REVIEW ARTICLE

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Sepsis and Septic Shock

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CME

Sepsis, a syndrome of life-threatening, acute organ dysfunction due to a dysregulated response to infection, is a major global health burden. Worldwide, an estimated 48.9 million cases of sepsis and 11 million related deaths occur annually.[1] In the United States, more than one third of in-hospital deaths are attributed to sepsis,[2] at costs exceeding $38 million in 2017, which makes sepsis both the most common cause of in-hospital death and the most expensive cause of hospitalization.[3]

Derived from the Greek word *sepo* (σηπω, translated as "I rot"), sepsis has been a leading cause of illness and death for millennia. According to the first modern definition, in 1992, sepsis was described as an overabundant inflammatory response to infection, recognized by the presence of the systemic inflammatory response syndrome (SIRS), which is defined as two or more abnormalities of temperature, heart rate, respiratory rate, or white-cell count.[4] Sepsis was subsequently reconceptualized as life-threatening acute organ dysfunction due to a dysregulated host response to infection[5] (Table 1). SIRS is no longer included in the definition of sepsis, since it may reflect a noninjurious host response, but recognition of the syndrome remains helpful for identifying infection.[5]

Global Epidemiology

Although sepsis is a global problem, the causes, incidence, and outcomes differ according to geographic region and age. Approximately 85% of cases and a disproportionate number of sepsis-related deaths occur in low- and middle-income countries,[1] with the highest age-standardized incidence in areas of greatest social vulnerability.[1] Sub-Saharan Africa is particularly affected, with 40% of cases worldwide.[9] The considerable diversity of the pathogens involved, including pathogens that cause malaria, typhoid, and dengue, as well as human immunodeficiency virus (HIV) and its interaction with tuberculosis, also places a strain on sub-Saharan Africa and other low- and middle-income countries.[1,9]

The most common sites of infection are pulmonary (accounting for 40 to 60% of cases), abdominal (15 to 30%), genitourinary (15 to 30%), bloodstream, and skin or soft tissue, with geographic variations.[10,11] A pathogen is identified in approximately 60 to 70% of cases,[10] and the percentage may increase as molecular testing for pathogen nucleic acids becomes more widespread.[12] The most common cause is gram-positive or gram-negative bacterial infection, followed by fungal or viral infection, although the incidence of viral sepsis can increase dramatically during pandemics.[10] In the United States, candida species are the third most common pathogen type cultured from blood, after gram-positive and gram-negative bacteria.[13]

Risk factors for candidemia include prolonged critical illness, candida colonization, indwelling catheters, mucositis, advanced liver disease, receipt of total parenteral nutrition, and immunocompromise. Other common causes of fungal sepsis

KEY POINTS

SEPSIS AND SEPTIC SHOCK

- Sepsis is a syndrome of life-threatening acute organ dysfunction due to bacterial, fungal, parasitic, or viral infection.
- Factors that affect the risk of sepsis include age, immune status, pathogen virulence, and pathogen burden.
- Sepsis is associated with long-term complications among survivors.
- Biologic features of sepsis include dysregulated inflammation, immunosuppression, and vascular injury.
- Management of sepsis focuses on prompt infection control and hemodynamic resuscitation.
- Research is ongoing to determine whether and how to modulate the host immune response in order to improve outcomes.

are endemic fungi and *Pneumocystis jirovecii*. Risk factors for these opportunistic pathogens include immunosuppression, prolonged neutropenia, environmental exposures, and chronic lung disease. Sepsis-inciting pathogens vary across the life span; both viral and diarrheal infections are more common in early childhood than later in life.[14] In a global point-prevalence study involving pediatric intensive care units (ICUs) in 26 countries, 21% of sepsis cases were attributed to viral infection.[15]

Sepsis can occur in patients of any age, but the incidence varies markedly across the life span (Fig. 1). The incidence worldwide is highest among children younger than 5 years of age, with the nadir beginning in middle childhood and adolescence, and an exponential increase occurs starting at approximately 60 years of age.[1] Of 11 million deaths from sepsis in 2017, 26% occurred in children younger than 5 years of age.[1] Immaturity of the immune system explains some of the excess risk in the neonatal and early childhood period, since immunocompromise increases the risk of sepsis and enhances the pathogenicity of opportunistic organisms. The incidence of sepsis is also high among persons with chronic conditions that impair immune function, particularly patients with cancer, severe immunodeficiency, or kidney disease requiring hemodialysis. More than 20% of hospitalizations for sepsis among U.S. adults occur in patients with cancer,[18] and the incidence of sepsis is increased by a factor of approximately 40 among patients receiving long-term hemodialysis.[19]

Evolving definitions and increasing recognition of sepsis have complicated the epidemiologic evaluation of the disorder.[20] The best available global data indicate that the incidence of sepsis and associated mortality decreased by approximately 35% and 50%, respectively, from 1990 to 2017.[1] In the United States, hospitalizations for sepsis have increased over the past two decades, but this increase appears to be largely explained by greater recognition and diagnostic coding of sepsis.[21] Studies based on clinical data suggest that the incidence and outcomes of sepsis are relatively stable over time in the United States.[22]

BIOLOGIC FEATURES

IMMUNE DYSREGULATION

The well-regulated molecular response to infection has not been defined, but the prevailing view is that sepsis is a dysregulated immune response resulting in organ dysfunction. Progression to sepsis is influenced by pathogen virulence and abundance, as well as host features, including innate immune activation, relative immunosuppression, and maladaptive tolerance mechanisms.[23,24] Many features of the expected inflammatory response — cytokine elaboration, excessive myelopoiesis, and generation of neutrophil–endothelial traps (NETs) — contribute to organ injury and perpetuate a disrupted immune homeostasis (Fig. 2).[25] (An expanded discussion of the biologic features of sepsis is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) Furthermore, molecular profiling has revealed multiple patterns of response in gene expression,[26,27] secreted proteins and metabolites,[28,29] and leukocyte populations[30,31] among patients. Specific high-risk molecular subphenotypes may have differential responses to certain therapies[28,32] and are the focus

Table 1. Sepsis Definitions over Time.*

Consensus Definition	Year	Conceptualization of Sepsis	Identification of Sepsis	Identification of Severe Sepsis	Identification of Septic Shock
Sepsis-1 definition: Bone et al.[4]	1992	Overwhelming inflammatory response to infection, as evidenced by SIRS	Infection plus two SIRS criteria as the result of infection: temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg (4.3 kPa), or white-cell count >12,000/mm^3 or <4000/mm^3 or >10% immature bands	Sepsis associated with organ dysfunction, hypoperfusion, or hypotension	Sepsis-induced hypotension (SBP <90 mm Hg or reduced from baseline by ≥40 mm Hg in the absence of other causes of hypotension) despite adequate fluid resuscitation, along with perfusion abnormalities that may include lactic acidosis, oliguria, and acute alteration in mental status
Sepsis-2 definition: Levy et al.[6]	2003	Overwhelming inflammatory response to infection, but the SIRS criterion is too narrow; the definition includes an expanded list of potential signs and symptoms of sepsis, reflecting bedside clinical experience	Infection plus two or more signs or symptoms of sepsis, including SIRS criteria, inflammatory markers (e.g., elevated C-reactive protein or procalcitonin), hemodynamic markers, organ-dysfunction markers, and tissue-perfusion markers	Sepsis complicated by organ dysfunction; unchanged from previous definition	Sepsis with acute circulatory failure characterized by persistent arterial hypotension (SBP <90 mm Hg, MAP <60 mm Hg, or SBP reduced from baseline by >40 mm Hg) despite adequate volume resuscitation and in the absence of other causes of shock
IPSCC definition: Goldstein et al.[7]	2005	Overwhelming inflammatory response to infection, as evidenced by SIRS	Infection plus two SIRS criteria resulting from infection; at least one SIRS criterion must be abnormal temperature or white-cell count	Sepsis with cardiovascular organ dysfunction, ARDS, or dysfunction of two or more other organs	Sepsis with cardiovascular dysfunction despite fluid administration of 40 ml/kg in 1 hour, defined as hypotension (<5th percentile or SBP <2 SD for age), need for vasoactive medication, or two or more of the following findings: unexplained metabolic acidosis, arterial lactate >2 times ULN, oliguria, prolonged capillary refill, or core-to-peripheral temperature gap
Sepsis-3 definition: Singer et al.[5]	2016	Dysregulated host response to infection, resulting in acute organ dysfunction; SIRS may reflect a normal, noninjurious response to infection; although SIRS may be helpful for identifying infection, it is no longer included in the definition of sepsis	Infection plus life-threatening, infection-related acute organ dysfunction; life-threatening, acute organ dysfunction may be identified by an increase from baseline of ≥2 points in Sequential Organ Failure Assessment score	Severe sepsis is no longer identified as a separate entity; acute organ dysfunction is required for sepsis	Sepsis plus hypoperfusion, identified by hypotension requiring vasopressor support to maintain MAP ≥65 mm Hg and serum lactate level ≥2.0 mmol/liter after adequate fluid resuscitation
Phoenix definition: Schlapbach et al.[8]	2024	Dysregulated host response to infection, resulting in acute organ dysfunction	Life-threatening organ dysfunction with suspected or confirmed infection, defined as a Phoenix Sepsis Score of ≥2; organ dysfunction may include respiratory, cardiovascular, coagulation, and neurologic systems	Severe sepsis is no longer identified as a separate entity; acute organ dysfunction is required for sepsis	Sepsis with cardiovascular organ dysfunction as indicated by severe hypotension for age; venous or arterial blood lactate level >5 mmol/liter (>45.05 mg/dl), or need for vasoactive medication

* The Sepsis-1, Sepsis-2, and Sepsis-3 definitions are for adult sepsis. The IPCC (International Pediatric Sepsis Consensus Conference) and Phoenix definitions are for pediatric sepsis. ARDS denotes acute respiratory distress syndrome, MAP mean arterial pressure, $PaCO_2$ partial pressure of carbon dioxide, SBP systolic blood pressure, SIRS systemic inflammatory response syndrome, and ULN upper limit of the normal range.

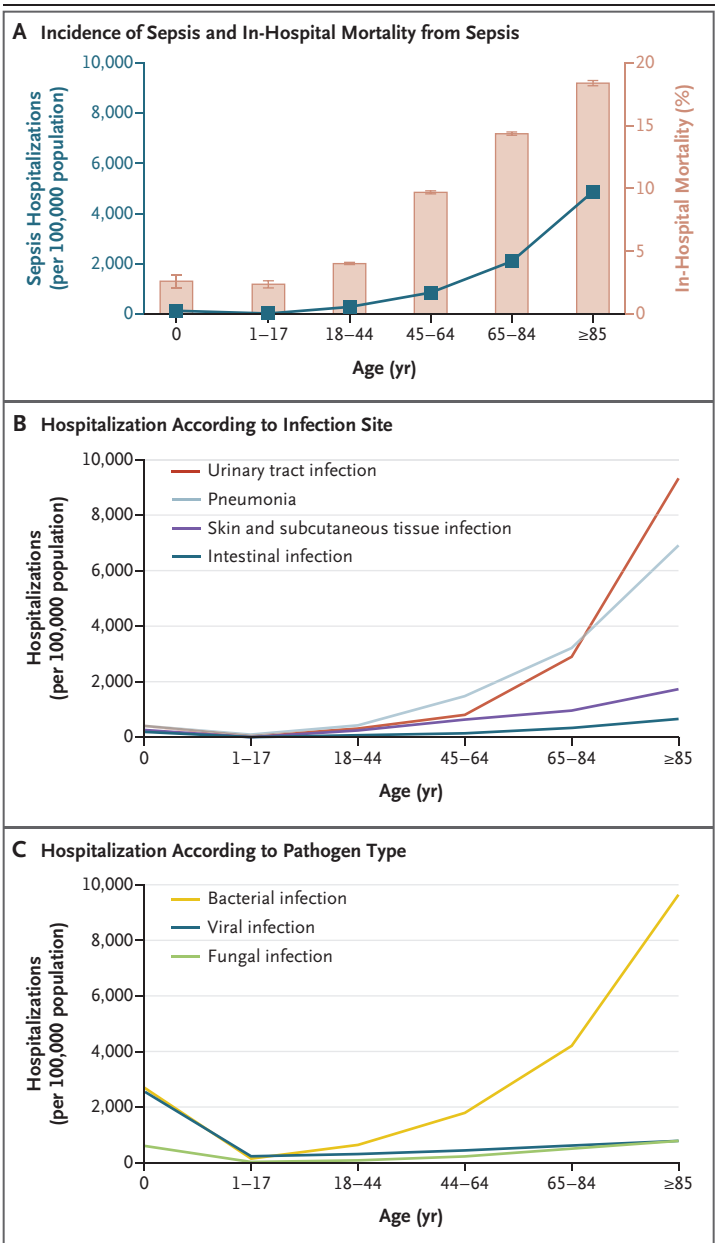

Figure 1. Epidemiologic Features of Sepsis in the United States According to Age Group.

All the data are from 2021 and were abstracted from the Nationwide Inpatient Sample with the use of HCUPnet (an online tool that uses data from the Healthcare Cost and Utilization Project) and grouped according to diagnosis with the use of categories from the Agency for Healthcare Research and Quality Clinical Classifications Software Refined (CCSR) categories.[16,17] I bars represent standard errors.

of clinical trials. Macrophage activation–like syndrome, a high-risk subtype, also has features of hyperinflammation and is under investigation in clinical trials.[33]

Along with excessive inflammation, patients with sepsis have suppression of innate and adaptive immune systems to varying degrees. Neutrophils, although more numerous, are relatively hypofunctional.[34] Peripheral-blood monocytes, which are major immune effector cells, have impaired cytokine secretion, a phenomenon termed endotoxin tolerance.[35] A specific subpopulation of monocytes, MS1 cells, is expanded during sepsis and augments immunosuppression.[31,36] Absolute lymphopenia (absolute lymphocyte count, <1000 per high-power field) is common during sepsis, and persistent lymphopenia is associated with an increased risk of death.[37] The reduced lymphocyte count is due to lymphocyte apoptosis[38] and reduced lymphopoiesis,[30] and expanded regulatory T cells suppress proliferation and effector functions of many other immune cells.[39]

Although concurrent hyperinflammation and immunosuppression during sepsis highlight the complexity of designing interventions to restore homeostasis, these seemingly opposing processes may be linked. Up-regulated immature neutrophils and MS1 cells stimulate ongoing myelopoiesis at the expense of typical hematopoiesis.[30,36] Early responses to pathogens and damage signals trigger a shift in energy production from oxidative phosphorylation to aerobic glycolysis.[40] With repeated cytokine stimulation, monocytes obtained from patients with sepsis are "immune paralyzed" and have deficient glycolysis, oxidative phosphorylation, and beta-oxidation.[40] These metabolic deficiencies are largely reversed in survivors of sepsis,[40] which suggests that metabolic failure prompted by the very high energy needs for early host defense may underlie sepsis-induced immunosuppression. Lymphocytes obtained from patients with sepsis often express markers of immune exhaustion,[41,42] which might be intrinsic to the specific T-cell population or reflect high T-cell activation.[43] Chronic stimulation of CD8+ T cells can produce exhausted, hypofunctional T cells, and studies have shown that dramatic T-cell activation in patients with sepsis is associated with an increased risk of death.[44,45]

DYSREGULATED VASCULATURE

The vasculature is a key site of injury in sepsis. The endothelium expresses abundant receptors for cytokines, chemokines, and damage signals

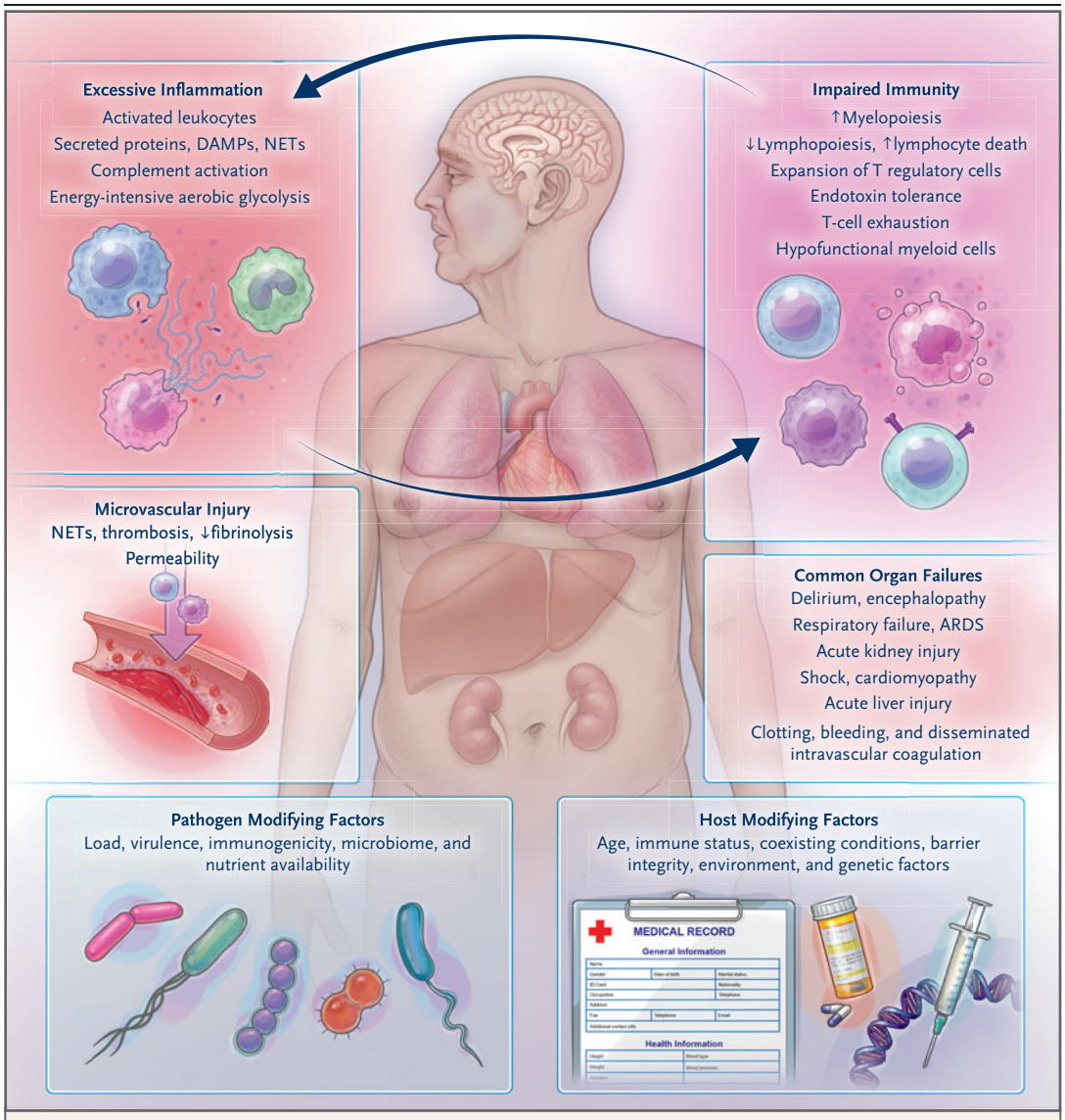

Figure 2. Pathobiology of Sepsis.

The pathobiology of sepsis is dominated by concurrent inflammation and hypofunctional immunity, with prominent microvascular injury. Activated neutrophils, macrophages, and cytotoxic T cells elaborate inflammatory and antimicrobial peptides and generate neutrophil–endothelial traps (NETs), which bind pathogens but further injure the endothelium. The bone marrow responds by generating more granulocytes — emergency myelopoiesis — at the expense of lymphopoiesis, and lymphocyte depletion is exacerbated by accelerated lymphocyte apoptosis. Neutrophils and macrophages have deficient cytokine production at the cellular level, and lymphocytes express markers for exhaustion. The vasculature is both permeable and activated, with a tendency toward increased thrombosis and reduced fibrinolysis. Host and pathogen factors dramatically influence the ways in which pathogens are introduced, detected, and responded to, as well as the resolution response. Given this variation in response, active research focuses on identifying features that best indicate a specific biologic dysregulation and that may thus predict a therapeutic response. The result of the pathobiologic process is organ injury and often multiorgan failure. ARDS denotes acute respiratory distress syndrome, and DAMP damage-associated molecular pattern.

and is thus primed to respond rapidly to pathogens and tissue injury. Although the vasculature is difficult to study — biopsies of blood vessels are rare — multiple defects have been identified. Vessels shed their glycocalyx, a protective barrier that insulates the endothelium from circulating

blood cells and platelets, resulting in a predisposition to NET formation and leukocyte and platelet adhesion.[46] Activation of the complement system is critical for the host defense,[47] yet exuberant complement activation incites substantial tissue damage and microvascular thrombosis.[48] In the healthy state, the permeability of the endothelial barrier is adjusted to recruit leukocytes and nutrients to the site of infection, but regulation of endothelial permeability is often lost during sepsis. Clinically, this vascular dysregulation is manifested as hypotension, third spacing of fluid (loss of intravascular fluid into the interstitium), and in rare cases, frank disseminated intravascular coagulopathy. Treatments to enhance vascular barrier function have increased survival in animal models of sepsis,[49] but data from clinical trials of these treatments are lacking. Several treatments that target both inflammation and vascular activation, including activated protein C and statins, have shown promise; however, signals that the treatment response is heterogeneous across patient subgroups have often been observed.[28,50]

CLINICAL PRESENTATION AND EVALUATION

The many combinations of infection site, pathogen, acute dysfunction of one or more organs, and baseline health status result in substantial heterogeneity of the clinical presentation. Patients often have general signs and symptoms of infection (e.g., fever or hypothermia and malaise) and symptoms that are specific to the site of infection (e.g., cough, dysuria, or erythema), as well as symptoms of acute organ dysfunction (e.g., confusion, oliguria, or dyspnea). However, timely recognition of sepsis can be challenging because the manifestations are heterogeneous, evolve over time, and may be subtle early in the disease process. Furthermore, common signs and symptoms are not specific to sepsis and may be masked by medications (e.g., beta-blockers or antipyretic agents).

Sepsis should be considered in all patients presenting with severe infection or acute organ dysfunction that is not clearly attributable to a noninfectious cause. For patients presenting with infection, clinicians should look for clinical and laboratory evidence of acute organ dysfunction. Altered mentation, hypotension, and tachypnea are particularly suggestive of sepsis among patients with infection, although the absence of these signs does not rule out sepsis.[5] Common laboratory findings that are characteristic of sepsis include leukocytosis or leukopenia, more than 10% immature granulocytes, hyperglycemia, and elevated levels of creatinine and lactate. Even in the absence of fever or localizing signs of infection, sepsis should be considered in patients with altered mentation, hypotension, dyspnea, and acute decompensation of chronic disease, such as diabetic ketoacidosis or decompensated cirrhosis.

The clinical evaluation focuses on confirming the site and cause of infection, as well as evaluating organ function and perfusion. Common testing to evaluate infection includes radiologic studies, microbial culture, antigen testing (e.g., tests for streptococcal and legionella antigen), and multiplex polymerase-chain-reaction pathogen-detection panels, depending on the suspected site. Three molecular diagnostic tests that determine the likelihood of sepsis are commercially available in the United States, but they have not yet been incorporated into routine practice. Lactate measurement is recommended in all patients to look for occult hypoperfusion.

MANAGEMENT

Management of sepsis focuses on infection control, restoration of perfusion, and organ support (Table S1 in the Supplementary Appendix). Restoration of immune homeostasis is also a goal but is the focus of ongoing research rather than a component of current clinical management. In this section, we focus on general treatment principles for infection control and resuscitation and highlight areas of ongoing research.

INFECTION CONTROL

Treatment of infection includes antimicrobial therapy, which is indicated for all bacterial and fungal infections and for many parasitic and viral infections causing sepsis, and procedural source control, which is indicated in some situations. The initial antimicrobial therapy is often empirical, since the causative pathogen is rarely known at the start of treatment. Prompt initiation of antimicrobial therapy is warranted because observational studies have indicated that mortality increases with delays in treatment administration,

particularly among patients with shock.[51] The empirical antimicrobial regimen should cover the most likely pathogens on the basis of the suspected site (or sites) of infection, local epidemiologic factors, and risk factors for atypical or resistant organisms. Knowledge of the local epidemiologic profiles of pathogens, including antimicrobial resistance profiles, is helpful in selecting the initial therapy.

In addition, clinicians should consider each patient's risk profile, including pathogens and susceptibilities on previous cultures, conditions or treatments that may confer a predisposition to specific infections, a social history that may involve exposure to atypical pathogens, and signs, symptoms, and diagnostic data that may suggest the site or type of infection. Patients with previous antibiotic exposure and contact with the health care system have an increased risk of infection with resistant bacteria, so guidelines recommend broader initial coverage for such patients.[52,53] Conversely, coverage should be withheld for pathogens that are unlikely to be the cause of infection in order to avoid adverse effects associated with antibiotic use. For example, the use of antianaerobic antibiotics depletes healthy enteric gut microbiota, is associated with adverse clinical outcomes,[54,55] and can be avoided in many patients.[55]

As further diagnostic information becomes available, antimicrobial therapy should be narrowed to cover the identified pathogen (or pathogens) and remove coverage of resistant organisms that have not been identified. The duration of antimicrobial therapy should be tailored to the site and type of infection and further guided by the clinical response, with shorter courses favored over longer courses of therapy.[53]

Even with appropriate antimicrobial therapy, some infections require source control to improve the chance of a cure or minimize the risk of complications. Source control encompasses surgical and procedural interventions to remove the source of infection, reduce the pathogen burden, or correct anatomical derangements that impede normal clearance of infection. Common procedures for source control include removal of infected organs (e.g., appendectomy), removal of infected intravascular devices, relief of anatomical blockage proximal to the site of infection (e.g., biliary or genitourinary strictures), and drainage of abscesses or infected fluid collections. Like antimicrobial therapy, source control is time-sensitive, and delays are associated with increased mortality, particularly among patients in shock.[51,56] Since all interventions come with risks, consultation between critical care and procedural teams is important to determine the benefit and urgency of procedural source control.

RESTORATION OF ADEQUATE PERFUSION

For patients with hypotension or evidence of inadequate perfusion (e.g., elevated lactate levels), timely restoration of perfusion is critical and is the focus of several previous or ongoing clinical trials (Table 2). Intravenous crystalloid fluid is the first-line treatment to correct intravascular volume depletion and restore preload, although the approach to resuscitation has evolved over time (as discussed in the Supplementary Appendix).

Guidelines suggest 30 ml per kilogram of body weight as a reasonable initial fluid volume for most adult patients.[53] Fluid should be delivered in serial boluses (e.g., 250 to 1000 ml for adults), with close monitoring of the clinical response in patients who may have unacceptable side effects with a volume of 30 ml per kilogram. Prospective implementation of resuscitation bundles that involve a 30 ml per kilogram fluid bolus was reported to be associated with improved survival among patients with sepsis, including those with intermediate lactate values (2 to 4 mmol per liter), chronic kidney disease, or heart failure.[76]

Both underresuscitation and overresuscitation are associated with harm, with observational studies showing a U-shaped relationship between fluid volume and outcomes.[76,77] The harms of overresuscitation may be particularly prominent in settings with limited oxygen or ventilator availability.[78] However, results of trials that suggest harm from higher resuscitation volumes have generally used fluid volumes far exceeding 30 ml per kilogram.[64] For example, randomization to the resuscitation protocol in the Simplified Severe Sepsis Protocol 2 (SSSP-2) trial resulted in a median of 3.5 liters of fluid (≥70 ml per kilogram) being administered in the first 6 hours, as compared with 2.0 liters (≥50 ml per kilogram) in the usual care group, and was associated with increased mortality.[64] The use of balanced solutions, such as lactated Ringer's

Table 2. Landmark Sepsis Clinical Trials since 2015.*

Trial or Trials	Patients	Intervention and Control	Outcome	Interpretation and Lessons Learned
ARISE,[57] ProCESS,[58] and ProMISe[59]	ARISE: 1600 patients with septic shock at 51 sites in Australia and New Zealand ProCESS: 1341 patients with septic shock at 31 U.S. sites ProMISe: 1260 patients with septic shock at 56 U.K. sites	ARISE: EGDT vs. usual care ProCESS: EGDT vs. protocol-based "standard" therapy vs. usual care ProMISe: EGDT vs. usual care	ARISE: 90-day mortality, 18.6% vs. 18.8% (P=0.90) ProCESS: 60-day in-hospital mortality, 21.8% vs. 18.2% vs. 18.9% (P=0.83) ProMISe: 90-day mortality, 29.5% vs. 29.2% (P=0.90)	These trials showed that outcomes were similar with EGDT and usual care. Patients in these trials were less sick than those in the Rivers et al. trial (e.g., baseline $ScvO_2$ 70% vs. 49%).[60] However, there was no indication of benefit with EGDT across any subgroups examined in a meta-analysis of data from individual patients, including more severely ill patients.[61] Although these trials suggest that EGDT and usual care yield equivalent outcomes, EGDT is more labor-intensive, and standard care has evolved away from it.
ADRENAL and[62] APROCCHSS[63]	ADRENAL: 3800 patients with septic shock at 69 sites in Australia, United Kingdom, New Zealand, Saudi Arabia, and Denmark APROCCHSS: 1241 patients with multiorgan failure and septic shock at 34 sites in France	ADRENAL: hydrocortisone vs. placebo APROCCHSS: hydrocortisone plus fludrocortisone vs. placebo (and activated protein C vs. placebo)	ADRENAL: 90-day mortality, 27.9% vs. 28.8% (P=0.50) APROCCHSS: 90-day mortality, 43.0% vs. 49.1% (P=0.03)	Glucocorticoids were associated with reduced mortality in APROCCHSS but not in ADRENAL, although secondary outcomes in ADRENAL favored glucocorticoids. After these trials, guidelines were updated to include a weak recommendation to use glucocorticoids for persistent septic shock.[53] However, the benefit varies among patients, so treatment decisions should be individualized.
SSSP-2[64]	209 Patients with sepsis and hypotension at 1 site in Zambia	6-Hr sepsis bundle (administration of fluid boluses guided by JVP, vasopressors, and blood transfusion) vs. usual care	In-hospital mortality, 48.1% vs. 33.0% (P=0.03)	The sepsis bundle was associated with increased fluid delivery (median, 3.5 liters [≥70 ml/kg] vs. 2.0 liters [≥50 ml/kg] in the first 6 hr) and worse outcomes, underscoring the difficulty of translating sepsis management across settings and the need for further study of sepsis management in low- and middle-income countries.
PHANTASi[65]	2689 Patients with sepsis, identified in ambulance, at 34 sites in the Netherlands	Antibiotic administration before arrival at hospital vs. in hospital	28-Day mortality, 7.8% vs. 8.2%	In-ambulance antibiotic therapy yielded numerically but not significantly lower mortality. However, the difference of 0.4 percentage points is consistent with effect sizes in observational studies adjusted for less severely ill trial participants.

SMART[66,67] and BaSICS[68,69]	SMART: 15,802 patients (1641 with sepsis) at 1 U.S. site BaSICS: 10,520 patients (1987 with sepsis) at 75 sites in Brazil	SMART: balanced fluids vs. saline (0.9% sodium chloride) for IV fluid administration, with cluster randomization BaSICS: balanced fluids vs. saline (0.9% sodium chloride) for IV fluid administration	SMART: major adverse kidney event in overall trial population, 14.3% vs. 15.4% (P=0.04); 30-day in-hospital mortality among patients with sepsis, 26.3% vs. 31.2% (P=0.01) BaSICS: 90-day mortality, 26.4% vs. 27.2% (P=0.47); 92% probability of benefit among patients treated with balanced fluids before enrollment	These trials showed that resuscitation with balanced solutions is associated with better outcomes than resuscitation with normal saline, particularly among patients with sepsis and when used from the onset of resuscitation.
ANDROMEDA-SHOCK[70,71]	424 Patients with septic shock and lactate level ≥2.0 mmol/liter at 28 sites in Argentina, Chile, Colombia, Ecuador, and Uruguay	Capillary refill normalization vs. lactate normalization	28-Day mortality, 34.9% vs. 43.4% (P=0.06)	Capillary refill–guided resuscitation was associated with better outcomes than lactate normalization. In practice, both methods can be used.
65 trial[72]	2600 patients ≥65 yr of age with vasodilatory shock at 65 U.K. sites	Low MAP target (60–65 mm Hg) vs. usual care	Unadjusted 90-day mortality, 41.0% vs. 43.8% (P=0.15)	A lower MAP target was associated with numerically lower mortality, a finding that suggests that a vasopressor-sparing approach is safe in older adults.
FRESH[73]	124 Patients with septic shock at 13 U.S. and U.K. sites	Personalized resuscitation strategy based on change in stroke volume after passive leg raise vs. usual care	Renal-replacement therapy, 5.1% vs. 17.5% (P=0.04); invasive mechanical ventilation, 17.7% vs. 34.1% (P=0.04)	This trial showed the feasibility and potential benefit of a personalized resuscitation strategy. Larger trials powered for important clinical outcomes are needed.
CLASSIC[74] and CLOVERS[75]	CLASSIC: 1554 patients with septic shock at 31 sites in Europe CLOVERS: 1563 patients with sepsis-induced hypotension	CLASSIC: fluid-restrictive resuscitation vs. usual care CLOVERS: fluid-restrictive vs. fluid-liberal resuscitation	CLASSIC: 90-day mortality, 42.3% vs. 42.1% (P=0.46) CLOVERS: 90-day mortality, 14.0% vs. 14.9%; estimated difference, –0.9 percentage points; 95% CI, –4.4 to 2.6 (P=0.61)	Fluid-restrictive and fluid-liberal resuscitation yielded similar outcomes in the overall trial populations, which suggests that more personalized approaches may be needed. Nearly all patients received ≥30 ml of fluids per kilogram, so these trials provide no data on the safety of limiting resuscitation to <30 ml/kg.

* ADRENAL denotes Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock, APROCCHSS Activated Protein C and Corticosteroids for Human Septic Shock, ARISE Australasian Resuscitation in Sepsis Evaluation, BaSICS Balanced Solution versus Saline in Intensive Care Study, CLASSIC Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care, CLOVERS Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis, EGDT early goal-directed therapy, FRESH Fluid Response Evaluation in Sepsis Hypotension and Shock, IV intravenous, JVP jugular venous pressure, PHANTASi Prehospital Antibiotics Against Sepsis Trial, ProCESS Protocolized Care for Early Septic Shock, ProMISe Protocolised Management in Sepsis, $ScvO_2$ central venous oxygen saturation, SMART Isotonic Solutions and Major Adverse Renal Events Trial, and SSSP-2 Simplified Severe Sepsis Protocol 2.

solution, are preferred over 0.9% normal saline in patients with sepsis, on the basis of accruing evidence of reduced mortality,[66,79] particularly when the solution is used for the entirety of resuscitation.[68]

For patients with ongoing hypotension and volume depletion after initial resuscitation, "fluid-liberal" and "fluid-restrictive" approaches to ongoing resuscitation have yielded similar outcomes (Table 2).[74,75] Personalized approaches to resuscitation that are based on dynamic physiological measures may be more effective than either a fluid-liberal or fluid-restrictive approach. Fluid responsiveness can be assessed on the basis of a change in stroke volume with a small fluid bolus (e.g., 4 ml per kilogram[80]) or a passive leg-raise maneuver,[81] which causes an "auto-bolus" by increasing blood return to the right ventricle. In a multicenter, randomized trial involving 124 patients with septic shock, patients who were assigned to receive fluid and vasopressor adjustment on the basis of a change in stroke volume (measured by a noninvasive cardiac output monitor) were less likely than patients assigned to usual care to require renal replacement therapy (5% vs. 17%, P=0.04) and invasive mechanical ventilation (18% vs. 34%, P=0.04), findings that support physiologically tailored resuscitation.[73] However, larger trials powered for important clinical outcomes are needed.

For patients with severe or persistent hypotension despite initial fluid administration, intravenous vasopressor therapy is warranted. Norepinephrine, the first-line vasopressor,[53] can be administered by means of central intravenous access or with the use of a high-quality peripheral intravenous catheter, with regular monitoring for extravasation.[82] Guidelines recommend targeting an initial mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets.[53] However, the 65 Trial suggests that a lower target of 60 to 65 mm Hg may be safe in some patients.[72] In this trial, which involved 2600 patients with vasodilatory shock who were 65 years of age or older, randomization to permissive hypotension (MAP target, 60 to 65 mm Hg) resulted in less use of vasopressor therapy and lower adjusted mortality at 90 days than usual care (adjusted odds ratio, 0.82; 95% confidence interval [CI], 0.68 to 0.98).[72]

Beyond MAP, the lactate level and capillary refill time provide additional information to guide resuscitation and vasopressor dosing. A meta-analysis of four small trials showed that targeting resuscitation to a reduction in the serum lactate level, in addition to MAP targets, was associated with decreased mortality.[83] In the ANDROMEDA-SHOCK trial, 424 patients with septic shock were randomly assigned to undergo capillary refill–guided resuscitation or lactate-guided resuscitation. Patients for whom the assigned resuscitation approach failed despite a MAP of 65 mm Hg or higher received additional fluids, higher MAP targets, and ionotropes.[70] The patients assigned to undergo capillary refill–guided resuscitation had numerically lower mortality than patients assigned to lactate-guided resuscitation (34.9% vs. 43.4%; P=0.06), and a Bayesian reanalysis showed more than a 90% probability of lower mortality with capillary refill–guided resuscitation across multiple assumed probability distributions.[71] For patients with a worsening clinical trajectory despite treatment with antimicrobial agents, fluids, and vasopressors, it is important to reconsider infection control and to determine whether broader antimicrobial agents, imaging studies to better define the site of infection, or source-control interventions are warranted.

For patients receiving ongoing vasopressor support, adjunctive "stress dose" glucocorticoids (hydrocortisone at a dose of 200 mg per day with or without fludrocortisone) should be considered. Meta-analyses have reached conflicting conclusions regarding a reduction in mortality but consistently show reductions in the duration of shock, mechanical ventilation, and ICU stay with adjunctive glucocorticoids.[84,85] A recent observational target trial emulation showed that the addition of fludrocortisone to hydrocortisone was superior to hydrocortisone alone (adjusted difference in mortality, −3.7 percentage points; 95% CI, −4.2 to −3.1; P<0.001), without a signal for harm, and the combination was associated with lower all-cause mortality than with hydrocortisone alone in a Bayesian network meta-analysis.[86,87] Although stress-dose glucocorticoids are beneficial in the average patient, the benefit varies among patients, so clinicians should weigh the severity of shock against the risk of glucocorticoid-associated adverse events when deciding whether to initiate and continue treatment with stress-dose glucocorticoids.[88] For patients with escalating norepinephrine requirements, the

addition of vasopressin — a noncatecholamine vasopressor — is recommended to spare catecholamine exposure. The dosage threshold for adding vasopressin is unclear and is currently being assessed in a multicenter trial (ClinicalTrials.gov number, NCT06217562).

RECOVERY AND LONG-TERM OUTCOMES

In addition to being an acutely life-threatening disorder, sepsis contributes to the development of other conditions, including cognitive impairment, functional impairment, and new or worsening chronic health conditions.[89] Among older adults, hospitalization with sepsis is associated with the development of new functional limitations (e.g., an inability to bathe or dress independently) and a large increase in the prevalence of moderate-to-severe cognitive impairment (6.1% before hospitalization vs. 16.7% after hospitalization).[90] Long-term complications are also common after pediatric sepsis. In a prospective cohort of 389 children with septic shock, 35% of surviving children had not regained their baseline health-related quality of life 1 year later.[91]

As a result of long-term health impairment, many patients who were employed before sepsis are unable to return to work. In a study involving 12,260 sepsis survivors in Norway who had worked before they were hospitalized for sepsis between 2010 and 2021, 40% had not returned to work at 6 months.[92]

Beyond the health impairments that develop during hospitalization for sepsis, patients are at increased risk for further health deterioration, hospital readmission, and death in the months to years after the resolution of sepsis, outcomes that are not fully explained by age or preexisting conditions.[89,93] A longitudinal study of sepsis survivors showed persistent activation of inflammatory and immunosuppressive markers in two thirds of the study participants, which was associated with increased all-cause mortality,[94] a finding that suggests that failure of the immune system to return to homeostasis may drive the risk of recurrent infection or progression of chronic conditions. Targeted therapies to enhance recovery from sepsis are lacking, but multicomponent interventions with primary care follow-up and proactive symptom assessment have been associated with improved survival.[95]

AREAS OF CONTROVERSY OR UNCERTAINTY AND FUTURE RESEARCH

DIAGNOSIS

Sepsis is recognized as a syndrome of acute organ dysfunction due to a dysregulated host response to infection. However, we lack a precise definition of the dysregulated host response and a diagnostic test to confirm its presence. Moreover, we have limited ability to confirm or characterize infection in real time. Up to one third of patients who have been treated for presumed bacterial sepsis had a noninfectious illness in hindsight.[96] Even among patients with sepsis, the cause of the infection is not determined in up to one third of cases.[10] Both protein-based and transcriptome-based tools have received U.S. and European approval for predicting the risk of sepsis, although whether their use changes outcomes is not yet known. As new tools are introduced,[97] their implementation in the clinical workflow and their effect on patient-centered outcomes should be tested.

SUBTYPES OF SEPSIS

The heterogeneity of sepsis has long been cited as an impediment to translation of preclinical studies and identification of targeted therapies.[98,99] Over the past decade, several studies have identified and described new subtypes of pediatric and adult sepsis, including subtypes based on gene expression in blood leukocytes[26,27]; clinical data, including pathogens[100,101]; and plasma biomarkers.[28] Furthermore, in several post hoc applications of these classifications to clinical trial data, qualitative differences in the treatment response have been identified.[32,100] Work is ongoing to translate these discoveries into improved management at the bedside.[102,103]

HETEROGENEITY OF TREATMENT EFFECT

Clinical trials yield an average treatment effect, which may poorly reflect the expected treatment effect for an individual patient with sepsis, given the broad heterogeneity of the disorder. There is strong interest in predicting treatment effects in individual patients in order to improve bedside management. In a post hoc analysis of clinical trial data that used machine learning to estimate individual treatment effects, there was marked variation in the benefit of glucocorticoids for septic

shock.[104] Prospective trials are needed to test clinical decision-making support in order to guide management based on individual treatment effects.

TARGETED TREATMENT

The management of sepsis focuses on antimicrobial agents, source control, resuscitation, and support for organ failure. Targeted therapies to address specific forms of host dysregulation, including vascular permeability, are lacking. Several pharmacologic agents and devices are being studied, and efforts are under way to identify and characterize host response traits in a clinically actionable time frame.

SEPSIS IN LOW- AND MIDDLE-INCOME COUNTRIES

Although low- and middle-income countries have a disproportionately high share of sepsis cases and deaths,[1] most clinical trials have been performed in high-income countries. It is risky to extrapolate findings across settings, given the substantial geographic variation in pathogens, chronic conditions, and health care resources.[78] A major opportunity to improve global sepsis outcomes is to enhance the health care infrastructure and research in areas that have the highest burden of sepsis.

CONCLUSIONS

Sepsis, defined as life-threatening acute organ dysfunction due to a dysregulated host response to infection, is a leading cause of illness and death worldwide. Tremendous variety in the infection site, causative pathogen, and the organs in which acute dysfunction occurs complicates both the recognition of sepsis and the identification of targeted therapies. Dysregulation of the host immune response is key to the pathogenesis of sepsis, but the current treatment approach focuses on the management of infection and restoration of perfusion. Research is ongoing to identify actionable subtypes of sepsis and develop targeted therapy for host dysregulation.

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