enables the development of targeted treatment strategies, ultimately improving clinical outcomes for patients. In managing AKI associated with sepsis, it is crucial to regulate the inflammatory response at the cellular level and employ biomarker-driven classification methods to better understand the complexities of this condition and determine appropriate treatment approaches. The objective is to provide more personalized and effective interventions through the integration of biomarkers and machine learning techniques.[15]

Within this framework, immunotherapy represents a critical step toward personalized treatment for sepsis patients. Additionally, investigations into the mechanisms underlying sepsis-related immunosuppression, diagnostic methodologies, and available treatment options are gaining increased attention. Sepsis disrupts immune function, resulting in an imbalance between inflammatory and immunosuppressive pathways.16 Given the heterogeneous immune profiles observed among septic patients, a standardized treatment protocol often fails to produce effective results. Therefore, it is recommended to develop specific treatment strategies tailored to each patient's immune status, utilizing regulatory biological agents, cytokine inhibitors, and immune modulators. This study highlights the potential to reduce sepsis-related mortality through personalized approaches and underscores the importance of classifying patient groups based on their immune profiles as a significant advancement in this endeavor.[7] Diagnosis can be facilitated through biomarkers such as immune cell profiling and cytokine levels, while treatment options include immunomodulatory therapies and blood products; however, further research is necessary to establish the efficacy of these interventions.[16]

Research defining four distinct subphenotypes based on variations in vital signs, including heart rate, respiratory rate, and body temperature, in septic patients represents a significant advancement in this field. These subphenotypes correlate with different clinical pathways and mortality rates, providing valuable insights for the development of more precise treatment strategies.[17]

MANAGEMENT OF SEPSIS

Sepsis and septic shock remain leading causes of mortality and morbidity in critically ill patients, despite advancements in medical care. Over the years, various treatment strategies have been proposed, with early goal-directed therapy (EGDT) being one of the most extensively studied interventions.18 This review compares the findings of key clinical trials, including Protocolized Care for Early Septic Shock (ProCESS), Protocolized Management in Sepsis (ProMISe), and Australasian Resuscitation in Sepsis Evaluation (ARISE), and incorporates insights from related studies to assess the role of EGDT in modern sepsis management.[18]

EGDT, initially introduced by Rivers et al.[19] in a landmark 2001 trial, revolutionized the approach to sepsis management by advocating for early, aggressive hemodynamic optimization. This approach focused on achieving specific physiological targets, including mean arterial pressure (MAP), central venous oxygen saturation ($ScvO_2$), and central venous pressure (CVP), within the first six hours of resuscitation. Nguyen et al.[18] emphasized that early initiation of EGDT led to improved survival rates, a concept that formed the basis of subsequent guidelines, such as those of the Surviving Sepsis Campaign.

The ProCESS, ProMISe, and ARISE trials played a crucial role in transforming the approach to sepsis management. These studies collectively enrolled thousands of patients and compared protocol-based EGDT to usual care.[20–22] However, despite initial success, these trials challenged the necessity of strict protocol-based interventions.[20–22] The ProCESS trial investigated whether protocol-based resuscitation improved outcomes compared to standard care in patients with septic shock. The study found no significant difference in 60-day mortality between the protocolized group and the usual care group, raising questions about the universal applicability of EGDT.[20]

Similarly, the ProMISe trial assessed the effectiveness of EGDT in individuals experiencing septic shock.[21] Despite utilizing a structured approach to care, the trial concluded that there was no significant benefit in mortality reduction compared to standard resuscitation practices. These findings align with the ARISE trial, which also failed to demonstrate a survival benefit for patients receiving targeted therapy.[22] The most likely explanation for these results is the significant advancement in

Table 2. Sepsis care bundles

3-hour resuscitation bundle	6-hour septic shock bundle
1. Measure initial serum lactate levels. 2. Obtain blood cultures before administering antibiotics. 3. Administer broad-spectrum antibiotics. 4. Administer 30 mL/kg of crystalloids for hypotension or lactate ≥4 mmol/L.	1. Administer vasopressors to maintain mean arterial pressure (MAP) ≥65 mmHg in patients with hypotension unresponsive to initial fluid resuscitation. 2. If persistent hypotension despite fluid resuscitation (septic shock) or lactate ≥4 mmol/L, measure central venous pressure (CVP) and central venous oxygen saturation ($ScvO_2$).

MAP: Mean arterial pressure; $ScvO_2$: Venous oxygen saturation; CVP: Central venous pressure.

the standard of care over time, which has rendered some of the aggressive EGDT components less critical in current practice.

Contrary to Rivers et al.'s[19] original findings, these trials demonstrated that protocolized EGDT did not achieve a significant mortality reduction compared to contemporary usual care, raising important questions regarding its universal applicability.

The researchers analyzed these findings and suggested that the discrepancies may be attributable to differences in baseline care across time periods. Advances in critical care, such as early antibiotic administration, fluid resuscitation, and source control, have become standard practice, potentially reducing the relative benefit of EGDT protocols.[18]

CARE BUNDLES

The Surviving Sepsis Campaign (SSC) has been instrumental in standardizing sepsis care worldwide. The 2018 update, presented by Levy et al.,[23] emphasized the need for timely and goal-directed interventions within the first few hours of sepsis diagnosis. These interventions include monitoring serum lactate levels, obtaining blood cultures, administering broad-spectrum antibiotics, and providing intravenous crystalloids to ensure adequate tissue perfusion in hypotensive patients.[23] These interventions, collectively referred to as the 3-hour and 6-hour bundles, have been shown to improve patient outcomes by minimizing the time to definitive treatment in sepsis patients. The recommendations are illustrated in Table 2.[8]

INITIAL RESUSCITATION

Initial resuscitation is a critical component in the management of sepsis and septic shock, aimed at stabilizing patients and improving outcomes. The SSC has consistently emphasized early intervention as a key factor in reducing mortality. According to the 2012 and 2016 guidelines, the initial resuscitation period (the first 3 to 6 hours) is crucial for optimizing patient outcomes and reducing the risk of organ failure and death.[8,24]

FLUIDS

Fluid resuscitation is a cornerstone of the initial treatment for sepsis. The SSC Guidelines recommend administering 30 mL/kg of intravenous crystalloids within the first three hours for patients with hypotension or a lactate level ≥4 mmol/L. The objective is to restore adequate tissue perfusion and oxygen delivery, thereby preventing further organ dysfunction. Although studies emphasize the importance of fluid resuscitation, indicating that early and adequate fluid administration is associated with improved survival, guidelines also caution against excessive fluid use, which can lead to fluid overload and increased morbidity, particularly in patients with preexisting cardiac or renal conditions. Both crystalloid and colloid solutions play a central role in the management of sepsis and septic shock.[8]

Crystalloids

Crystalloids, such as Ringer's lactate and saline, are typically the first-line fluids recommended for resuscitation in sepsis due to their availability, lower cost, and favorable safety profile. Meta-analyses have demonstrated that the use of crystalloids in early targeted therapy results in similar outcomes compared to more expensive colloid solutions, particularly in terms of mortality reduction. Crystalloids effectively restore intravascular volume and are generally associated with fewer complications, such as renal impairment or coagulopathy.[25]

Colloids

Colloid solutions, including hydroxyethyl starch (HES), have been used in resuscitation due to their theoretical advantage of remaining in the intravascular space for a longer duration. However, recent evidence has raised concerns about their safety in sepsis. In a landmark trial, Perner et al.[26] compared HES 130/0.42 with Ringer's acetate in patients with severe sepsis. Their findings revealed that patients receiving HES had a higher risk of AKI and required more renal replacement therapy (RRT). This study highlighted significant concerns regarding the use of synthetic colloids in critically ill patients.

No significant difference was observed when pentastarch and albumin were compared in terms of their effects on coagulation; however, pentastarch was associated with a 45% reduction in factor VIII levels. Consequently, Rackow et al.[27] concluded that in patients with severe sepsis, albumin and pentastarch are equivalent for fluid resuscitation.

VASOPRESSORS

If hypotension persists despite adequate fluid resuscitation, vasopressors should be initiated to maintain a mean arterial pressure of 65 mmHg or higher. Guidelines recommend norepinephrine as the first-choice vasopressor. According to the SSC guidelines, maintaining an adequate MAP is essential for ensuring organ perfusion, particularly for vital organs such as the kidneys and brain.[8]

Guidelines also recommend advanced hemodynamic monitoring, including measurement of CVP and $ScvO_2$, for patients who remain hypotensive with septic shock to guide further interventions. Some studies suggest that a targeted approach, based on dynamic parameters such as fluid responsiveness, may help optimize outcomes in this population.[8]

ANTIMICROBIALS

An equally crucial aspect of initial resuscitation in septic patients is the rapid initiation of broad-spectrum antibiotic therapy. Source control of the infection is also vital for improving sepsis outcomes. The SSC guidelines emphasize the need to administer antibiotics within one hour of recognizing sepsis or septic shock. Early and appropriate antibiotic therapy is associated with reduced mortality, whereas delayed antibiotic administration has been shown to significantly worsen outcomes. Risk factors for resistant bacterial infections should be considered in the initial selection of antimicrobials (Table 3). Antimicrobial therapy should then be reviewed based on culture results.[8]

Moreover, the SSC guidelines emphasize that identifying and controlling the source of infection, whether through surgical intervention, drainage, or debridement, is paramount in reversing the septic process. Failure to achieve source control may result in persistent infection, perpetuating the cycle of sepsis and organ dysfunction.[8]

The guidelines do not recommend the use of procalcitonin in conjunction with clinical assessment to determine when to initiate antimicrobial therapy in adults suspected of sepsis or septic shock, compared to clinical assessment alone. However, they do recommend the combined use of procalcitonin and clinical assessment instead of relying solely on clinical evaluation for discontinuing antibiotic therapy.[8]

LACTATE CLEARANCE

Lactate levels serve as an important marker of tissue hypoperfusion and are used to guide resuscitation efforts. Elevated lactate levels (>4 mmol/L) are associated with a higher risk of mortality, and the SSC guidelines recommend serial lactate measurements to monitor the effectiveness of resuscitation.[8]

VENTILATION

The treatment of respiratory insufficiency in critically ill patients has evolved significantly. However, since the introduction of non-invasive ventilation (NIV), there has been no substantial new data reviewed regarding its benefits over mechanical ventilation (MV), leading to a lack of updated recommendations. Nonetheless, two recent systematic review studies investigating low tidal volume ventilation (LTVV), which involves reducing tidal volume from 10 to 6 mL/kg, found that LTVV improved outcomes in mechanically ventilated critically ill patients.[28]

Elevation of intrathoracic pressure resulting from NIV or MV can impact cardiac function by reducing venous return, which consequently decreases cardiac output. High-flow nasal cannula (HFNC) has been suggested for patients with acute hypoxic respiratory failure to mitigate these effects. HFNC delivers oxygen at a high flow rate, while simultaneously heating and humidifying the air, resulting in a lower upper positive airway pressure. It enhances oxygenation, reduces respiratory rate and inspiratory effort, and consequently improves survival rates in patients with acute hypoxic respiratory failure.[29]

Although HFNC is increasingly used for critically ill patients, there is a lack of consistent data regarding its effectiveness in sepsis and septic shock, primarily because its application was limited when the SCC guidelines were first issued. Nevertheless, the SSC guidelines recommend HFNC therapy over NIV for patients with sepsis and hypoxic respiratory failure.[8] The recommendations for the current management of sepsis are summarized in Table 4.

RENAL REPLACEMENT THERAPY

Currently, AKI related to sepsis warrants significant attention. AKI results from a compromised oxygen and nutrient supply to organs during septic episodes, negatively impacting patient prognosis.[7,15] Factors such as impaired renal microcirculation, abnormal inflammatory responses, and disruptions in cellular energy metabolism contribute to the onset of AKI. During sepsis, diminished oxygen supply to kidney tissues, coupled with increased oxygen demand, leads to cellular damage and AKI progression. The

Table 3. Risk factors for multi-drug resistant pathogens

Methicillin-Resistant *Staphylococcus aureus* (MRSA)	1. Previous infection or colonization with MRSA in the last 12 months. 2. Hemodialysis or peritoneal dialysis. 3. Presence of central venous catheters or intravascular devices. 4. Administration of multiple antibiotics in the last 30 days, particularly cephalosporins or fluoroquinolones. 5. Immunodepression. 6. Immunosuppressive therapy. 7. Rheumatoid arthritis. 8. Drug addiction. 9. Patients from long-term care facilities or those with hospitalization in the last 12 months. 10. Close contact with patients colonized by MRSA.
Extended-Spectrum Beta-Lactamase (ESBL)-Producing Bacteria	1. Previous infection or colonization with ESBL-producing bacteria in the last 12 months. 2. Prolonged hospitalization (>10 days), particularly in intensive care units (ICU), hospices, or long-term care facilities. 3. Presence of a permanent urinary catheter. 4. Administration of multiple antibiotics in the last 30 days, particularly cephalosporins or fluoroquinolones. 5. Patients with percutaneous endoscopic gastrostomy.
Pseudomonas aeruginosa	1. Previous infection or colonization with *Pseudomonas aeruginosa* in the last 12 months. 2. Administration of multiple antibiotics in the last 30 days, particularly cephalosporins or fluoroquinolones. 3. Pulmonary anatomic abnormalities with recurrent infections (e.g., bronchiectasis). 4. Elderly patients (>80 years). 5. Poor glycemic control in diabetic patients. 6. Presence of a permanent urinary catheter. 7. Prolonged steroid use (>6 weeks). 8. Neutropenic fever. 9. Cystic fibrosis.
Candida spp.	1. Immunodepression. 2. Presence of central venous catheters or intravascular devices. 3. Patients receiving total parenteral nutrition. 4. Prolonged hospitalization (>10 days,) particularly in an ICU. 5. Recent surgery, particularly abdominal surgery. 6. Prolonged broad-spectrum antibiotic use. 7. History of necrotizing pancreatitis. 8. Recent fungal infection or colonization.

MRSA: Methicillin-resistant *Staphylococcus aureus*; ESBL: Extended-spectrum beta-lactamases; MRS: Methicillin-resistant *Staphylococci*.

excessive release of inflammatory mediators, augmented oxidative stress, and mitochondrial dysfunction may further exacerbate AKI development.[15]

Given that both immunosuppression and AKI play critical roles in sepsis management, there is a pressing need for further research in these areas. A deeper understanding of the interplay between sepsis, immunosuppression, and AKI is essential for optimizing treatment strategies and improving patient outcomes.[7,15]

The SSC guidelines recommend against initiating RRT in the absence of a definitive indication. If RRT is required, either continuous or intermittent RRT is suggested.[8]

Table 4. Pillars of sepsis treatment and management discussed in this manuscript

Pillars of treatment	Contemporary management guidelines
Antimicrobials	- Obtain culture samples before administering antimicrobials. - Immediate treatment (ideally within one hour) is recommended for septic shock or high-probability sepsis. - For sepsis without shock, if the evaluation process is completed and sepsis is still suspected, treatment should start within three hours. - Procalcitonin should be used alongside clinical evaluation. - Short durations of antimicrobial therapy may be necessary.
Source control	- Source control involves interventions, such as abscess drainage, removal of infected implants, or surgical procedures to eliminate the infection source. - Source control should be initiated as soon as possible, ideally within 12 hours of recognizing the infection, to reduce the risk of worsening outcomes or increased mortality. - If surgical or procedural intervention is required, it should be coordinated with other treatments, including fluid management and antibiotic therapy, tailored to the patient's specific clinical status and risk factors.
Fluids	- Balanced crystalloids are the preferred fluid choice. - Albumin should be administered in patients requiring large volumes of crystalloids. - Hydroxyethyl starch (HES) is associated with increased mortality and higher risk of renal replacement therapy. - For sepsis-related hypoperfusion, at least 30 mL/kg of intravenous (IV) crystalloids should be administered within the first three hours.
Vasoactive agents	- Vasoactive agents, specifically vasopressors, are necessary if a patient's mean arterial pressure (MAP) remains below 65 mmHg despite fluid resuscitation. - The first-choice vasopressor is norepinephrine. - If the target MAP cannot be reached with norepinephrine, vasopressin should be added rather than continuously increasing the norepinephrine dose. - In patients with septic shock and cardiac dysfunction, if signs of hypoperfusion persist despite adequate fluid therapy and blood pressure, dobutamine should be added to norepinephrine, or adrenaline may be used alone.
Oxygenation and ventilation support	- High-flow nasal cannula (HFNC) oxygen therapy is preferred over non-invasive ventilation in adults with sepsis-related hypoxemic respiratory failure. - A low tidal volume strategy (6 mL/kg) should be used. - In cases of sepsis-related severe acute respiratory distress syndrome (ARDS), the upper limit of airway pressure should not exceed 30 cmH_2O. - In adults with moderate to severe ARDS due to sepsis, prone positioning should be considered for more than 12 hours per day. - HFNC may be used in septic patients with hypoxic respiratory failure.
Other treatments	1. Heparin - Low-molecular-weight heparin (LMWH) is preferred over unfractionated heparin (UFH) for venous thromboembolism (VTE). - In adults with sepsis or septic shock, the use of mechanical VTE prophylaxis alone is not appropriate; it should be combined with pharmacological prophylaxis.

Table 4 (cont). Pillars of sepsis treatment and management discussed in this manuscript

2. Insulin
- Insulin should be used to maintain a target glucose level of 144-180 mg/dL.
3. Proton Pump Inhibitors
- Proton pump inhibitor (PPI) therapy may be necessary to prevent stress ulcers.
4. Renal Replacement Therapy
- The use of renal replacement therapy is not recommended for adults with sepsis or septic shock and acute kidney injury unless there is a clear indication.
5. Steroids
- Hydrocortisone may be considered in patients with vasopressor-resistant hypotension and inadequate MAP.
6. Sodium Bicarbonate
- Sodium bicarbonate therapy is recommended for adults with septic shock, severe metabolic acidosis (pH≤7.2), and acute kidney injury (AKI, stages 2 or 3).
7. Acetaminophen
- Acetaminophen should be administered for symptomatic relief.
8. Vitamin C
- The use of intravenous (IV) vitamin C is not recommended in adults with sepsis or septic shock.
9. Nutrition
- In adult patients with sepsis or septic shock who can be fed enterally, early enteral nutrition (within 72 hours) is recommended.
10. Immunoglobulin
- Immunoglobulin is not recommended for patients with sepsis or septic shock.
11. Blood transfusion
- Restrictive red blood cell transfusion is recommended in adults with severe sepsis or septic shock. Transfusion should be restricted until hemoglobin (Hb) falls below 7.0 g/dL. Transfusion is not recommended when Hb is above 9.0 g/dL, unless ischemic heart disease, severe hypoxemia, or active bleeding is present.

HES: Hydroxyethyl starch; MAP: Mean arterial pressure; HFNC: High-flow nasal cannula; ARDS: Acute respiratory distress syndrome; LMWH: Low molecular weight heparin; VTE: Venous thromboembolism.

In 2021, the Infectious Diseases Society of America (IDSA) published a position paper opposing the National Severe Sepsis and Septic Shock Early Management Bundle (SEP-1), which shares similar recommendations with the SSC guidelines, such as immediate antibiotic administration, a 30 mL/kg fluid challenge, and lactate measurements. The IDSA stated that the evidence supporting the impact of early antibiotic treatment on mortality is strong for septic shock but weak for sepsis without shock. The IDSA recommends that the SEP-1 bundle focus exclusively on septic shock and emphasizes that algorithms should be limited to "strongly supported recommendations." Additionally, due to ambiguity in the definition of "time zero," the IDSA expressed concerns regarding the reliability of SEP-1 abstraction, citing its complex rules for identifying this critical time point.[30]

Similarly, it has been noted that sepsis quality measures carry comparable risks, as the symptoms of sepsis are non-specific and subjective, particularly in the early hours of presentation. It has been reported that approximately 40% of patients treated for sepsis initially have a low probability of bacterial infection. Therefore, enforcing rapid initiation of treatment may expose many patients to the adverse effects of antibiotics without providing significant benefits.[30]

Initiating the sepsis treatment process too early not only leads to unnecessary antibiotic administration but also delays the diagnostic process for important differential diagnoses. The IDSA argues that the perception that any delay in antibiotic treatment leads to worse outcomes in sepsis patients, regardless of disease severity, results in unnecessary antibiotic prescriptions and conveys a misleading message to healthcare providers.[30]

It has been emphasized that SIRS complicates the diagnostic process, and its removal has been recommended, as the presence of shock and infection is considered sufficient for diagnosis. Additionally, the definition of "persistent hypotension" should be revised based on stronger evidence, as the current 30 mL/kg fluid criterion lacks robust scientific support. The requirement for documenting suspected septic shock has also been deemed unnecessary, as clinical diagnosis is considered more effective than relying solely on suspicion.[30]

The measurement of lactate has been suggested for removal, as it is not specific to infection, and the evidence supporting its clinical benefits is limited. Furthermore, the recommendation to remeasure lactate if the initial level is greater than 2 mmol/L has also been proposed for removal, as it is considered non-specific.[30]

FUTURE RESEARCH

Sepsis has a complex pathophysiology, involving an inappropriate inflammatory response, coagulopathy, mitochondrial damage, neuroendocrine network disorders, and organ injury.[31] In the pathogenesis of sepsis, the coagulation system and inflammatory reaction may lead to an imbalance between coagulation and anticoagulation, resulting in an uncontrolled coagulation cascade. Sepsis-induced mitochondrial damage or dysfunction can cause cellular metabolic disorders, insufficient energy production, and oxidative stress, which may lead to the apoptosis of organ and immune cells, ultimately resulting in immune dysfunction.[31] As a result, recent clinical and experimental research has focused particularly on anti-inflammatory mechanisms for the treatment of sepsis. Some studies investigating the cholinergic anti-inflammatory pathway have reported positive effects on sepsis-induced cognitive deficits by reducing neuroinflammation[32] or minimizing anabolic failure in the liver.[33] Additionally, trials examining capsaicin have found beneficial effects of this novel anti-inflammatory agent in reducing sepsis-induced injury in the liver,[34] lungs,[35] heart,[36] and neuronal tissue.[37] Furthermore, mesenchymal stem cells have been shown to weaken the immune response to sepsis and reprogram the immune system to reduce host tissue damage, thereby improving early-phase survival in sepsis patients.[38]

Genistein, an isoflavone derived from soy, is recognized for its anti-inflammatory and antioxidant effects, primarily through the inhibition of the nuclear factor kappa B (NF-κB) pathway, a key regulator of the body's inflammatory response. This mechanism positions genistein as a promising agent in managing chronic inflammatory diseases, such as cardiovascular disorders and certain cancers, by reducing pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). However, its effects are not universally beneficial. Recent studies indicate that in acute sepsis cases, genistein supplementation may actually intensify inflammation rather than alleviate it. In septic patients, genistein has been associated with elevated markers of inflammation and increased mortality, suggesting that in acute conditions, its use may exacerbate the inflammatory process, ultimately worsening patient prognosis in critical care settings.[39]

Vitamin D plays a crucial role in modulating inflammation and controlling pathogens, with studies demonstrating its antimicrobial effects. Vitamin D deficiency is common in intensive care unit (ICU) patients, and a large-scale study found that low vitamin D levels serve as a predictor of sepsis and an increased risk of mortality. However, the exact relationship between vitamin D deficiency and ICU outcomes remains unclear, highlighting the need for routine monitoring and potential supplementation.[40] As demonstrated above, many unresolved questions remain regarding the pathogenesis and treatment of sepsis and septic shock. These areas should be considered for future laboratory and clinical investigations.

According to current data, future research should focus on anti-inflammatory pathways and differing immune responses due to sepsis subphenotypes.

CONCLUSION

In conclusion, early diagnosis, source control, appropriate antimicrobial therapy, and initial resuscitation are essential components of sepsis and septic shock management, significantly influencing patient outcomes. Rapid fluid resuscitation, primarily with crystalloids, is crucial for restoring adequate tissue perfusion and preventing organ dysfunction. While vasopressors play a key role in managing persistent hypotension, their use should be guided by careful hemodynamic monitoring. The timely initiation of broad-spectrum antibiotics is equally critical in improving survival rates and underscores the importance of addressing the source of infection.

Additionally, recent guidelines proposed by the IDSA30 have sparked debate within the medical community, particularly regarding recommendations for antibiotic use and treatment duration. The IDSA's objections emphasize the need for a balanced approach to antimicrobial therapy and fluid resuscitation, aiming to optimize patient outcomes. As our understanding of sepsis continues to evolve, ongoing research and discussions surrounding these guidelines are essential for improving treatment protocols and enhancing patient care. Ultimately, establishing guidelines based on high-quality evidence and adopting a multifaceted approach to resuscitation will improve the chances of survival for patients facing this complex and life-threatening condition.

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