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Review article

Sepsis in 2026: from *bundles* to biology. A critical review

Sepsis en 2026: del *bundle* a la biología. Revisión crítica

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Abstract

Sepsis remains associated with a substantial burden of morbidity and mortality despite more than two decades of Surviving Sepsis Campaign (SSC) recommendations. The 2026 update reinforces early recognition, resuscitation, timely antimicrobial therapy, source control, and reassessment, yet the benefit of increasingly intensive implementation of standardized measures may be approaching a ceiling. A central limitation is treating sepsis as a homogeneous entity despite the wide variation in etiologies, host susceptibility, immune responses, and clinical trajectories. Artificial intelligence, host-response biomarkers, rapid microbiological diagnosis, and pharmacokinetic/pharmacodynamic optimization provide new opportunities to shorten the time to effective intervention. In parallel, transcriptomic, genomic, and routine clinical data can identify subphenotypes and endotypes associated with different prognoses and potentially different treatment responses. Secondary analyses of clinical trials illustrate how an intervention that is neutral overall may be beneficial in biologically defined subgroups. The next step should combine SSC bundles with biological stratification, adaptive trial designs, and point-of-care tools capable of matching treatment to patient profile in real time. This review proposes a transition from standardized sepsis management toward precision medicine: the right treatment for the right patient at the right time.

Keywords: Sepsis. Precision medicine. Subphenotypes. Surviving sepsis campaign.

Resumen

La sepsis continúa asociándose a una elevada carga de morbimortalidad pese a más de dos décadas de recomendaciones de la Surviving Sepsis Campaign (SSC). La actualización de 2026 consolida la detección precoz, la resucitación, el tratamiento antimicrobiano oportuno, el control del foco y la reevaluación, pero el beneficio de una aplicación cada vez más intensa de medidas estandarizadas puede estar acercándose a un techo. Una limitación central es considerar la sepsis como una entidad homogénea cuando engloba etiologías, susceptibilidades, respuestas inmunológicas y trayectorias clínicas muy diferentes. La inteligencia artificial, los biomarcadores de respuesta del huésped, el diagnóstico microbiológico rápido y la optimización farmacocinética/farmacodinámica ofrecen nuevas oportunidades para acortar el tiempo hasta una intervención efectiva. Paralelamente, la transcriptómica, la genómica y las variables clínicas rutinarias permiten identificar subfenotipos y endotipos con diferente pronóstico y potencial respuesta terapéutica. Los análisis secundarios de ensayos clínicos ilustran que una intervención globalmente neutra puede resultar beneficiosa en subgrupos biológicamente definidos. El siguiente paso debería combinar los bundles de la SSC con estratificación biológica, diseños adaptativos y herramientas point-of-care capaces de asignar tratamientos al perfil adecuado en tiempo real. Esta revisión propone una transición desde la estandarización del manejo hacia una medicina de precisión en sepsis: el tratamiento correcto para el paciente correcto y en el momento correcto.

Palabras clave: Sepsis. Medicina de precisión. Subfenotipos. Surviving sepsis campaign.

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Introduction

Sepsis has historically been defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. It is the most severe clinical presentation of infectious diseases, and, although some populations are known to be more vulnerable, we still do not fully understand why it develops with such severity in particular patients. Despite improvements in both early detection and supportive care recommended by international guidelines [1], incidence and mortality remain high [2]. Nearly a quarter of a century has passed since the Barcelona Declaration to combat sepsis, which marked the beginning of these guidelines with the participation of several scientific societies. Since then, the first Surviving Sepsis Campaign (SSC) recommendations [3] have been updated as new evidence has emerged (**Figure 1**), culminating in the 2026 version [1].

The SSC played a pivotal role in raising awareness of this serious condition. It approached sepsis from a holistic perspective, extending beyond clinicians to involve political institutions and society, and issued management recommendations spanning prevention, early diagnosis, and care at different stages of the disease. These recommendations gave rise to the bundle concept: the superiority of applying several coordinated interventions simultaneously, with a multiplicative effect when all are delivered at the appropriate time. The initial SSC declaration aimed to reduce relative mortality from sepsis by 25% over the following five years [4]. Decades later, after an initial period characterized by the implementation of these measures and a modest reduction in mortality [5], it is reasonable to ask why incidence and mortality have increased in some age groups [2] or have remained broadly unchanged in recent years. Have SSC recommendations reached a ceiling effect? (**Figure 2**).

From SSC recommendations to personalized medicine in sepsis

Unlike other time-dependent diseases in which early intervention is clearly linked to prognosis, such as acute myocardial infarction or stroke, sepsis is not easily detected in its earliest stages. Its clinical presentation is heterogeneous and varies among patients according to factors including immune status, comorbidity, and the causative pathogen. Reported incidence is variable and therefore difficult to compare; registries differ across countries; socioeconomic conditions have a major influence; and even the definition of the disease has been the subject of disagreement in recent years [6].

The question now is whether we have reached the maximum benefit that SSC recommendations can provide and whether a further step is possible to improve the poor prognosis of sepsis. The plateau in mortality should not be interpreted as failure of the bundles recommended by scientific societies; these measures have become widely implemented and have undoubtedly contributed to improved prognosis and evidence-based standardization of care. Rather, it may be inaccurate to consider sepsis a homogeneous

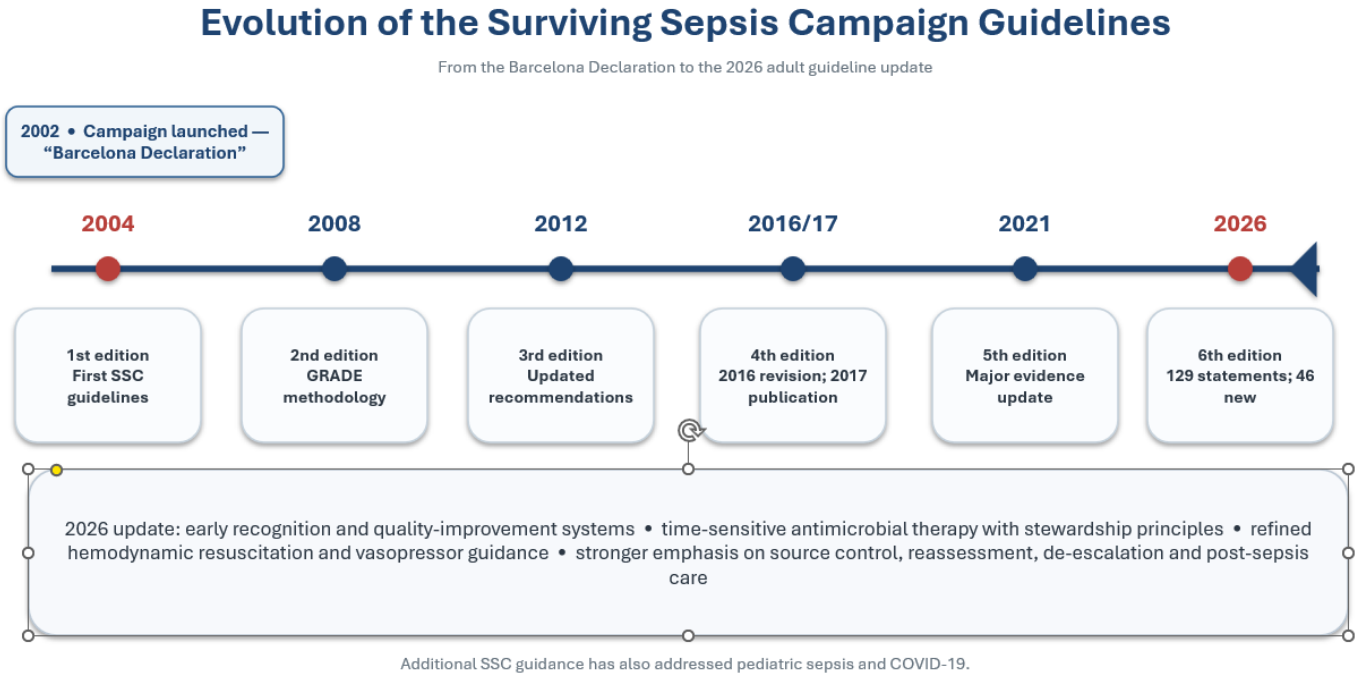

Figure 1. Timeline of major adult Surviving Sepsis Campaign (SSC) guideline editions. The latest adult guideline was published in 2026 and updates the 2021 recommendations. Adapted from Prescott et al. [1]

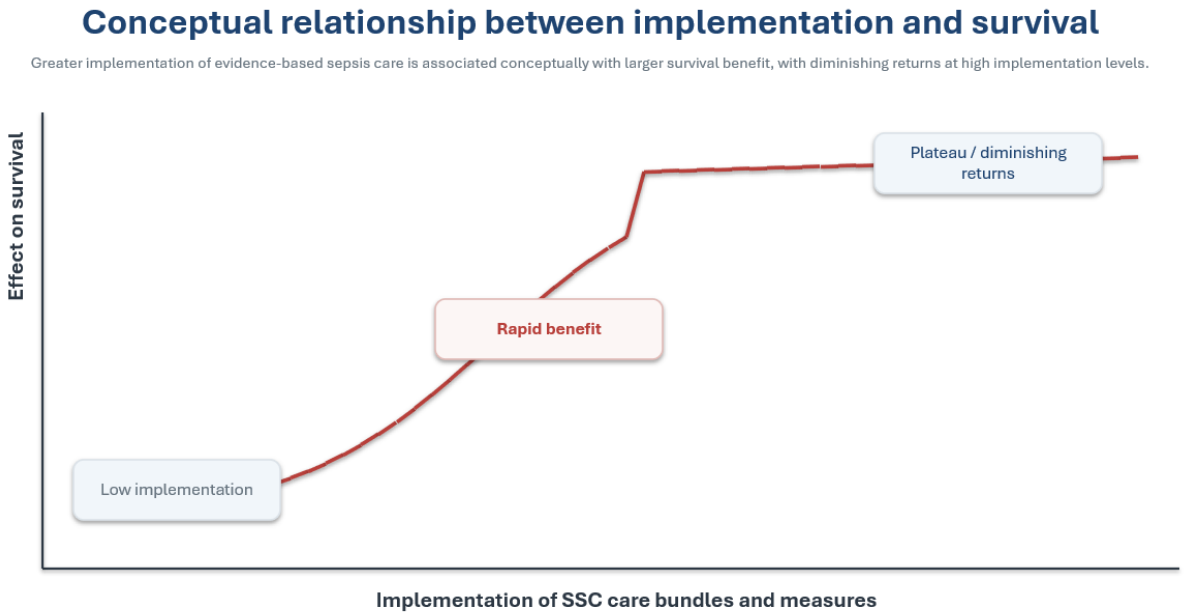

Figure 2. Conceptual model illustrating the expected relationship between implementation of Surviving Sepsis Campaign recommendations and survival. The curve is illustrative and does not represent a quantitative effect estimate or a specific dataset

nosological entity. Sepsis encompasses a broad spectrum of diseases, microbiological etiologies, genetic susceptibilities, and individual immune responses. This heterogeneity may help explain why clinical trials of immunomodulatory therapies have repeatedly failed to improve outcomes and raise questions about how those studies were designed and whether the traditional structure of clinical trials should be reconsidered in diseases with such individualized responses [7]. Applying the same therapeutic intervention to every patient can dilute beneficial effects in specific subgroups while exposing others to potentially harmful responses. Guiding interventions according to phenotypic profile, therefore, opens an important opportunity for sepsis treatment. Progress toward precision medicine requires characterization of patient heterogeneity through phenotypes, defined as observable clinical, laboratory, or imaging characteristics; subphenotypes, identified within the sepsis population using multivariable statistical analyses or machine-learning clustering; and endotypes, defined by specific underlying pathophysiological and molecular biological mechanisms.

The future of sepsis care requires us to consider which interventions can be added to those that have already proved useful. Artificial intelligence offers opportunities for earlier detection and for classification of patient subphenotypes and may also accelerate the investigation of new therapeutic compounds [8]. New biomarkers, such as mid-regional pro-adrenomedullin, have shown promising results for identifying septic patients at an early stage, potentially allowing intervention before organ failure develops [9-11]. Molecular microbiology has transformed the management of time in this disease and can also provide detailed information on resistance mechanisms, enabling more precise antimicrobial treatment [12,13]. Improved understanding of the pathophysiology of critical illness has likewise advanced individualized prescribing based on antimicrobial PK/PD. With regard to immunomodulatory therapies, it is increasingly plausible that some failed to generate positive evidence not because they were intrinsically ineffective but because biological stratification was lacking. This approach could lead to truly personalized sepsis treatment based not only on patient profile but also on disease stage, source of infection, and etiology. **Figure 3** summarizes potential opportunities to improve sepsis treatment.

Biological stratification as a therapeutic target

Traditional clinical trials focus on population averages rather than individual variability. In diseases such as sepsis, with marked heterogeneity in clinical expression and treatment response, it may be useful to design studies capable of rigorously evaluating how an individual responds to different treatments over time, thereby identifying whether that patient is a responder to a given intervention. Artificial intelligence could enable aggregation of standardized individual-level trial results and generate useful knowledge for population subgroups and potentially for the broader population. This will not be straightforward. The European Health Data Space remains constrained by insufficient data harmonization, unequal digital

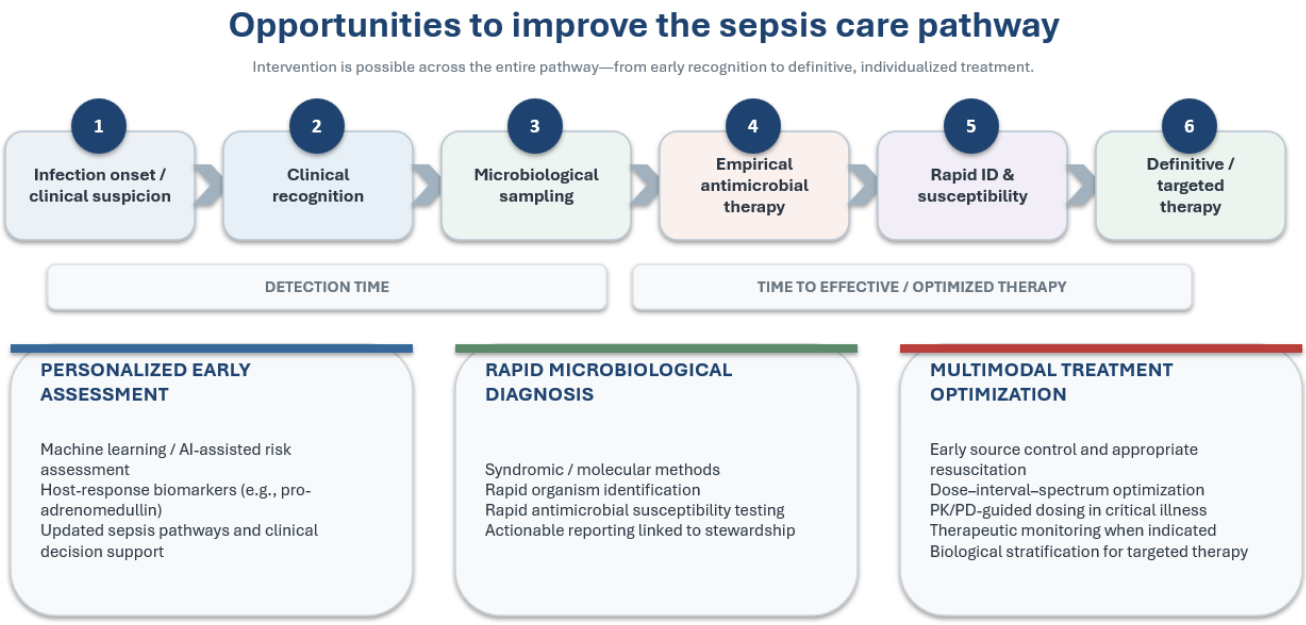

Figure 3. Potential intervention points throughout the sepsis pathway. Earlier recognition, rapid microbiological diagnosis, antimicrobial stewardship, source control, resuscitation, and individualized PK/PD-informed therapy can shorten time to effective treatment and support precision care

maturity across countries, legal complexity, and the need for multinational governance. Sepsis has been proposed as a model in which artificial intelligence applied to shared data could be particularly valuable for personalized clinical decision-making [14].

A recent example is the broad indication of corticosteroids for SARS-CoV-2 pneumonia [15]. Subsequent analyses showed that generalizing this treatment was not beneficial for every patient: distinct clinical phenotypes had different responses, and treatment was not beneficial in at least one subgroup [16]. This illustrates why successful immunomodulatory therapies have been difficult to identify in sepsis. Restoring homeostasis during sepsis cannot be reduced to a single uniform strategy and requires a deeper understanding of sepsis immunopathogenesis.

Identification of subphenotypes enables key enrichment strategies in both research and clinical practice. Prognostic enrichment selects patients with a higher probability of experiencing a clinical event, such as mortality, thereby increasing study power; predictive enrichment selects patients who, on the basis of their underlying biology, are more likely to respond favorably to a specific therapy.

Characterization of subphenotypes and endotypes in sepsis

Transcriptomic and genomic subphenotypes

In an early intensive-care study classifying patients according to pathophysiological mechanisms, the GAinS investigators analyzed gene expression in peripheral-blood leukocytes in a prospective discovery cohort of 265 patients with sepsis and organ dysfunction due to community-acquired pneumonia and subsequently validated their findings in 106 additional patients [17]. They identified two sepsis response transcriptomes: one characterized by relative immunosuppression, endotoxin tolerance, lymphocyte and monocyte exhaustion, metabolic reprogramming, and higher 14- and 28-day mortality; and another characterized by a more immunocompetent, hyperactive adaptive response and lower relative mortality. This study illustrates how patient populations can be biologically characterized to support personalized treatment according to individual profiles. Scicluna et al. [18] identified four molecular sepsis endotypes through analysis of the expression of 140 genes and defined biomarkers associated with each endotype. These studies demonstrated the feasibility of classifying patients into immunological-metabolic subphenotypes, including hyperinflammatory profiles characterized by high expression of pro-inflammatory genes such as cytokine and complement pathways; adaptive profiles with preservation of adaptive immune pathways; and coagulopathic profiles with marked abnormalities in genes related to endothelial dysfunction, coagulation, and hemostasis.

Subphenotypes based on routine clinical variables

Importantly, classification of septic patients does not necessarily require complex gene-expression studies. Patients can also be grouped into subphenotypes using routinely available bedside variables.

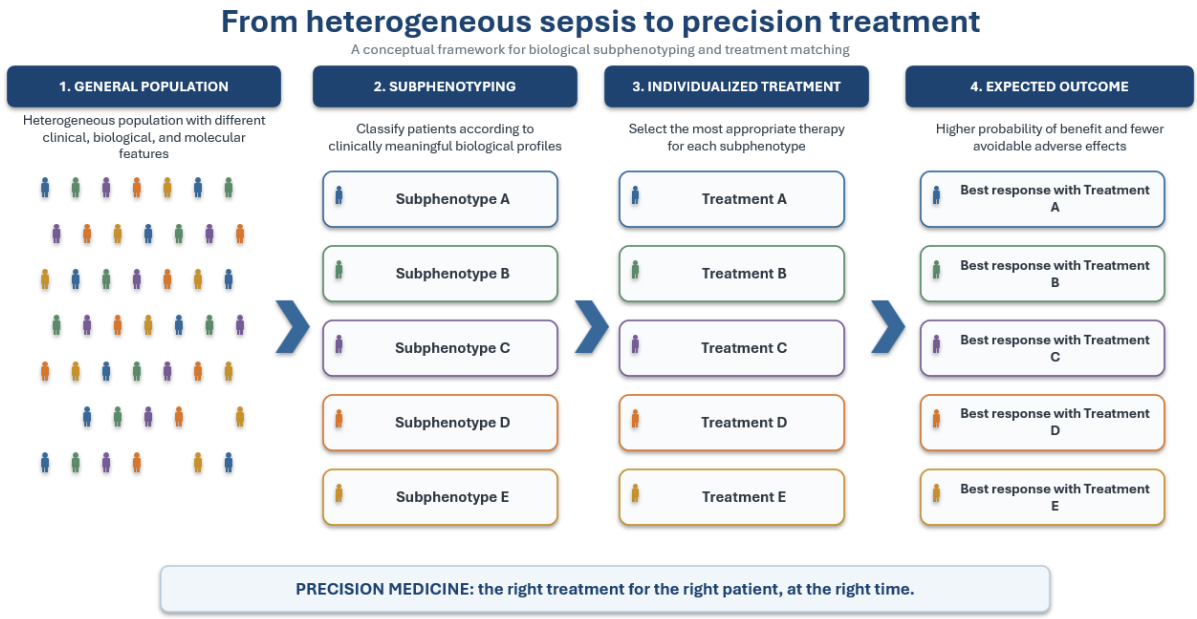

Figure 4. Conceptual framework for precision medicine in sepsis: a heterogeneous population is stratified into clinically relevant subphenotypes, each visually linked to a matched treatment and expected response. Colors and patient icons illustrate the continuity from biological profile to treatment selection and outcome; categories are illustrative rather than validated

Large-scale studies including more than 20,000 patients with sepsis described four clinical phenotypes derived from demographic data, vital signs, and standard laboratory tests [19]. These phenotypes correlated with patterns of host response and clinical outcomes and help illustrate the heterogeneity underlying responses to generalized sepsis treatment.

Heterogeneity of treatment effect

Reassessment of clinical trials through retrospective analyzes stratified by subphenotype shows that responses to therapeutic interventions can vary substantially between subgroups. Treatment guided by phenotypic profile, therefore, represents a logical starting point for personalized sepsis care (**Figure 4**).

A contemporary approach to sepsis should continue to apply SSC-recommended bundles but should also move beyond them by exploiting clinical decision-support tools that were not available only a few years ago, including artificial intelligence. It is also plausible to investigate immunomodulatory treatments according to phenotypic profile rather than applying them indiscriminately. As a hypothesis, corticosteroid therapy might be more coherent in patients with sepsis and an inflammatory subphenotype, whereas in patients without such a profile, corticosteroids may provide no benefit and could potentially increase adverse effects through worsening immunoparalysis. The HARP-2 trial of simvastatin in acute respiratory distress syndrome (ARDS) provides an illustrative example. Although simvastatin was initially considered safe but without overall clinical benefit [20], a secondary analysis stratifying participants into two subphenotypes found a significant reduction in 28-day mortality only in the hyperinflammatory subgroup, with no effect in the hypoinflammatory subgroup [21]. Similarly, fluid-resuscitation strategies in sepsis may need to reflect patient profile; restrictive fluid approaches could be considered in hyperinflammatory or coagulopathic subphenotypes to avoid worsening capillary leak and pulmonary edema. Lung-protective ventilation has been shown to reduce levels of pro-inflammatory interleukins [22,23], and in sepsis-associated lung injury patients with a hyperinflammatory subphenotype may plausibly benefit from higher PEEP and lower tidal volumes to improve alveolar recruitment.

Future perspectives: parallels with oncology and point-of-care diagnosis

Successful implementation of precision medicine in septic shock and sepsis will require critical care to move from a traditional infection-centered paradigm toward a model analogous to medical oncology, where immunotherapy and molecularly targeted treatment have undergone decades of development [24]. Just as oncology no longer treats only “lung cancer” but also specific molecular alterations such as EGFR or ALK, sepsis care should aim to identify and treat molecular endotypes, for example, immunosuppressed versus hyperinflammatory endotypes. The

development of quantitative real-time PCR, microfluidic platforms, or proteomic panels capable of classifying a patient's subphenotype within 1–2 hours of arrival in the emergency department or ICU could be crucial for early decisions, which are also those most likely to influence prognosis. This framework should be accompanied by adaptive platform trials and targeted immunotherapy, with interventions assigned dynamically according to real-time molecular signatures.

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Author contributions

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Conflicts of interest

The authors declare that there is no commercial or financial conflict of interest for this research.

AI statement

The authors declare that no artificial intelligence tools (such as ChatGPT, Copilot, Gemini, or others) have been used in the writing, analysis, or review of this article.

References

1. Prescott HC, Antonelli M, Alhazzani W, Møller MH, Alshamsi F, Azevedo LCP, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock 2026. Crit Care Med. 2026;54(4):725-812. Available from: https://doi.org/10.1097/CCM.0000000000007075
2. GBD 2021 Global Sepsis Collaborators. Global, regional, and national sepsis incidence and mortality, 1990-2021: a systematic analysis. Lancet Glob Health. 2025;13(12). Available from: https://doi.org/10.1016/S2214-109X(25)00356-0
3. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med. 2004;30(4):536-55. Available from: https://doi.org/10.1007/s00134-004-2210-z
4. Slade E, Tamber PS, Vincent JL. The Surviving Sepsis Campaign: raising awareness to reduce mortality. Crit Care. 2003;7(1):1-2. Available from: https://doi.org/10.1186/cc1876
5. Gutiérrez Junco SM, Paipa Merchán AJ, Heredia Rodríguez M, Gómez Herreras JI, Tamayo Gómez E. The Resuscitation Bundle of the Surviving Sepsis Campaign beyond early goal-directed therapy: what's next? Crit Care Med. 2015;43(8). Available from: https://doi.org/10.1097/CCM.0000000000000960
6. 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. Available from: https://doi.org/10.1001/jama.2016.0287
7. Estella Á. Pneumonía, "The Young friend" of mechanical ventilator. Med Intensiva (Engl Ed). 2026;50(7):502502. Available from: https://doi.org/10.1016/j.medine.2026.502502
8. Estella Á, Armengol de la Hoz MÁ, González del Castillo J; Grupo de trabajo INFURG-SEMES. Open data and artificial intelligence: a window of opportunity for septic patients in emergency departments. Emergencias. 2025;37(5):373-81. Available from: https://doi.org/10.55633/s3me/056.2025
9. Valenzuela-Sánchez F, Valenzuela-Méndez B, Rodríguez-Gutiérrez JF, Estella-García Á, González-García MÁ. New role of biomarkers: mid-regional pro-adrenomedullin, the biomarker of organ failure. Ann Transl Med. 2016;4(17):329. Available from: https://doi.org/10.21037/atm.2016.08.65
10. Cusack R, Garduno A, Cumpf S, Reyes-Morales P, Leone M, Blanco Fernández A, et al. Mid-regional pro-adrenomedullin as a translational biomarker of microcirculatory dysfunction in sepsis: a prospective observational study. Med Sci (Basel). 2026;14(1):117. Available from: https://doi.org/10.3390/medsci14010117
11. Spoto S, Basili S, Cangemi R, D'Avanzo G, Lupoi DM, Romiti GF, et al. Mid-regional pro-adrenomedullin can predict organ failure and prognosis in sepsis? Int J Mol Sci. 2023;24(24):17429. Available from: https://doi.org/10.3390/ijms242417429
12. Candel FJ, Salavert M, Cantón R, del Pozo JL, Galán-Sánchez F, Navarro D, et al. The role of rapid multiplex molecular syndromic panels in the clinical management of infections in critically ill patients: an experts-opinion document. Crit Care. 2024;28(1):440. Available from: https://doi.org/10.1186/s13054-024-05224-3
13. Candel FJ, Soriano C, Estella Á. Syndromic panels in critically ill pneumonia: beyond diagnosis. Enferm Infecc Microbiol Clin (Engl Ed). 2026;44(7):503227. Available from: https://doi.org/10.1016/j.eimce.2026.503227
14. Carbajo RS, Palma J, Martin-Loeches I. The next frontier in sepsis: connected ICU data for real-world clinical decision making. Intensive Care Med. 2026;52(2):301-8. Available from: https://doi.org/10.1007/s00134-025-08284-3
15. RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med. 2021;384(8):693-704. Available from: https://doi.org/10.1056/NEJMoa2021436
16. Moreno G, Ruiz-Botella M, Martín-Loeches I, Gómez Álvarez J, Jiménez Herrera M, Bodí M, et al. A differential therapeutic consideration for use of corticosteroids according to established COVID-19 clinical phenotypes in critically ill patients. Med Intensiva (Engl Ed). 2023;47(1):23-33. Available from: https://doi.org/10.1016/j.medine.2021.10.016
17. Davenport EE, Burnham KL, Radhakrishnan J, Humburg P, Hutton P, Mills TC, et al. Genomic landscape of the individual host response and outcomes in sepsis: a prospective cohort study. Lancet Respir Med. 2016;4(4):259-71. Available from: https://doi.org/10.1016/S2213-2600(16)00046-1

18. Scicluna BP, van Vught LA, Zwinderman AH, Wiewel MA, Davenport EE, Burnham KL, et al. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. Lancet Respir Med. 2017;5(10):816-26. Available from: https://doi.org/10.1016/S2213-2600(17)30294-1
19. Seymour CW, Kennedy JN, Wang S, Chang CH, Elliott CF, Xu Z, et al. Derivation, validation, and potential treatment implications of novel clinical phenotypes for sepsis. JAMA. 2019;321(20):2003-17. Available from: https://doi.org/10.1001/jama.2019.5791
20. McAuley DF, Laffey JG, O'Kane CM, Perkins GD, Mullan B, Trinder TJ, et al. Simvastatin in the acute respiratory distress syndrome. N Engl J Med. 2014;371(18):1695-703. Available from: https://doi.org/10.1056/NEJMoa1403285
21. Calfee CS, Delucchi KL, Sinha P, Matthay MA, Hackett J, Shankar-Hari M, et al. Acute respiratory distress syndrome subphenotypes and differential response to simvastatin: secondary analysis of a randomised controlled trial. Lancet Respir Med. 2018;6(9):691-8. Available from: https://doi.org/10.1016/S2213-2600(18)30177-2
22. Ranieri VM, Suter PM, Tortorella C, De Tullio R, Dayer JM, Brienza A, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. JAMA. 1999;282(1):54-61. Available from: https://doi.org/10.1001/jama.282.1.54
23. Pinheiro de Oliveira R, Hetzel MP, dos Anjos Silva M, Dallegrave D, Friedman G. Mechanical ventilation with high tidal volume induces inflammation in patients without lung disease. Crit Care. 2010;14(2). Available from: https://doi.org/10.1186/cc8919
24. Durant JR. Immunotherapy of cancer: the end of the beginning? N Engl J Med. 1987;316(15):939-41. Available from: https://doi.org/10.1056/NEJM198704093161509