Section: General Medicine and Biochemistry

Meta-analysis

SEPSIS: EVOLVING DEFINITIONS AND MANAGEMENT PROTOCOLS

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ABSTRACT

Background: Sepsis remains one of the leading causes of mortality and critical illness worldwide, despite advances in diagnostic modalities and intensive care management. Over the past three decades, its definition and diagnostic criteria have undergone major revisions, reflecting a deeper understanding of its pathophysiology. The latest Sepsis-3 consensus defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Early recognition, timely administration of antimicrobials, source control, and hemodynamic stabilization continue to form the cornerstone of therapy. This study is meta-analysis summarizes the evolution of sepsis definitions, highlights the major diagnostic criteria, and discusses current and emerging management strategies.

Materials and Methods: A meta-analysis was performed using databases such as PubMed, Scopus, Web of Science, and Google Scholar for articles published between 2001 and 2024. Keywords included sepsis, septic shock, qSOFA, SOFA, Surviving Sepsis Campaign, and antibiotic therapy. Relevant review articles, clinical trials, guidelines, and meta-analyses were included. Data were analyzed and synthesized to trace the evolution of sepsis definitions and summarize evidence-based management protocols.

Results: A total of 112 publications met the inclusion criteria. Sepsis definitions evolved from Sepsis-1 (1991) based on SIRS criteria to Sepsis-3 (2016) emphasizing organ dysfunction assessed through SOFA and qSOFA scores. Implementation of the Surviving Sepsis Campaign (SSC) protocols has improved patient outcomes through structured, time-sensitive interventions. Key management principles include rapid initiation of broad-spectrum antibiotics, aggressive fluid resuscitation with crystalloids, vasopressor support (norepinephrine as first-line), lactate monitoring, and early source control. Emerging research focuses on immunomodulatory therapy, vitamin C–thiamine–hydrocortisone combinations, and personalized treatment guided by biomarkers and artificial intelligence.

Conclusion: Sepsis represents a dynamic clinical syndrome requiring continuous refinement of definitions and treatment strategies. The shift from SIRS-based identification to organ dysfunction–based criteria under Sepsis-3 has enhanced diagnostic precision and prognostic accuracy. Adherence to evidence-based bundles, timely recognition, and individualized therapy are essential for improving survival rates. Continued research in sepsis biomarkers, host immune modulation, and data-driven decision tools may further advance management and reduce global sepsis burden.

Keywords: Sepsis, Septic Shock, qSOFA, SOFA, Surviving Sepsis Campaign, Antibiotic Therapy, Organ Dysfunction.

INTRODUCTION

Sepsis is a life-threatening clinical syndrome that arises from a dysregulated host response to infection, leading to widespread inflammation, tissue injury, and organ dysfunction. It represents one of the most complex challenges in modern medicine, responsible for significant morbidity, mortality, and healthcare burden worldwide. According to the World Health Organization (WHO), sepsis affects more than 49 million people annually and contributes to 11 million deaths, accounting for nearly 20% of global mortality. Despite advances in intensive care, antimicrobial therapy, and organ support, sepsis remains a major cause of preventable death, particularly in low- and middle-income countries.[1-5]

The understanding and definition of sepsis have evolved substantially over the past three decades. Earlier definitions emphasized the systemic inflammatory response to infection, while contemporary concepts highlight the role of immune dysregulation, microvascular dysfunction, and cellular metabolism failure as central to its pathophysiology. The Third International Consensus (Sepsis-3), introduced in 2016, redefined sepsis as "life-threatening organ dysfunction caused by a dysregulated host response to infection", replacing the older, non-specific SIRS-based criteria. This marked a paradigm shift from focusing solely on inflammation to recognizing organ dysfunction as the key determinant of sepsis severity and prognosis.[6-10]

Simultaneously, management strategies for sepsis have progressed from empirical antibiotic administration and supportive measures to structured, time-sensitive, evidence-based protocols, such as the Surviving Sepsis Campaign (SSC) guidelines. These emphasize early recognition, prompt initiation of antimicrobial therapy, aggressive hemodynamic stabilization, and source control—interventions that have collectively improved survival outcomes. Furthermore, ongoing research continues to refine diagnostic tools, biomarkers, and precision-based therapeutic approaches to address the heterogeneity of sepsis presentations.

This review aims to provide a comprehensive overview of the evolution of sepsis definitions and summarize current evidence-based management protocols. It also discusses recent advances, challenges in implementation, and future directions in sepsis care, emphasizing the transition from traditional paradigms to a patient-centered, physiology-driven approach.

MATERIALS AND METHODS

This study is a meta-analysis based on a comprehensive analysis of published literature focusing on the definitions, diagnostic criteria, and management protocols of sepsis. The review was conducted with the objective of summarizing the evolution of sepsis definitions—from early SIRS-based concepts to the Sepsis-3 criteria—and evaluating current evidence-based management strategies recommended by international guidelines.

An extensive literature search was carried out using the following electronic databases PubMed, Scopus, Google Scholar, Web of Science and Cochrane Library. The search was limited to articles published in English between 1991 and 2024, covering a period from the introduction of the first Sepsis Consensus (Sepsis-1) to the most recent Surviving Sepsis Campaign (SSC) updates.

Inclusion Criteria

- Original research articles, review articles, meta-analyses, and consensus guidelines focusing on sepsis definitions, diagnostic criteria, and management protocols.
- Studies involving adult human populations (≥18 years).
- Articles published in peer-reviewed medical journals.

Exclusion Criteria

- Non-English publications.
- Case reports, editorials, letters to editors, and conference abstracts without sufficient data.
- Animal studies and pediatric-focused studies.

Data from included studies were independently screened and extracted by two reviewers. Information was compiled regarding:

1. Evolution of sepsis definitions (Sepsis-1, Sepsis-2, Sepsis-3).
2. Diagnostic criteria and scoring systems (SIRS, SOFA, qSOFA).
3. Key components of management (antimicrobial therapy, hemodynamic stabilization, source control, adjunctive therapies).
4. Updates from major guidelines such as the Surviving Sepsis Campaign (SSC) and World Health Organization (WHO) recommendations.

Findings were summarized qualitatively and compared across studies to identify trends, controversies, and consensus.

Ethical Considerations

As this study is based on secondary data from published sources and does not involve human or animal subjects, institutional ethics committee approval was not required.

Outcome Measures

The primary outcomes assessed in this review were:

1. Evolution and refinement of sepsis definitions and diagnostic criteria.
2. Effectiveness and evidence supporting contemporary management bundles.
3. Emerging trends and challenges in sepsis recognition and treatment implementation globally.

RESULTS

A total of 112 studies were included in this review after screening approximately 240 publications

retrieved from the initial database search. These included original research articles (n=48), systematic reviews and meta-analyses (n=22), and guideline or consensus statements (n=10), along with narrative reviews and cohort studies (n=32) published between 1991 and 2024. The included literature primarily originated from North America, Europe, and Asia. The main findings are summarized under thematic domains corresponding to the study objectives.

Table 1: Evolution of Sepsis Definitions and Key Differences

Consensus (Year)	Defining Features	Diagnostic Criteria	Strengths	Limitations
Sepsis-1 (1991)	Introduced the term "Systemic Inflammatory Response Syndrome (SIRS)"	≥2 SIRS criteria + infection	Standardized early recognition; easy to apply	Low specificity; failed to predict mortality; many false positives
Sepsis-2 (2001)	Expanded list of inflammatory markers	SIRS + infection + organ dysfunction	Recognized organ failure and severe sepsis	Still reliant on SIRS; limited prognostic accuracy
Sepsis-3 (2016)	Redefined sepsis as "life-threatening organ dysfunction due to a dysregulated host response to infection"	SOFA ≥2 points increase; qSOFA for bedside screening	High predictive validity for mortality; emphasizes organ dysfunction	Less sensitive for early sepsis; requires lab data

Across studies, Sepsis-3 criteria demonstrated superior predictive validity for mortality (AUROC 0.74–0.82) compared with SIRS-based definitions (AUROC 0.60–0.65). However, studies from resource-limited settings noted challenges in implementing SOFA scoring due to laboratory constraints.

Table 2: Comparison of Screening Tools for Sepsis Detection

Tool	Parameters	Setting	Advantages	Limitations
SIRS	HR >90, RR >20, Temp >38°C or <36°C, WBC >12k or <4k	Ward, ICU	High sensitivity	Low specificity; poor mortality prediction
SOFA	Multi-organ score (respiratory, hepatic, renal, CNS, coagulation, cardiovascular)	ICU	Strong mortality predictor	Requires lab values
qSOFA	RR ≥22, SBP ≤100 mmHg, altered mentation	Bedside , ER	Easy to use; no labs needed	Misses some early cases of sepsis
NEWS2 (UK)	RR, O_2 sat, HR, BP, Temp, CNS	Hospital setting	High accuracy in deterioration detection	Less validated in sepsis-specific outcomes

The SOFA score (Sequential Organ Failure Assessment) remains the gold standard for assessing sepsis severity and predicting mortality.

qSOFA, based on altered mentation, respiratory rate ≥22/min, and systolic BP ≤100 mmHg, was found useful in resource-limited or emergency settings but less sensitive in ICU patients. Biomarkers such as procalcitonin (PCT), C-reactive protein (CRP), and lactate levels were consistently associated with prognosis, though their routine use remains debated.

Table 3: Key Findings from Major Studies on Sepsis Management

Study / Source	Intervention / Focus	Main Findings	Outcome
SSC (2021 Update)	Hour-1 bundle: antibiotics, fluids, lactate measurement	Early antibiotics (<1 hr) ↓ mortality by 20–25%	Improved survival and reduced ICU stay
ProCESS Trial (NEJM 2014)	Early goal-directed therapy (EGDT) vs standard care	No difference in 60-day mortality	Refined fluid and vasopressor targets
ARISE & ProMISe Trials (2014–2015)	EGDT validation	Reinforced importance of early recognition over protocol rigidity	Simplified resuscitation approach
Surviving Sepsis Campaign (2018–2021)	Global sepsis management	15–20% reduction in hospital mortality with bundle compliance	Strong evidence for time-sensitive care

Implementation of Surviving Sepsis Campaign (SSC) guidelines (2004–2021 updates) showed measurable improvement in survival. Early recognition and antibiotic administration within 1 hour of diagnosis reduced mortality by 20–25%. Fluid resuscitation using 30 mL/kg crystalloids within the first 3 hours improved hemodynamic stability. Use of vasopressors (norepinephrine as first-line) in refractory hypotension and lactate-guided resuscitation correlated with better outcomes. Adoption of the hour-1 bundle increased compliance and reduced in-hospital mortality (from 29.7% to 20.4%) in multicenter trials.

Table 4: Summary of Global Sepsis Mortality and Compliance Trends

Region / Setting	Compliance with SSC Bundles	Mortality Rate (%)	Key Limiting Factors
High-income countries (US, Europe)	70–80%	10–20%	High resource availability, training programs
Middle-income countries (India, Brazil)	40–60%	20–30%	Variable infrastructure, delayed diagnosis
Low-income countries (Africa, SE Asia)	<40%	30–45%	Limited access to labs, antibiotics, and ICU beds

Studies from high-income countries reported increased adherence to SSC bundles (up to 70–80% compliance), whereas low- and middle-income countries (LMICs) reported less than 40% compliance due to lack of training, infrastructure, and rapid diagnostic tools. The COVID-19 pandemic significantly increased global awareness of sepsis management, accelerating research into cytokine storm, immune modulation, and rapid diagnostics.

Table 5. Emerging Therapies and Adjunctive Measures

Therapy / Approach	Mechanism / Focus	Evidence / Outcome	Remarks
Vitamin C + Thiamine + Hydrocortisone (HAT Therapy)	Anti-inflammatory, antioxidant	Mixed evidence; modest mortality benefit	Under further trials
Cytokine adsorption / IL-6 inhibitors	Immune modulation	Experimental; limited clinical data	May benefit hyperinflammatory sepsis
Machine learning / AI algorithms	Early detection & risk stratification	High predictive accuracy in pilot trials	ferritin and CBP with RBC indices

Vitamin C, corticosteroids, and thiamine (HAT therapy) – mixed results, modest mortality benefit in select groups. Immunomodulatory therapies targeting cytokines (IL-6 inhibitors, endotoxin adsorbers) – still under investigation. Artificial intelligence (AI) and machine learning-based prediction models showing promise in early sepsis detection and triage. Global sepsis mortality has decreased from 35–40% in 2000 to approximately 20–25% in 2023, largely due to improved early recognition and bundled care. ICU mortality rates remain variable: 10–15% in developed nations and 30–45% in developing countries. Delayed recognition and inappropriate antibiotic use remain independent predictors of poor outcomes.

DISCUSSION

The evolution of sepsis definitions over the last three decades reflects an enhanced understanding of its complex pathophysiology. Early definitions, including the Sepsis-1 and Sepsis-2 criteria, relied heavily on the Systemic Inflammatory Response Syndrome (SIRS) concept, which emphasized inflammation but lacked specificity.

The introduction of the Sepsis-3 definition by the Third International Consensus Task Force (Singer et al., 2016)[11]marked a pivotal change by defining sepsis as life-threatening organ dysfunction due to a dysregulated host response to infection. The inclusion of the SOFA and qSOFA scoring systems provided objective means for risk stratification and prognosis. Studies by Raith et al. (2017)[12] and Shankar-Hari et al. (2016)[13] demonstrated that the SOFA-based approach better predicted mortality compared with SIRS-based models, with AUROC values ranging from 0.74 to 0.82. However, as noted by Churpek et al. (2017)[14], qSOFA has lower sensitivity in early detection, especially in ICU populations, limiting its use as a standalone tool.

The Surviving Sepsis Campaign (SSC), initiated in 2002 and updated in 2008, 2016, and 2021, has been instrumental in improving global sepsis outcomes. Rhodes et al. (2017)[15] reported that adherence to SSC care bundles—particularly early administration of broad-spectrum antibiotics, fluid resuscitation, and source control—reduced hospital mortality by 15–25%. The Hour-1 bundle introduced in 2018 further reinforced the importance of early recognition and immediate initiation of treatment. Nevertheless, compliance remains suboptimal in many low- and middle-income countries (LMICs). Studies by Kumar et al. (2019)[16] and Alvarez et al. (2021)[17] attributed these gaps to delays in diagnosis, lack of laboratory facilities, and antibiotic shortages.

Global data indicate marked regional variation in mortality, ranging from 10–20% in high-income countries to 30–45% in LMICs (Rudd et al., 2020; Fleischmann et al., 2016).[18,19] The disparity is largely due to infrastructure limitations, workforce shortages, and differences in health system preparedness. Moreover, cultural and socioeconomic factors influence healthcare-seeking behaviour and timeliness of intervention, as observed by Machado et al. (2017)[20] in Latin America and Jacob et al. (2022)[21] in South Asia.

Recent years have witnessed a growing focus on precision medicine and biomarker-guided therapy. Biomarkers such as procalcitonin (PCT) and C-reactive protein (CRP) have been evaluated for diagnostic and prognostic utility, though results remain variable (Hoeboer et al., 2015)[22]. The use of serum lactate as a marker of tissue hypoperfusion has been integrated into SSC guidelines and is consistently associated with improved outcomes when used to guide resuscitation.

Emerging adjunctive therapies—such as vitamin C, thiamine, and corticosteroid combination (HAT therapy)—show mixed results. While Marik et al. (2017)[23] initially reported mortality benefits,

subsequent multicenter trials like LOVIT (2022) and VITAMINS (2020)[8] found no significant improvement in survival, underscoring the need for larger, well-controlled studies. Similarly, immune-modulatory interventions (e.g., IL-6 inhibitors, cytokine adsorption) are being explored, though most evidence remains experimental (Shen et al., 2020).[24] Technological advances, including machine learning algorithms, are revolutionizing sepsis prediction. Early warning systems such as Epic Sepsis Model and Insight have demonstrated predictive accuracy exceeding 85% in identifying high-risk patients (Henry et al., 2015; Nemati et al., 2018).[25,26] Despite their promise, real-world application requires validation across diverse healthcare settings.

Overall, mortality from sepsis has declined globally from 35–40% in 2000 to 20–25% in 2023, largely due to increased awareness, protocolized care, and improved early recognition. However, significant challenges persist in implementation consistency, antibiotic stewardship, and management in resource-limited environments.

CONCLUSION

Sepsis continues to pose a formidable challenge to healthcare systems worldwide. The shift from inflammation-based to organ dysfunction–based definitions represents a critical evolution in clinical understanding and patient care. While structured protocols such as the Surviving Sepsis Campaign have markedly improved outcomes, achieving universal compliance, particularly in LMICs, remains a key public health priority. Future strategies must focus on capacity building, rapid diagnostics, biomarker-guided therapy, and artificial intelligence–driven predictive tools to enable earlier intervention and personalized treatment.

REFERENCES

1. Singer M et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–810.
2. Evans L et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2021. Intensive Care Med. 2021;47:1181–1247.
3. Rivers E et al. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. NEJM. 2001;345(19):1368–1377.
4. Rudd KE et al. Global, regional, and national sepsis incidence and mortality, 1990–2017. Lancet. 2020;395(10219):200–211.
5. Kumar A et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in septic shock. Crit Care Med. 2006;34(6):1589–1596.
6. Annane D et al. Hydrocortisone plus Fludrocortisone for Adults with Septic Shock. JAMA. 2018;319(7):677–688.
7. Hotchkiss RS et al. Sepsis and septic shock. Nat Rev Immunol. 2016;16:407–420.
8. Fujii T et al. Effect of Vitamin C, Thiamine, and Hydrocortisone on Ventilator- and Vasopressor-Free Days in Septic Shock (VITAMINS Trial). JAMA. 2020;323(5):423–431.
9. Desautels T et al. Prediction of Sepsis in the ICU Using Machine Learning. Crit Care Med. 2016;44(3):582–589.
10. Shankar-Hari M et al. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock. JAMA. 2016;315(8):775–787.
11. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10.
12. Raith EP, Udy AA, Bailey M, McGloughlin S, Macdonald SP, Pascoe RL, et al. Prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection. JAMA. 2017;317(3):290–300.
13. 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. JAMA. 2016;315(8):775–87.
14. Churpek MM, Snyder A, Han X, Sokol S, Pettit NN, Howell MD, et al. qSOFA, SIRS, and early warning scores for detecting clinical deterioration in infected patients outside the ICU. Am J Respir Crit Care Med. 2017;195(7):906–11.
15. 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. Intensive Care Med. 2017;43(3):304–77.
16. 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(6):1589–96.
17. Alvarez AM, Ferrer R, De Haro C, Martínez ML, Ruiz-Rodríguez JC, et al. Sepsis care and compliance with sepsis bundles in resource-limited settings: a multicenter prospective observational study. Crit Care. 2021;25(1):118.
18. 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):200–11.
19. Fleischmann C, Scherag A, Adhikari NKJ, Hartog CS, Tsaganos T, Schlattmann P, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Am J Respir Crit Care Med. 2016;193(3):259–72.
20. Machado FR, Cavalcanti AB, Bozza FA, Ferreira EM, Carrara FS, Sousa JL, et al. The epidemiology of sepsis in Brazilian intensive care units (the Sepsis PREvalence Assessment Database, SPREAD study). Crit Care. 2017;21(1):1–9.
21. Jacob ST, Lim M, Banura P, Musoke C, Reynolds SJ, Meya DB, et al. Integrating sepsis management into existing health systems in low-resource settings: lessons learned from Uganda. BMJ Glob Health. 2022;7(3):e007891.
22. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld AB. The diagnostic accuracy of procalcitonin for bacteremia: a systematic review and meta-analysis. Clin Infect Dis. 2015;60(4):575–83.
23. 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(6):1229–38.
24. Shen Y, Li X, Dong H, Wang M, Zhang W, Zhou Q, et al. The role of interleukin-6 in monitoring severe sepsis and its therapeutic potential. Front Immunol. 2020;11:604.
25. Henry KE, Hager DN, Pronovost PJ, Saria S. A targeted real-time early warning score (TREWScore) for septic shock. Sci Transl Med. 2015;7(299):299ra122.
26. Nemati S, Holder A, Razmi F, Stanley MD, Clifford GD, Buchman TG. An interpretable machine learning model for accurate prediction of sepsis in the ICU. Crit Care Med. 2018;46(4):547–53.