Sepsis

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Sepsis is defined as a dysregulated host response to infection that leads to life-threatening organ dysfunction. The infectious insult triggers a dysregulated immune response that variably activates and suppresses multiple body system functions. Susceptibility to either developing or succumbing to sepsis is influenced by pathogen load and virulence; site of infection; host factors, including genetics, biological variability, comorbidities, immunosuppression, and extremes of age; and a wide range of external influences, such as social deprivation and local environment. Increasing appreciation of the underlying pathobiology has identified differing biological signatures with variable temporal evolution. This variability highlights the requirement to individualise treatment with targeted interventions guided by rapidly accessible biomarkers. Although improved outcomes have been obtained with better prevention, early recognition, and treatment, sepsis is a major cause of global mortality and morbidity. All populations having the benefits currently enjoyed by a privileged few is imperative. This Seminar aims to unravel the complexity of the condition, describing epidemiology and pathophysiology, evolving fundamental shifts, patient management, current challenges, and future developments.

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Introduction

Sepsis is a syndrome defined conceptually as the development of life-threatening organ dysfunction resulting from a dysregulated host response to infection.[1] This definition can apply to any pathogen—for example, COVID-19 disease when it leads to acute respiratory failure. For clinical operationalisation, two newly acquired points on the Sequential Organ Failure Assessment score, over and above the usual baseline of a patient, represent the minimum deterioration in organ function that distinguishes sepsis from an uncomplicated infection.[1] This score incorporates six organ systems (brain, cardiovascular, respiratory, hepatic, renal, and coagulation) and was updated in 2025.[2] However, other organ systems are frequently affected, including gastrointestinal dysfunction, bone marrow depression, myopathy, and peripheral neuropathy (figure 1).

Septic shock describes profound circulatory, cellular, and metabolic irregularities that are associated with a greater mortality risk than sepsis alone. The clinical criteria include a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or more and a serum lactate concentration of more than 2 mmol/L (18 mg/dL) despite correction of hypovolaemia.[1] Equivalent definitions and criteria for children were published in 2024.[3] There, sepsis is characterised as a 2 point or more rise in the Phoenix Sepsis score, which identifies dysfunction in respiratory, cardiovascular, coagulation, and neurological systems.

Many challenges persist in clinical practice. Diagnosis can be problematic, especially at first presentation and in patients with multimorbidity and/or communication issues. Infection might not be verified until positive microbiological results return. Nonetheless, causative organisms are often unidentified; therefore, infection is presumed and frequently overdiagnosed. Furthermore, acute organ dysfunction might be difficult to distinguish from pre-existing chronicity, and attributable to infection.

Epidemiology

Sepsis epidemiology (figure 2) is realised with diagnostic coding, scrutiny of death certificates, and, in informatics-rich settings, interrogation of electronic health-care record data. All approaches have limitations, with data incompleteness and inaccuracies, diagnostic subjectivity, and temporal changes following sepsis awareness campaigns, evolving definitions, and initiatives to improve coding.[4–7] Nevertheless, clear consensus exists that sepsis represents a major global health-care problem.

The Global Burden of Disease study extrapolated data from hospital diagnosis codes and death certificates to estimate 49 million sepsis cases and 11 million worldwide deaths in 2017.[8] Incidence was higher in the young, old, and people with pre-existing medical conditions, with children accounting for 30% of deaths. Burden differed widely in different countries, with 85% of cases and deaths in resource-limited settings. Age-standardised incidence and mortality rates inversely correlated with sociodemographic index, and was 15-fold higher in sub-Saharan Africa compared with western Europe. Encouragingly, sepsis incidence was reported to have fallen by 37%, and mortality by 53%, between 1990 and 2017. However, comparative estimates for the USA, obtained with an electronic health-care record approach between 2009 and 2014, found that sepsis cases were 88% higher and deaths 55% higher than those reported in the Global Burden of Disease study, with unchanged incidence and mortality.[9]

Search strategy and selection criteria

We searched PubMed for articles published between Jan 1, 1990 and June 1, 2025. The following search terms were used: "sepsis" , "septic shock", and "bacteremia/bacteraemia". Only studies published in English were considered, with a particular focus on pathophysiology, epidemiology, and randomised controlled trials.

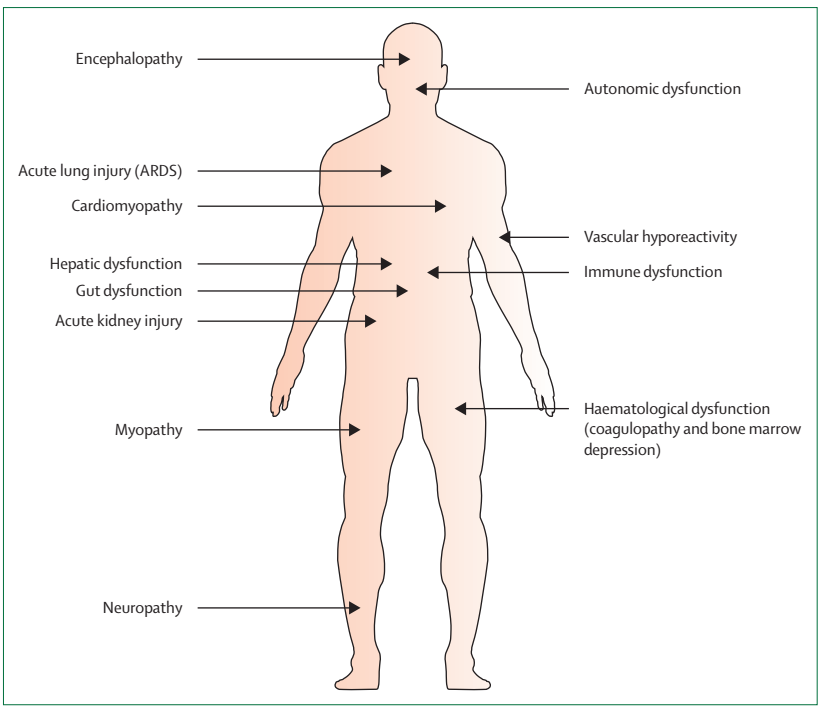

Figure 1: **Organ dysfunctions in sepsis**
Created in BioRender. Singer, M (2025) https://BioRender.com/l1o1l55. ARDS=acute respiratory distress syndrome.

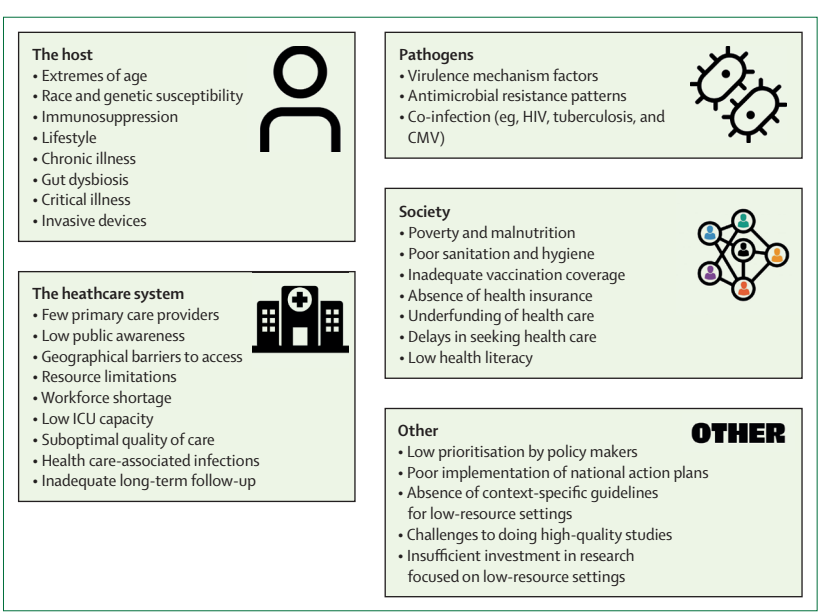

Figure 2: **Risk factors for infection and progression to sepsis**
ICU=intensive care unit. CMV=cytomegalovirus.

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The higher burden of sepsis in resource-limited settings relates to poor sanitation, low vaccine coverage, overstretched primary care, delays in seeking health care, limited hospital access, shortages of health-care personnel, overcrowding, and insufficient intensive care unit (ICU) beds.[10,11] Antimicrobial resistance (AMR) is common due to antibiotic overuse, a scarcity of stewardship programmes, and high nosocomial infection rates.[8]

Sepsis cases are mainly community-acquired. Hospital-acquired sepsis accounts for 10–15% of cases, but is associated with worse outcomes.[12,13] A large multinational point prevalence study done in ICUs reported an overall in-hospital mortality of 30·3%.[13] Mortality from septic shock exceeds 40%.[1] The most common sites of infection are the respiratory tract, abdomen, bloodstream, and urinary tract.[8,13] Diarrhoeal illnesses predominate in low-resource settings. Bacterial organisms, particularly Gram-negative bacilli, most often cause sepsis, followed by viruses, fungi, and protozoa, alone or in combination with bacteria.[13] In resource-limited settings, malaria, leptospirosis, melioidosis, typhus, tuberculosis disease, and viral infections, including dengue, measles, and influenza, are prevalent.[8]

Pathophysiology

The host response to infection requires recognition of the invading pathogen, its constituents (eg, DNA, lipopolysaccharides, and peptidoglycans), and other danger signals produced by both the immune system and non-immune cells, such as the epithelium and endothelium.[14] Both cell surface (eg, toll-like) and intracellular (eg, nucleotide-binding oligomerisation domain-like) pattern recognition receptors identify pathogen-associated molecular patterns, triggering host immune responses aimed at clearing the infection. However, these responses can inadvertently affect host cellular functionality, resulting in cell injury with the release of damage-associated molecular patterns, such as DNA, mitochondria, and heat shock proteins.[14,15] Damage-associated molecular patterns also act as danger signals, amplifying the host immune response. The net result is activation of pro-inflammatory pathways, in combination with immune dysfunction, including leukocyte anergy, lymphopenia, depletion of regulatory T cells and myeloid-derived suppressor cells, and reduced HLA-DR isotype expression by antigen-presenting cells. The altered functionality of both the innate and adaptive immune systems increases susceptibility to secondary infection from either external or intrinsic sources. Intrinsic sources include bowel microorganisms, such as Gram-negative bacteria and fungi[16] and viral reactivation.[17] Such infections impact recovery and can cause late deaths.

The dysregulated immune response has been reframed as altered homoeostasis, with pathological disruption of immune-driven resistance, disease tolerance, resilience, and resolution (figure 3).[18] Resistance refers to effector mechanisms that reduce the pathogen burden. Tolerance is an evolutionarily conserved defence strategy that limits disease severity without directly affecting pathogen burden.[19] Resilience, with respect to the immune system, is the capacity to rapidly restore the pre-illness regulated

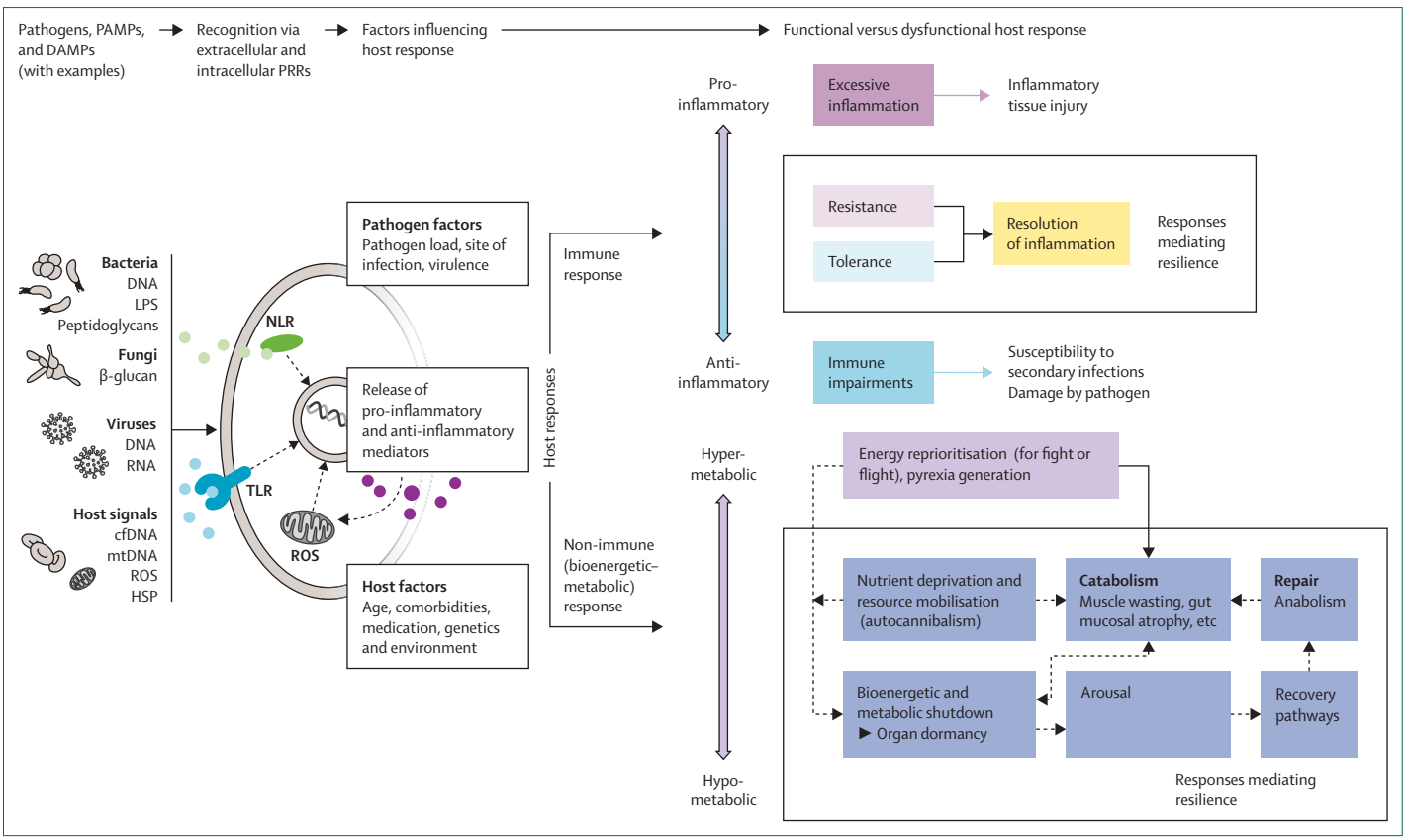

Figure 3: **Reframing conceptual fundamentals underlying immune and non-immune responses**
DAMPs=damage-associated molecular patterns. cfDNA=cell-free DNA. mtDNA=mitochondrial DNA. HSP=heat shock protein. LPS=lipopolysaccharide. NLR=nucleotide-binding oligomerisation domain-like receptor. PAMPs=pathogen-associated molecular patterns. PRRs=pathogen recognition receptors. ROS=reactive oxygen species. TLR=toll-like receptor.

state while limiting the inflammatory cost to the host. Resolution is the regulated process that restores tissue homoeostasis following inflammation. This model represents competing host defence strategies. For example, low pathogen loads can be dealt with by a resistance response, whereas a high pathogen load induces energy-saving catabolic and maintenance responses, such as autophagy and tolerance.[20] As every organ has a different immune architecture, the site of infection also influences clinical outcomes.[21]

The dysregulated immune response triggers multiple downstream effects, including altered neural control mechanisms, endothelial activation, and loss of vasoregulatory control, with alterations in macrovascular and microvascular blood flow affecting tissue perfusion (figure 4). Metabolic substrate use initially increases and then falls, shifting from glucose towards fat and protein. Marked endocrine changes occur early, with an increased release of most pituitary hormones, increased circulating concentrations of cortisol and catecholamines, and peripheral inactivation of anabolic hormones.[22,23] These endocrine responses induce catabolism to generate metabolic substrates and haemodynamic modifications that are essential for survival, while attempting to prevent excessive inflammation and allow pro-resolving pathways to mediate a return to homoeostasis.[22,23] Altered neuroendocrine–immune crosstalk contributes to organ dysfunction.[24] Coagulopathy occurs, with both pro-thrombotic and increased bleeding tendencies, although overt disseminated intravascular coagulation is increasingly rare.[25] Thrombin generation amplifies the inflammatory response. At the cellular level, organelle injury and dysfunction are apparent—for example, endoplasmic reticulum stress and mitochondrial dysfunction. Mitochondrial dysfunction is hallmarked by an availability, but decreased use, of oxygen (cytopathic dysoxia), affecting ATP production.[26]

Notably, other than gut epithelium and immune cells, cell death is not a major feature of organ dysfunction in sepsis;[27,28] thus, even poorly regenerative organs can regain functionality. Nonetheless, activation of various cell death pathways can potentially be targeted to impact outcomes.[29]

From an evolutionary perspective, an excessive insult in the pre-ICU era would have rapidly progressed to death. Nowadays, early deaths can be avoided or delayed by organ support. This prolongation has revealed different

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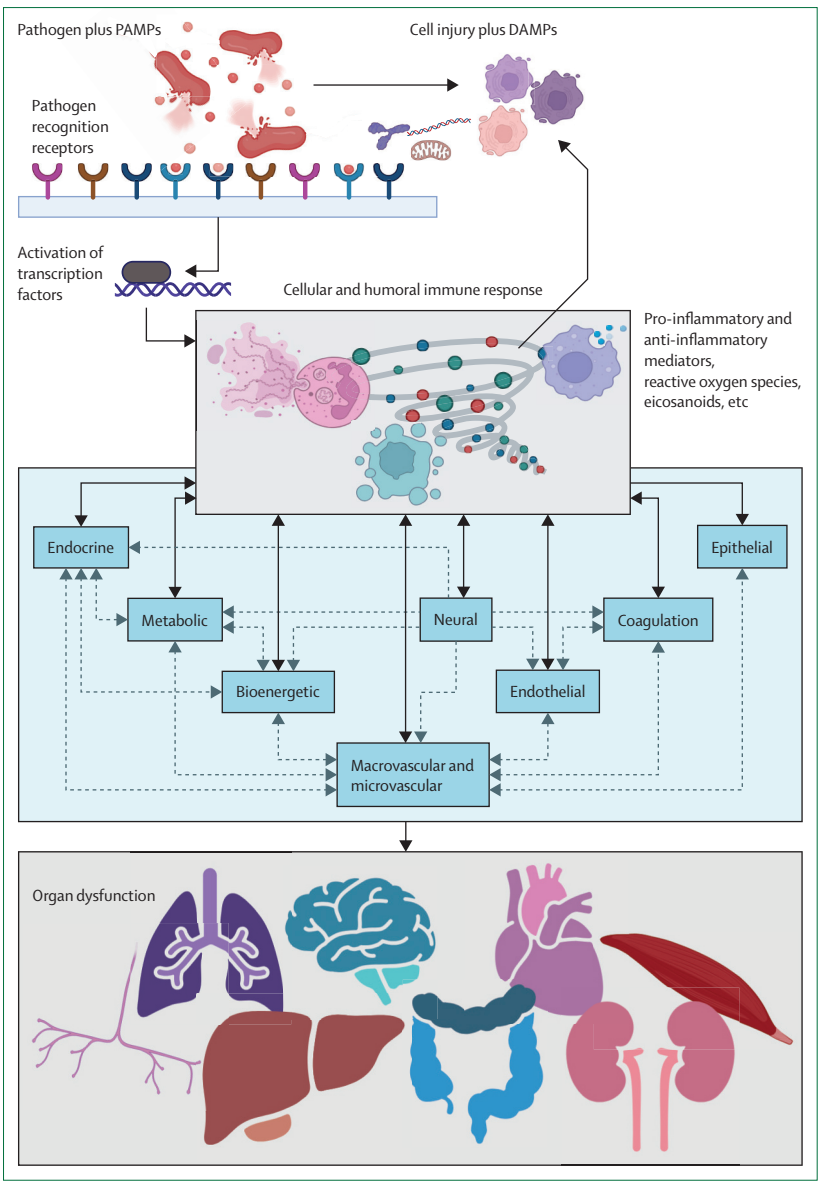

Figure 4: **Schematic of sepsis pathophysiology, highlighting substantial crosstalk**
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phases of the septic illness, from an early, adaptive fight-or-flight response with an increase in metabolic rate to a subacute bioenergetic shutdown of several organ systems to economise energy expenditure, followed by either recovery or persisting organ dysfunction (figure 3).[26] Persisting organ dysfunction is a pathophysiological state that exceeds any natural time course that would have enabled evolution to select survival pathways. Initially, beneficial metabolic, endocrine, and bioenergetic adaptations become potentially deleterious in prolonged critical illness,[22,30–32] an example of which is the uniform suppression of all hypothalamus–pituitary axes.[22,23,32,33] Processes underlying host resilience, including metabolic, bioenergetic, and endocrine adaptations that contribute to recovery are poorly characterised.

Diagnosis

Sepsis is a time-sensitive condition: prompt identification and treatment are key. No single best screening tool exists as settings and presentations vary. Most approaches alert to signs and symptoms of infection, including markers of systemic inflammation,[34,35] clinical deterioration with bedside early warning scores such as the National Early Warning Score-2 and quick Sequential Organ Failure Assessment,[36–38] and illness severity (organ dysfunction and lactate).[39,40] Manual screening tools are inefficient, and automated tools built in to many electronic health record systems are also not failsafe, and often alert excessively, causing alarm fatigue.[41–43]

Accurate and timely diagnosis of infection is a major challenge, especially in low-resource settings. Diagnostic precision is essential to administer the appropriate anti-infective agents and, if needed, early and effective source control. However, current diagnostics are far from failsafe. Patients with sepsis can present atypically—for example, apyrexial or with normal or marginally elevated inflammatory biomarkers.[44,45] Bacterial infection is verified in only 60–70% of patients treated for bacterial sepsis.[13,46,47] Non-identification of a pathogen does not necessarily exclude sepsis, and a positive culture might reflect colonisation rather than infection. Overdiagnosis is commonplace, as sepsis mimics can present with clinical and laboratory features similar to sepsis.[48–50] Examples of such non-infectious inflammatory conditions include pulmonary embolism, heart failure, acute lymphomas, drug reactions, and allergic reactions. An erroneous label of sepsis exposes the patient to unnecessary treatment and can distract from diagnosing and treating the true cause.

A comprehensive approach maximises diagnostic precision and improves outcomes. A detailed history evaluates the risks for specific types of infection and includes individual comorbidities, such as immunosuppression, environmental exposures (eg, recent admission to hospital), and geographical and travel locations to establish community exposure to specific pathogens. Thorough physical examination assesses both potential sites of infection and organs directly or indirectly affected by the septic process. Identifying the site of infection optimises the type, dosing, and duration of antibiotics[51] and the need for source control—for example, abscess drainage, viscus perforation repair, and indwelling device removal.[52]

Microbiological and radiological evaluations identify the organism and infection site. Blood cultures should ideally be collected before initiating antibiotics. A positive blood culture enables the most targeted antibiotic approach; however, positivity occurs in only 20–30% of patients with sepsis,[12] and the lag time can be several days. Guided by the likely site of infection,

samples, such as sputum, bronchoalveolar lavage, urine, pleural fluid, cerebrospinal fluid, and pus are taken to increase the likelihood of identifying the specific infection. Multiplex PCR platform assays that detect specific pathogen molecular patterns are now commercially available for various body fluids, with most offering a selection of AMR genes. These panels provide a rapid diagnosis that can facilitate early, targeted antimicrobials.[53–56] Prospective randomised trials are still scarce and have yet to show clear outcome benefits.[54–56] Such platforms might yield false-positive results due to their high sensitivity in, for example, detecting commensals and contaminants, and will not detect less common microorganisms. The choice of radiological procedure (x-ray, CT, or MRI) depends on local availability and is directed by the most likely site or sites of infection, as assessed by bedside evaluation. Ultrasonography (including echocardiography) might be indicated from history and examination findings.

Blood tests are also taken for urgent identification of markers of systemic inflammation (eg, white blood count, C-reactive protein, and procalcitonin), electrolyte disturbances, and organ dysfunction. Lactate measurement is useful for risk stratification and assessing treatment response.[40] The absence of hyperlactataemia does not necessarily exclude substantial disease severity or risk of death.[1] Numerous host response biomarkers, either singly or in combination, of inflammation, coagulation, and immunological pathways have been proposed. However, none are absolute diagnostics at present.[34,35] The lack of diagnostic surety from such tests is particularly relevant in borderline cases of sepsis, in which most uncertainty resides. Rapid host response biomarkers measuring mRNA or proteins can reasonably discriminate bacterial from non-bacterial infections, but are likelihood-based rather than conclusive.[57–59]

Management

Debates are still ongoing about best treatment (figure 5), especially with prospective trials offering neutral or even conflicting results across a wide range of interventions, such as fluid therapy, vasoactive drugs, nutrition, and immunomodulation.[60] Promising initial results have not been reproduced in larger multicentre studies:[61,62] even with sepsis caused by a single pathogen (SARS-CoV-2), multicentre studies generated inconsistent findings.[63,64] These inconsistencies are multifactorial and are in part related to study design and performance and the populations being treated.[65,66] Short-term gains, such as elevating blood pressure with a specific agent, do not necessarily translate into longer-term outcome benefits. There is increasing recognition that the individual patient's underlying biological signature (subphenotype) can predict a beneficial, harmful, or neutral response to therapy (eg, corticosteroids).[67,68] Such signatures might prove useful in guiding therapy and improving outcomes.[66,69]

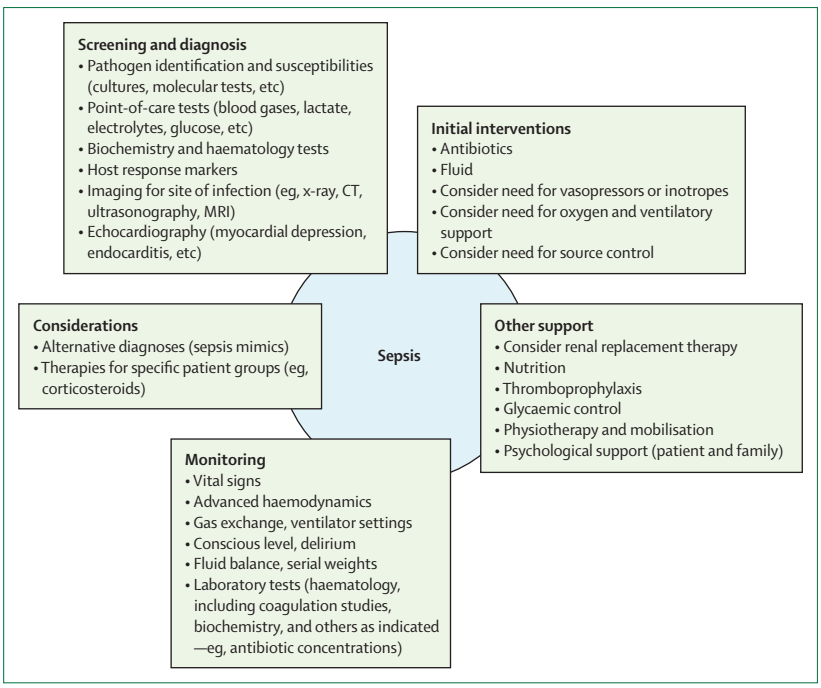

Figure 5: **Sepsis management summary**
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The Surviving Sepsis Campaign (SSC) offers regularly updated evidence-based guidelines to assist patient management.[70] In view of the aforementioned issues and the resulting dearth of high-quality or even moderate-quality evidence, the strength of recommendations is mainly graded as weak. A revised version is expected in 2026.

Prompt intervention

Intervention in the proximal part of the illness course is the best way to mitigate progressive organ dysfunction and poor outcomes. SSC guidelines emphasise key actions, such as prompt intravenous antibiotic administration and circulatory (intravenous fluid ± vasopressors) support within the first hours.

Control and eradication of infection

Timely antibiotic administration is the only component of sepsis resuscitation bundles that is consistently associated with lower mortality.[71,72] However, a balance should be struck between the harms associated with administering unnecessary antibiotics to patients with non-bacterial sepsis or non-infectious mimics (eg, encouragement of AMR) and multiple direct complications, including deleterious effects on the microbiome.[16,73] Risk stratification can help clinicians navigate the tension between early antibiotics versus limiting overtreatment. The association between time-to-antibiotics and mortality is strongest and most consistent in patients with septic shock.[72,74,75] However, this association is weak or absent in

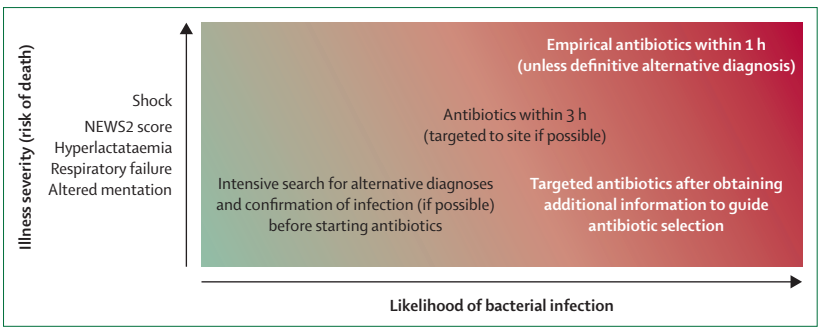

Figure 6: **Timing of antibiotic initiation and illness severity**
Created in BioRender. Singer, M (2025) https://BioRender.com/y9ci3ya. NEWS2=National Early Warning Score-2.

non-shocked patients unless delays exceed 5–6 hours,[72,74] a finding verified by prospective studies.[76,77] If the diagnosis of bacterial sepsis is unclear, clinicians can investigate whether a patient who is non-shocked is infected and, if so, whether the infection is most likely to be bacterial or non-bacterial before administering antibacterials (figure 6). SSC guidelines recommend administering antibiotics within 3 h if concern for infection persists, as per the precautionary principle.[70] UK guidelines stratify response time by the bedside National Early Warning Score-2 score, with 1, 3, and 6 h windows, depending on severity.[78] Such time windows are maxima; once a decision is made to give antibiotics, prescription or administration should not be delayed.[70,78,79]

Antibiotic choice should be informed by the patient-specific likelihood of infection by a resistant organism. Physicians usually overestimate the risk for drug-resistant organisms,[80] although resistance rates are higher with hospital-onset sepsis and in many resource-limited settings.[81,82] To reduce the risk of AMR and other antibiotic-related complications, antibiotic de-escalation, including a shift to a narrow-spectrum antibiotic, should be implemented once the pathogen and its antimicrobial susceptibilities are known. Future advances in rapid diagnostics might facilitate increased initial use of narrow-spectrum antibiotics. Multiple prospective studies show equal efficacy with shorter antibiotic courses:[83–85] in general, 5–7 day courses are sufficient unless the infection is deep-seated or a specific pathogen requires an extended course. As with early antibiotics, prompt, adequate source control is associated with reduced mortality.[76,86] Results vary between studies; therefore, some room for discretion exists to vary source control time targets depending on the patient substrate, clinical syndrome, and the complexity and safety of providing source control.

Organ support

Signs suggestive of organ hypoperfusion—for example, protracted capillary refill time, livedo, altered consciousness, oliguria, hypotension, and hyperlactataemia—should prompt early resuscitation efforts. Most patients with sepsis are hypovolaemic, albeit to varying degrees, because of decreased fluid intake, increased losses (eg, sweating, vomiting, and diarrhoea), and increased vascular leak, resulting in fluid redistribution from intravascular to extravascular compartments. In the initial resuscitation phase, up to 30 mL/kg of intravenous crystalloids (preferably balanced electrolyte solutions) might be needed. Frequent re-evaluation is necessary to establish regular fluid requirements. Resuscitation should be based on the clinical context and assessments of fluid responsiveness, ideally with dynamic measures, such as capillary refill and passive leg raising.[87] A fluid challenge in adults represents a bolus of 200–500 mL given over 5–10 min.

Prompt and adequate fluid resuscitation is crucial, although care should be taken to avoid fluid overload. Peripheral oedema reflects engorgement in other organs. An increasingly positive fluid balance is associated with a progressively higher mortality risk.[88,89] Once stabilised, fluid accumulation should be reversed with restricted fluid inputs and, if needed, judicious use of diuretics or renal replacement therapy. This approach might be challenging in low-resource settings, where patients who are critically ill are frequently managed outside the ICU, with low respiratory and renal support capacity to deal with complications arising from fluid overload.[90,91]

Vasopressor infusion should begin, via peripheral access, if necessary, within the first hour in cases of life-threatening hypotension or when hypotension persists despite initial fluid resuscitation. Norepinephrine is the current recommended first-line agent,[70] although in low-resource settings, epinephrine or dopamine are reasonable alternatives. Early vasopressor use might improve haemodynamics by mobilising the unstressed venous volume and avoiding excess fluid loading. Due to potentially harmful effects from high doses of catecholamines,[92] a multimodal approach is recommended, ensuring an adequate intravascular volume, maintaining a mean arterial pressure generally within the 65–70 mm Hg range, and adding vasopressin as a second-line vasopressor[70] and low-dose hydrocortisone (50 mg four times per day) to improve vascular responsiveness to catecholamines. Inotropes might be required for ongoing hypoperfusion related to sepsis-induced myocardial dysfunction.

In patients with respiratory failure (acute respiratory distress syndrome), support can initially be given with high-flow nasal oxygen or non-invasive ventilation. Patients with more severe respiratory failure usually require sedation and mechanical ventilation and, occasionally, extracorporeal support. Although mechanical ventilation carries its own complications (ventilator-induced lung injury), delayed intubation can increase oxygen consumption and result in self-inflicted lung injury by spontaneous hyperventilation.[93] A lung-protective approach should be taken in mechanically ventilated patients with low tidal volumes (~6 mL/kg predicted bodyweight) and a plateau pressure (end-inspiratory airway pressure when airflow ceases) of less

than 30 cm H_2O.[70] Deep sedation and neuromuscular blockade should be limited to severe cases, and hyperoxaemia avoided. When appropriate, early ventilator and sedation adjustments to enable spontaneous breaths might avoid substantial respiratory muscle atrophy and facilitate weaning.

Acute kidney injury is multifactorial, with contributions from hypoperfusion, inflammatory mediators, and mitochondrial dysfunction.[94] Haemodynamic optimisation alone might not reverse acute kidney injury. Early renal replacement therapy does not improve outcomes and should be reserved for substantial hyperkalaemia, uraemia, or refractory acidosis.[94]

General supportive measures

General supportive measures are key for recovery. Patients, families, and caregivers should also be engaged early to discuss prognosis and goals of care, and to offer psychological support. Nutritional support can be enteral and/or parenteral and should commence beyond the acute phase; early, aggressive feeding is associated with increased harm.[95–97] Optimal dose and formulation are uncertain and overfeeding should be avoided. Enteral nutrition should generally begin within 3–4 days in the absence of contraindications, such as ongoing shock or gastrointestinal complications.[97] Parenteral nutrition should be considered in cases of protracted insufficient enteral nutrition. Hyperglycaemia is commonplace in sepsis and is multifactorial due to insulin resistance, counter-regulatory hormones, and the use of therapies, such as corticosteroids, catecholamines, and parenteral nutrition. Intravenous insulin should be administered to patients with persistent hyperglycaemia.

Muscle weakness can arise directly from the inflammatory, bioenergetic, and metabolic processes of sepsis, resulting in myopathy and/or peripheral neuropathy.[98] Muscle weakness is further compounded by nutritional deficiencies and autocannibalism, with the use of muscle protein by other organs and prolonged immobility, particularly in patients requiring long-term mechanical ventilation. Mobilisation and physical rehabilitation can accelerate recovery, shorten time in hospital, and confer long-term benefits for increased functional independence. However, early mobilisation has no impact on mortality.[99] Immobility combined with the pro-coagulopathic tendency of sepsis[100] puts patients at increased risk of deep vein thrombosis. Unless contraindicated, patients should receive thromboprophylaxis with subcutaneous low-molecular weight heparin.[101] Similarly, stress ulcer prophylaxis in patients who are mechanically ventilated reduces the risk of gastrointestinal bleeding.[102]

Special populations

Patients who are immunosuppressed

Immunosuppressive therapies for malignancy, autoimmune diseases, and solid-organ and stem-cell transplantations have improved quality and quantity of life at the expense of increased susceptibility to opportunistic, community-acquired and hospital-acquired infections that can evolve into sepsis.[103] Notably, despite the increased risk, not all immunocompromised conditions are associated with worse sepsis survival; patients with suspected sepsis who received a solid-organ transplant have higher survival rates than other patient populations of equivalent illness severity, including patients who were previously immunocompetent.[104,105]

Diagnosing sepsis in this population is challenging as immunosuppressive agents can impair the typical host response to infection, resulting in, for example, the lack of fever.[103,104] An absence of inflammatory signs and symptoms can hinder patient recognition of a severe infection and clinician awareness of evolving sepsis. The resulting delay to delivery of antimicrobials and supportive care interventions can impact survival. The threshold to suspect sepsis and initiate appropriate treatment should be low to truncate sepsis evolution and improve outcomes. Non-bacterial causes of sepsis—for example, fungal infections and endemic mycoses, such as *Candida* spp and histoplasmosis—should be considered. The reactivation of viruses, such as cytomegalovirus and herpes simplex virus, which occur in ICU patients who are both immunocompetent and immunocompromised, is less common. These viruses are associated with worse survival outcomes—whether reactivation is simply a disease severity marker or has a causal effect, thus requiring treatment, is unclear.

Neonates and children

Most sepsis cases and related deaths affect the young and the old. In 2017, the estimated 20·3 million sepsis cases in children under 5 years of age (with 2·9 million deaths) make up 41·5% of all incident cases.[8,106] The high incidence in young children is mainly driven by an absence of protective adaptive immunity that develops via exposure to infection or immunisation.[107] Vaccination against multiple viral and bacterial pathogens during early childhood is highly effective in decreasing the incidence of sepsis.

Neonates are particularly susceptible to life-threatening infections.[108] Worldwide, perinatal infections (mostly bacterial) and prematurity encompass almost half of all deaths in young children, with most occurring in low-resource countries. The 2024 definition of paediatric sepsis[3] is similar to the adult sepsis definition, but no consensus definition for neonatal sepsis exists, hindering understanding and study design. Diagnosing neonatal sepsis is challenging due to non-specific presenting signs, an inability to communicate symptoms, and low blood volumes that decrease culture sensitivity. Even in highly resourced countries, early onset sepsis affects 1 in 1000 newborns, mainly caused by *Escherichia coli* and *Streptococcus agalactiae* (group B streptococcus), and disproportionately burdening those born prematurely.

Optimising and identifying interventions that effectively prevent neonatal sepsis is a global imperative.

Obstetric patients

WHO defines obstetric sepsis as a life-threatening condition characterised as "organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or postpartum period for up to 42 days following the end of a pregnancy."[109] The global cumulative incidence of maternal sepsis is 13·2 per 10 000 pregnancies, ranging from 6·3 per 10 000 in the Americas to 129·2 per 10 000 in Africa.[110] Risk factors include an age of 35 years or more, multiparity, diabetes, pre-eclampsia or eclampsia, hypertension, obesity, and caesarean delivery. A 2025 WHO systematic review identified 252 972 deaths from maternal sepsis (6·6% of all maternal deaths), two-thirds of which occurred postpartum.[111]

Diagnosing sepsis during pregnancy is challenging as physiological, biochemical, and immunological changes, as well as efforts during labour, can obscure clinical signs.[112] Pregnancy-adjusted sepsis screening tools only did better than non-pregnancy-adjusted tools after 20 weeks gestation until 3 days postpartum, and high false-positive rates were reported throughout.[113] The main pregnancy-related sources are chorioamnionitis, endometritis, abortion due to sepsis, and mastitis; however, non-pregnancy-related infections should be considered—for example, wound infection, pyelonephritis, and pneumonia. As few prospective studies exist, management guidelines are largely derived from evidence drawn from the general adult population.

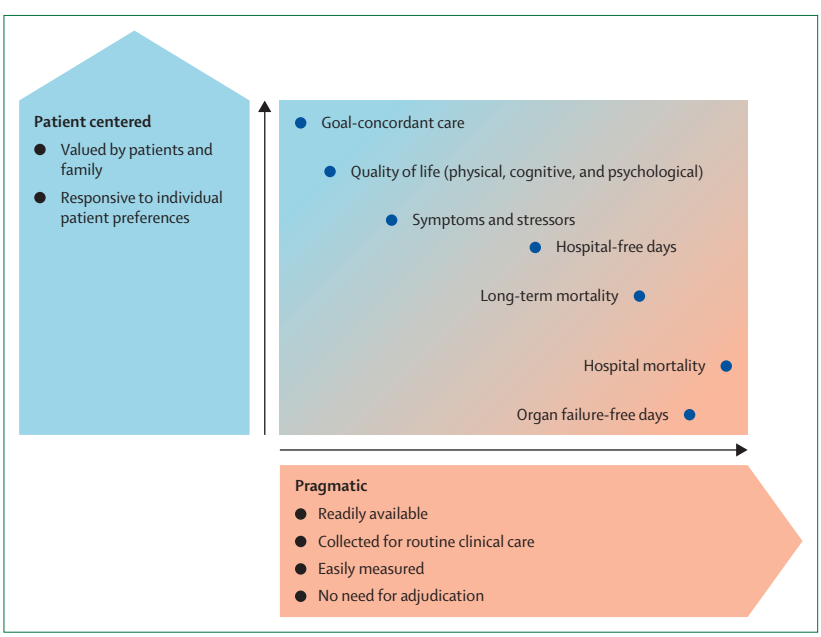

Figure 7: **Patient-centred versus pragmatic outcomes**
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Recovery

Recovery from sepsis implies a resolution of both the inciting infection, which generally occurs within the first days of onset, and the related organ dysfunctions. The acute recovery phase is often measured objectively as short-term mortality, collected at hospital discharge, or collected within 30 days of admission to hospital. Although mortality is an obviously important outcome, it is not necessarily superior to other more patient-centred outcomes that capture the consequences of sepsis, such as persisting organ dysfunction and impaired quality of life (figure 7).[114–120] Approximately half of patients with sepsis who survive to leave hospital make a complete or near-complete recovery, one in six have severe, persistent physical disability or cognitive impairment, and one in three die within a year, half of which are directly related to sepsis complications.[116]

The long-term physical, cognitive, and psychological consequences of critical illness are collectively described as postintensive care syndrome.[114,115] However, these complications are not restricted to intensive care survivors, as shown by long COVID. Underlying mechanisms are not fully understood, but involve environmentally induced epigenetic changes, such as altered DNA methylation and telomere shortening that occur early during the intensive care stay and are detectable years later.[121–123] Some of these changes are attributable to treatments given while in hospital and are thus potentially modifiable.

Future prospects

Sepsis is a complex syndrome. As understanding continues to evolve, both definitions and management guidelines will be updated. Important imperatives and encouraging developments will arise in the years ahead. These include the need for an increasing emphasis on prevention and early intervention, tailoring evidence-based management to different health-care systems, including resource-limited settings,[123,124] aftercare in survivors, an increasing role of artificial intelligence (AI) in patient management, accessibility to affordable molecular biomarkers to accelerate accurate diagnosis, and identifying tools to guide personalised interventions that can either halt the progression of sepsis or promote recovery.

Most sepsis develops in the community, yet care only begins in the hospital. Better prevention in the community could dramatically reduce the burden of sepsis. A roadmap for the launch of such efforts in sepsis was described in 2025,[125] laying out some complementary strategies, such as boosting vaccination rates, raising awareness, implementing improved screening in outpatient settings, and targeted monitoring of high-risk groups.

The agenda for resuscitation and early management should switch from trials attempting to fine-tune how to resuscitate to an implementation science platform

addressing the question: how can evidence-based resuscitation be delivered promptly to everyone? Given that initial care is inadequate or delayed for many patients, establishing what strategies best help health systems to ensure prompt care for all patients would likely yield much larger benefits than further trials addressing questions such as the choice of fluid or vasopressor during initial resuscitation. Barriers to prompt resuscitation for all patients are numerous, complex, and variable—ascertaining what solutions work most efficiently in specific settings would be a major advance. In particular, this advance applies to resource-poor settings, where research capacity and collaboration should be enhanced.

As mentioned previously, sepsis is an extraordinarily heterogeneous syndrome that is difficult to clearly differentiate from non-infectious inflammatory conditions, especially at the early stages of illness. Thus, considerable research efforts are being expended on identifying biomarkers for rapid, accurate detection of the sepsis-defining dysregulated host response, and the underlying pathogen and its antimicrobial susceptibility. The global diagnostic market is predicted to reach US$6·8 billion in 2029.[126] Within the scope of biomarker development, a further important requirement is the identification of patients who would qualify for a host response-modifying intervention to prevent deterioration or hasten recovery. This need is highlighted by the repeated failure of multiple clinical trials, when tested in unstratified populations, to reproduce the benefits seen in preclinical models. Biomarkers, such as gene transcripts, proteins, metabolites, and cell surface markers, can help to identify patients with systemic biological signatures—for example, hyperinflammatory—or to indicate specific upregulated or downregulated pathways.[127] These biomarkers could be used theragnostically to target patients responsive to a particular intervention (predictive enrichment) or avoid interventions in those likely to be harmed. Such therapies might be either new, previously tested, or repurposed, such as corticosteroids, immunostimulators, and monoclonal antibodies.[69,127,128] This approach can be facilitated by post-hoc analyses of existing biobanked materials from previous interventional trials or observational studies.

A further heterogeneity surrounds the highly variable involvement of different organs. Although growing evidence indicates the importance of tissue-bound host responses, clinical assessment still largely relies on blood biomarkers, with possible divergent responses in organs, such as the lungs.[129] An inflammatory injury could progress unrecognised by conventional blood chemistry, as witnessed by the beneficial effects obtained with anti-inflammatory interventions during COVID-19 in the absence of a serum cytokine storm.[130] This occurrence calls for novel diagnostic approaches, for example based on the exhalome of the patient.[131]

Finding interventions that hasten resolution of organ dysfunction after successful resuscitation would considerably reduce the cost and burden of sepsis. Nowadays, many patients are effectively resuscitated rapidly, such that cardiovascular instability and life-threatening hypoxaemia have largely resolved within the first 48–72 h. Patients then often face weeks of treatment in hospital, with ongoing organ dysfunction including, but not limited to, delirium and cognitive issues, muscle weakness, failure to wean from mechanical ventilation and/or renal replacement therapy, and immunosuppression with an increased risk of secondary infection. These conditions can extend well beyond hospital discharge. Current care focuses on supporting individualised recovery and preventing new complications. Recovery research is scarce, missing both foundational models and adequately nuanced clinical trials.

Although the onset of sepsis is widely regarded as an immunological occurrence, other mechanisms—for example, metabolic, bioenergetic, and disrupted neuroendocrine control—are more likely to cause delayed recovery.[22,132] Organ dysfunction has been conceptualised as a potentially reversible hibernation-like response.[133,134] Therapies that can regenerate functioning mitochondria and activate metabolism might be useful in this regard.[135,136] However, the application of organ repair or regeneration strategies will require a precision approach. As a useful lesson, non-targeted treatment with growth hormone to promote anabolism and enhance recovery from critical illness doubled the mortality in two parallel randomised controlled trials.[137]

Finally, the information available within high-dimensional, patient-derived datasets renders the rapidly evolving tools related to AI as intriguing options for unsupervised identification of biomarker patterns directly from electronic health-care records. This application holds particularly true for cohorts of patients usually excluded from randomised trials—eg, people with HIV or metastatic cancer.[75] Barriers ranging from non-reproducibility of signatures to regulatory hurdles in applying AI in the clinical context still exist.[138,139] However, the application of AI tools in caring for the critically ill is likely to offer breakthrough improvements in practical care and outcomes by early recognition, rapid initiation, and adherence to structured interventions.[139,140]

Contributors

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