Sepsis: Key Insights, Future Directions, and Immediate Goals - A Review and Expert Opinion

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Take home message: The characterisation of sepsis is evolving, and more precise guidelines integrating clinical, biochemical, and microbiological data are needed. Embracing personalised medicine and emerging technologies and ensuring accessibility and standardisation are crucial for improving sepsis care and outcomes.

Introduction

Characterising diseases and syndromes is crucial for guiding diagnosis, treatment and research [1]. Sepsis continues to be a significant cause of illness and death worldwide, underscoring the need for ongoing quality and safety improvement initiatives [2]. Establishing a robust framework for sepsis surveillance, performance evaluation, and management enhancement initiatives is essential. This expert opinion discusses current challenges in sepsis characterisation and explores potential solutions that may become available in the short-to-medium term. While this paper incorporates elements of a narrative review by summarising and discussing relevant literature, it is primarily structured as an opinion piece, reflecting the authors' perspectives and proposed ideas. To enhance clarity and credibility, a thorough literature search was conducted.

Current challenges

Defining sepsis has long been debated, with three iterations published since 1991. It is currently designated as a life-threatening condition triggered by a dysregulated host response to infection [3]. As per current Sepsis-3 definitions, if there is no evidence of organ dysfunction, the condition is not classified as sepsis but rather as an uncomplicated infection. Organ dysfunction distinguishes sepsis from less severe infections and indicates a much higher risk of poor outcomes. Indeed, patients cannot die without organ dysfunction. The accompanying clinical criteria require a change of ≥2 points in the Sequential Organ Failure Assessment (SOFA) score to operationalise the definition by providing a quantifiable measure of organ dysfunction [3]. Although broadly generalisable and in the process of being updated from its original 1996 iteration, the score cannot capture early-stage infection before any effect is seen on organ function. Early detection of organ dysfunction enables prompt intervention [4].

Terminology should also be consistent for shock. The Sepsis-3 group defined septic shock in 2016 as "*a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean*

arterial pressure ≥ 65 mmHg and serum lactate level >2 mmol/l without hypovolaemia" [3]. These clinical criteria were based on a consensus process using a comprehensive systematic review, surveys and cohort studies to identify the best cut-offs for predicting mortality [5]. The systematic review performed for Sepsis-3, supported by a more recent systematic review of the literature [6], identified multiple criteria being applied to identify 'shock' with mortality varying from below 20% to over 80%. The extensive data analysis underpinning the Sepsis-3 criteria for septic shock indicated hospital mortality of 42.3% compared to 25-30% for sepsis without shock [5]; this ballpark figure has been replicated in multiple studies worldwide. Of note, hypotension on its own had a mortality rate of 30%, high serum lactate on its own had a mortality rate of 25%, and organ dysfunction with a normal serum lactate and normal blood pressure had a mortality rate around 25%. The Sepsis-3 criteria did not characterise "refractory" septic shock. Antonucci *et al.* found that the most commonly applied criterion was the persistence of a hyperdynamic shock state despite adequate fluid resuscitation and high doses of norepinephrine (≥ 1 μg/kg/min) [6]. This necessarily excludes patients receiving non-catecholamine agents such as vasopressin, phenylephrine and angiotensin II. While characterising refractory septic shock will make minimal differences to bedside management, a consensus definition of refractory septic shock would be helpful for epidemiological purposes as mortality in such patients will be considerably higher than those patients fulfilling minimum entry criteria for septic shock.

Another challenge — perhaps the most pressing — lies in actually determining whether infection is the driving trigger. Multiple non-infectious inflammatory conditions, e.g. severe trauma, pancreatitis, ischaemia-reperfusion injury, vasculitis, and adverse reactions to drugs or blood products, can present with symptoms, signs and laboratory findings similar to those of sepsis – more challenging, they can even be associated with "a real septic insult. As a result, there is a risk of over-diagnosing sepsis in 15-40% of cases due to these 'sepsis mimics' [7-9]. Therefore, the clinical criteria for diagnosing sepsis should be applied carefully, in conjunction with clinical criteria, ideally using additional diagnostic tools to identify the presence of infection as accurately as possible. This approach helps ensure optimal patient management, including appropriate use of antibiotics and other co-adjuvant treatments (such as steroids, immunoglobulins, etc.) if clinical trials and guidelines recommend them [10].

The challenge of achieving global consensus and standardisation in sepsis diagnosis and management remains significant due to disparities in healthcare systems and resources and ongoing uncertainties surrounding optimal management. A cross-sectional comparison of sepsis care found considerable differences between high-income countries (HICs~~)~~ and low-middle-income countries (LMICs~~)~~ [11]. HICs offer a more sophisticated approach with better equipped staff~~-~~and more availability to use innovative technologies for diagnosis, monitoring and treatment. On the other hand, sepsis management in LMICs often faces systemic issues such as scarce resources, ~~training issues~~ and weak infrastructure [12]. Given the differences in healthcare infrastructure, patient populations, and disease epidemiology, clinical features and reference standards produced in HICs may not be relevant or implementable in LMICs [3]. Unsurprisingly, all these problems impact upon patient outcomes. Consequently, the recognition and management of sepsis in LMICs may be less efficient than in HICs, leading to a cycle of poor recognition, inadequate management, and unfavourable outcomes. This highlights the need for context-specific approaches to sepsis care. However, knowledge and awareness deficits are not exclusive to LMICs. HICs also face challenges, with delayed or incorrect diagnoses among healthcare professionals and even more so among the public, often leading to delayed presentation and treatment. This issue emphasises the global need for improved sepsis education and early recognition strategies [13].

Early Warning Scores

We rely heavily on regular observation, clinical skills and well-organised alert structures that can identify clinical deterioration as early as possible. Early Warning Scores (EWS) play a pivotal role in healthcare settings by empowering healthcare providers, especially those less experienced, to promptly detect physiological distress from whatever cause and to summon assistance from appropriately skilled clinicians. While a sepsis-specific EWS would be ideal, in the absence of a rapid and reliable (both sensitive and specific) diagnostic biomarker, we must accept that there remains considerable overlap between sepsis and any other condition causing acute physiological derangement. All can impact upon heart rate, blood pressure, respiratory rate, body temperature, level of consciousness and/or oxygen saturation. Although no EWS is explicitly designed for sepsis, such scores can nonetheless effectively identify individuals at risk of developing organ dysfunction. It is important to stress here that

the quick SOFA (qSOFA) score, which is based on abnormalities in systolic blood pressure, mental status and respiratory rate, was never intended as a specific screening tool for sepsis but instead designed to offer a rapid (~3 minutes) bedside assessment tool to identify those patients with suspected infection who are at increased risk of adverse outcomes [3]. Metanalyses comparing qSOFA against systemic inflammatory response syndrome (SIRS) [14] or other tools as a sepsis diagnostic are therefore misguided, as this was never the purpose of qSOFA, which does not utilise laboratory measurements such as white blood count and lactate. The predictive ability of qSOFA was superior to SIRS in the Emergency Department but equivalent to SIRS and inferior to SOFA on ICU admission [15-17]. qSOFA uses three of the seven physiological variables incorporated in the National Early Warning Score (NEWS)-2 [15-17], so the latter bedside score is more sensitive in identifying the need for intensive care and mortality risk, albeit taking slightly longer to perform.

Point-of-care and rapid laboratory diagnostics

Biomarkers are repetitively presented as the ultimate weapon to classify and predict outcomes in patients with suspected sepsis [18]. Recent technological advances have enabled rapid pathogen diagnostic tests based on the detection of genetic material. These tests have high sensitivity to detect pathogens in samples that could serve for fast confirmation of infection and improved decision-making in selecting appropriate antimicrobials, including avoidance of unnecessary treatment, for example, antibacterials for a viral infection. A negative test could act as a rule-out test, which could prompt a re-evaluation of a sepsis diagnosis. On the other hand, a negative test, especially in blood samples, does not categorically rule out infection, while misinterpretation due to high sensitivity may lead to an over-diagnosis of sepsis and over-use of antibiotics. Pre-analytics are also critical here, as a contaminated sample or an irrelevant collection site can lead to inaccurate results and wrong decisions. Ongoing studies are assessing the performance of these tests and their impact on outcomes, but the current level of evidence supporting their use remains moderate. Finally, their cost precludes use in many countries. In the future, as these tests are often accessible and could be available 24/7 as a point-of-care tool, they could represent a solution to improve diagnosis in an era where microbiologists may not be available. Such a strategy has been

previously implemented to detect malaria [19]. However, guidelines must define how to use rapid diagnostic tests at the bedside to ensure quality.

Predictive biomarkers are less useful as clinicians rarely rely on a single test to stop treatment. A more applicable use of a biomarker would be 'theranostic', i.e., monitoring the patient and their response to treatment. The immune response of patients with sepsis includes both hyperinflammatory and exhausted immune reactions [20]. Differentiating patients based on their immune response will result in individualised treatments. For example, increased serum ferritin has been associated with a hyperinflammatory macrophage activation-like syndrome and indicates patients may respond positively to the blockade of the pro-inflammatory cytokine interleukin (IL)-1. On the other hand, low monocyte HLA-DR expression reflects immunoparalysis, which may respond to immune system stimulation, e.g., interferon-gamma or IL-7. Such a dual strategy has been assessed in a recently completed trial that has yet to be reported [21]. Even the choice of vasopressor may be guided by biomarkers. Angiotensin-2 could be used adjunctively with norepinephrine [22]. However, not all patients respond equally to this drug, which may be more beneficial for those patients with a high serum renin concentration [23].

Technology-based criteria

More nuanced measures than are available in current EWS may facilitate more precise identification of sepsis. Artificial intelligence (AI) systems will play an ever-increasing integral role in healthcare in areas ranging from disease identification and management, drug development, prediction of antibiotic resistance and improved epidemiological monitoring [24]. AI offers a solution because of its sophisticated ability to recognise patterns of derangement in physiology and laboratory data that are not yet visible to the human brain. Cloud-based computerised clinical decision support systems can leverage advanced algorithms to analyse real-time patient data and generate actionable insights [25]. This could provide an earlier alert than current paper-based EWS and potentially discriminate sepsis from other acute conditions [26]. By integrating AI systems into sepsis identification protocols, healthcare providers may achieve higher precision and timeliness, addressing the limitations of existing EWS and enhancing patient care. However, sepsis presents a considerable

challenge due to its variable presentation and the overlap with many other pathologies. Multiple publications on AI-based sepsis alert systems have already been generated, though they have been primarily based on single-centre electronic healthcare record systems analysed retrospectively. External validation and prospective multicentre studies are needed to confirm accuracy and generalisability and avoid problems such as alert fatigue [27].

Clinical decision support systems (CDSS) are being developed to enhance patient management by continuously monitoring clinical data, allowing for the detection of patterns that may indicate impending sepsis. By integrating and evaluating this information, these systems could improve diagnostic accuracy, facilitate timely interventions, and improve adherence to evidence-based guidelines. However, for CDSS to be effective, they must seamlessly integrate into clinical workflows and be tailored to the specific needs of healthcare providers and institutions to ensure usability and impact on patient outcomes. Crucially, there must also be a personalised approach as guidelines suit populations rather than individuals. Clinical expertise should determine whether guidelines apply to a particular situation or patient and whether and how they should be adapted. AI systems must integrate these important subtleties as studies repeatedly confirm that one size does not fit all. Furthermore, AI will have to meet the considerable challenge of dealing with diagnostic uncertainty, for example when pathogen cultures and molecular diagnostics are negative [28], or when infection is potentially complicating pancreatitis, burn injury or non-infectious ARDS.

Future directions

Despite scientific and technological advances, sepsis remains a complex challenge in clinical practice. Table 1 describes possible future directions in sepsis management and research. There are still challenges in capturing the diverse nature of sepsis, particularly at an early stage and in cases with non-typical presentations. Precision can be further enhanced by integrating clinical, biochemical and microbiological data, augmented by novel, rapid molecular techniques (*e.g.* 'omics), wireless monitoring, and percutaneous biosensors (Figure 1). An important role exists for AI to sift through these data, identify deterioration patterns at an early stage, and recommend appropriate and effective interventions. However, hospital electronic health record systems and cloud computing will have to keep pace, meaning costs

are likely to be substantially higher than at present. Similarly, rapid diagnostic tools will deliver relevant time-critical information to healthcare providers, facilitating patient management. Yet, solid economic and health outcome arguments will be needed to justify the additional expenditure.

The Surviving Sepsis Campaign Research Priorities Committee recently identified areas for future investigation [29], of which two stand out prominently. First, the optimal approach for screening and identifying patients with sepsis must be ascertained, including exploring the potential of predictive modelling to facilitate timely recognition. Second, the root causes of organ injury and dysfunction should be better understood, emphasising the importance of clearly characterising these phenomena and devising dependable detection techniques.

Speed, reliability and affordability of novel diagnostics are essential prerequisites, especially as healthcare systems worldwide are increasingly struggling with cost pressures and patient expectations. We should also recognise the need to support resource-constrained settings with greater demands. Simplicity is also relevant in environments lacking laboratory facilities and expertise. Technology, including telemedicine and AI, may also help to mitigate shortages in experienced healthcare professionals by providing bedside decision support to junior staff.

Improved diagnostics and greater availability of useful technology allied with ongoing training of healthcare providers will minimise interpretation variability and strengthen patient management consistency across different healthcare settings. Concerted and coordinated efforts are needed from multiple stakeholders - healthcare providers, policymakers, researchers, industry, charities and international organisations - to address these challenges and improve sepsis care worldwide. The battle against malaria is an excellent example of this already happening [30]. By effectively collaborating and leveraging available resources, disparities in sepsis management can be reduced, ultimately saving lives. Tailored guidelines and protocols designed to address specific challenges in resource-constrained settings have been proposed, but these require external validation [31].

Individualised care should remain at the core of management [32]. To effectively address sepsis heterogeneity, the focus should be broadened beyond simple subtyping to include

identifying underlying biological signatures indicating dominant mechanisms. However, at present, multiple clinical, transcriptomic, proteomic and metabolic (sub)phenotypes have been proposed with little overlap between them [33]. Much research is needed before such signatures can be incorporated into routine practice. Similarly, considerable efforts are required to reframe dysregulated immune responses as altered homeostasis with disruptions in resistance, tolerance, resilience, and resolution; this new paradigm may uncover new treatment targets and improve future immunomodulation strategies [33].

Research is also imperative to validate new sepsis criteria, novel technologies and management strategies in real-world scenarios. It must determine what patient and health-economic benefits are brought through these innovations, be it a point-of-care diagnostic or machine-learning decision support software. Such research should also include low-resource settings where cost benefit is even more critical. While validation should ideally be confirmed through high-quality multi-centre, prospective trials, this poses logistical challenges and demands substantial resources. Time and cost efficiency can be achieved by organising well-conducted platform trials. A faster and cheaper approach involves leveraging multiple registries and databases, abetted by machine learning tools, to provide valuable insights into the performance of new criteria and technologies across diverse patient populations and healthcare settings. Machine learning models can predict both short- and long-term mortality and morbidity, even from the time of admission [34]. The impact of a new technology can be assessed in real-life practice by before-after observational studies.

Conclusion

The journey to characterise and manage sepsis has been marked by ongoing debate and evolution. While current clinical frameworks offer valuable guidance, significant work remains to enhance precision in sepsis care. Future guidelines should integrate clinical, biochemical, and microbiological parameters more effectively, and there is a need for specific sepsis biomarkers and improvements in accessing microbiological data, especially in resource-constrained settings. Embracing a personalised medicine approach and leveraging emerging technologies such as novel diagnostics and AI could greatly enhance sepsis care. Ensuring accessibility and fostering standardisation and collaboration are essential to prevent

exacerbating healthcare disparities and to achieve consistency and equity in sepsis management.

Sepsis management in HICs benefits from accessible resources and established guidelines, leading to more effective treatment. In contrast, LMICs face severe challenges due to limited resources. Addressing these issues requires mobilising resources to develop robust monitoring systems, enhance training curricula, and adapt guidelines to fit the LMIC context. By addressing these constraints, we can ensure that sepsis management is optimised and practical for every patient, regardless of location.

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Table 1. Critical aspects of future directions in sepsis management and research.

Key Aspect	Description
Sepsis Complexity	Despite technological advances, sepsis remains difficult to diagnose, especially in non-typical cases, highlighting the need for precision and early intervention.
Integration of Data	Combining clinical, biochemical, and microbiological data with rapid molecular techniques (e.g., 'omics) and wireless monitoring can improve sepsis detection.
Role of AI in Sepsis	AI can analyze complex data, identify early deterioration patterns, and suggest interventions. Requires advanced hospital IT infrastructure and cloud computing.
Economic Considerations	High costs associated with new technologies, such as AI and rapid diagnostics, require a strong economic rationale for healthcare investments.
Future Research Priorities	Key areas include better screening methods for sepsis, understanding organ injury mechanisms, and developing predictive modeling for timely recognition.
Individualized Care	Personalizing sepsis care by identifying molecular mechanisms and reframing immune responses as disruptions in homeostasis to find new treatment targets.
Challenges in Global Sepsis Care	Current guidelines need better integration of clinical, biochemical, and microbiological data, especially in resource-constrained settings. Personalized care and new technologies could enhance sepsis management.
Technology and Accessibility	Telemedicine and AI can support resource-limited settings by providing bedside decision support, particularly for less experienced healthcare professionals.
Improved Diagnostics	Speed, affordability, and reliability are critical for diagnostics, especially under economic pressures and in resource-limited environments.
Collaboration for Sepsis Care	Coordinated efforts among healthcare providers, policymakers, and researchers are necessary to address sepsis management disparities globally.
Research Needs	Research is needed to validate new sepsis criteria and technologies, with a focus on health-economic benefits and practical utility in both well-resourced and low-resource settings.
Leveraging Technology	Machine learning can predict outcomes (e.g., mortality) from admission and facilitate faster, cost-effective trials using existing registries and databases.