SEPSIS

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Sepsis can be caused by various types of infections, including bacterial, viral, fungal, or parasitic and can affect people of all ages.

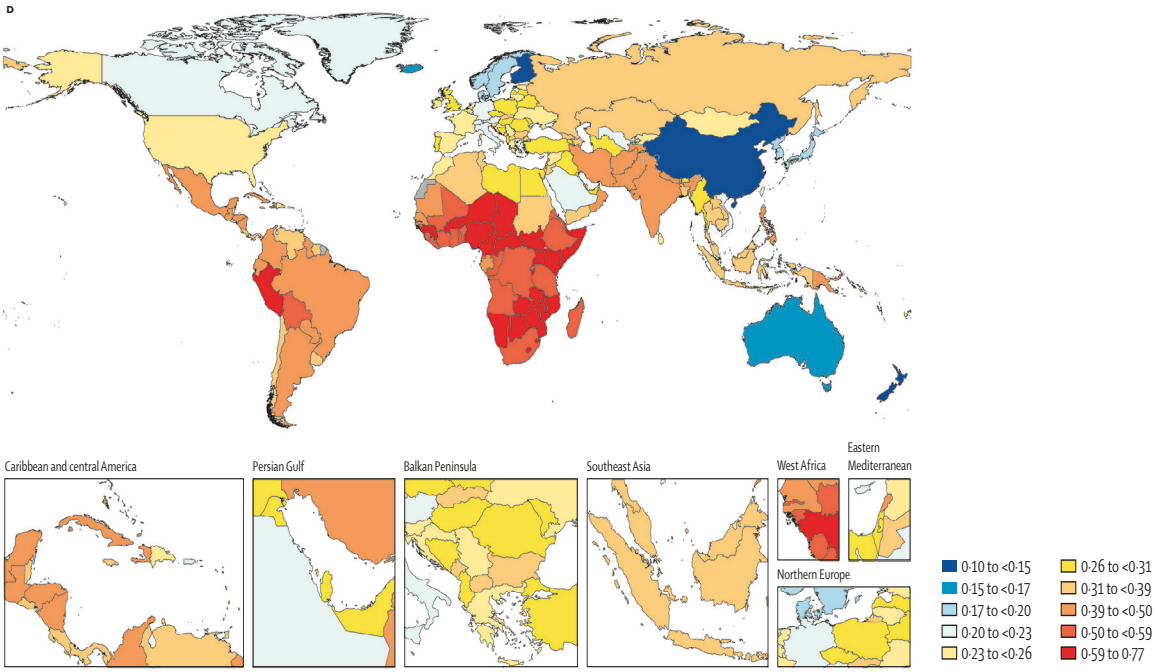
Septic shock is a subset of sepsis, characterized by a critical reduction in tissue perfusion, where acute failure of multiple organs (such as lungs, kidneys, etc.) can occur. Septic shock is associated with a higher risk of mortality compared to sepsis alone.

BURDEN AND EPIDEMIOLOGY

- **Burden of sepsis:** In 2017 there were 48.9 million cases and 11 million sepsis-related deaths worldwide, which accounted for almost 20% of all global deaths. Almost half of all global sepsis cases occurred among children, with an estimated 20 million cases and 2.9 million global deaths in children under 5 years of age.[2]
- **Economic burden:** Sepsis places a significant economic burden. For instance, the average hospital stay costs for a patient with sepsis in France were estimated to be €11,400.[3] And sepsis estimated to account for 5.2% of the total cost of U.S. hospital care in 2011.[4]
- **Mortality rate:** Sepsis is associated with a high mortality rate, especially in severe cases. Mortality rates can range from 10% in mild cases to over 40% in cases of septic shock.[5] Early recognition and appropriate treatment are essential for improving outcomes.
- **Global impact:** Sepsis has a substantial global impact, with varying rates in different regions. Low- and middle-income countries may face unique challenges in sepsis diagnosis and management due to limited resources. Approximately 85% of sepsis cases and sepsis-related deaths worldwide occurred in low- and middle-income countries.[2]

Figure 1: Sepsis fraction of all-case deaths, all ages, by country, in 2021

Reproduced from: GBD 2021 Global Sepsis Collaborators. Global, regional, and national sepsis incidence and mortality, 1990–2021: a systematic analysis. Lancet Glob Health. 2025 Dec;13(12):e2013–e2026.



CLINICAL PRESENTATION

SIGNS AND SYMPTOMS OF SEPSIS

- Shivering, fever, or very cold
- Extreme pain or discomfort
- Clammy or sweaty skin
- Confusion or disorientation
- Shortness of breath
- Increased heart rate

PATHOPHYSIOLOGY OF SEPSIS [6]

- Sepsis is characterized by an overwhelming release of inflammatory mediators, in response to an infection.
- During the immune response to infection, the body's defenses recruit and activate, circulating immune cells such as NK cells, dendritic cells, platelets, monocytes and eosinophils, at the site of infection. The Pathogen Recognition Receptors (PRRs) on the surface of these cells can detect Pathogen-Associated or Damage-Associated Molecular Patterns (PAMPs or DAMPs) on the surface of the pathogen. This interaction initiates intracellular signaling and an immuno-inflammatory cascade, including cytokine release, that may lead to a "**cytokine storm**".
- Additionally, a compensatory anti-inflammatory response can become dysregulated, leading to an imbalance between pro- and anti-inflammatory processes and the development of an **immunosuppression** that may contribute to **organ damage**.

CAUSES OF SEPSIS

Figure 2: Global sepsis-related deaths co-occurring with infectious and non-infectious underlying causes, for all ages and by age group, 1990-2021

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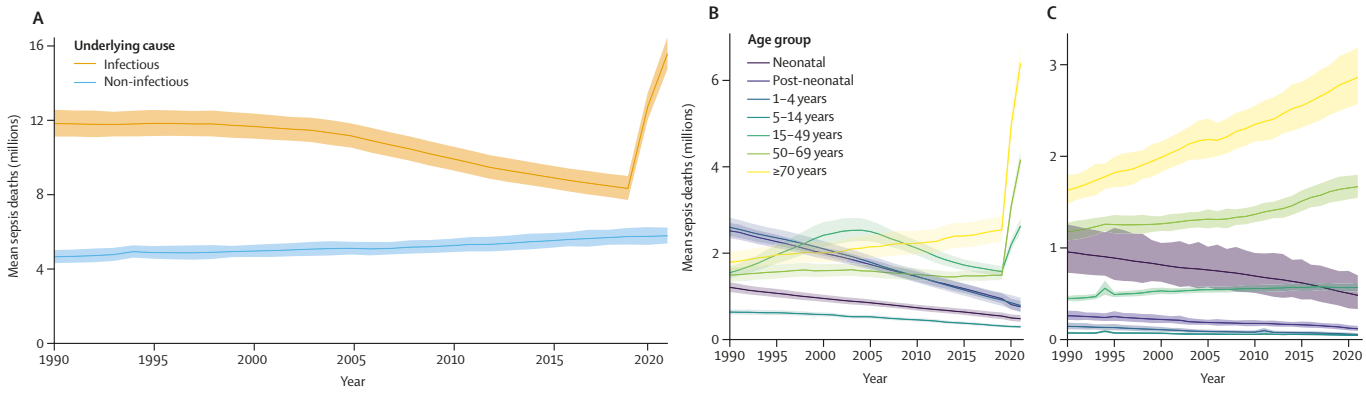
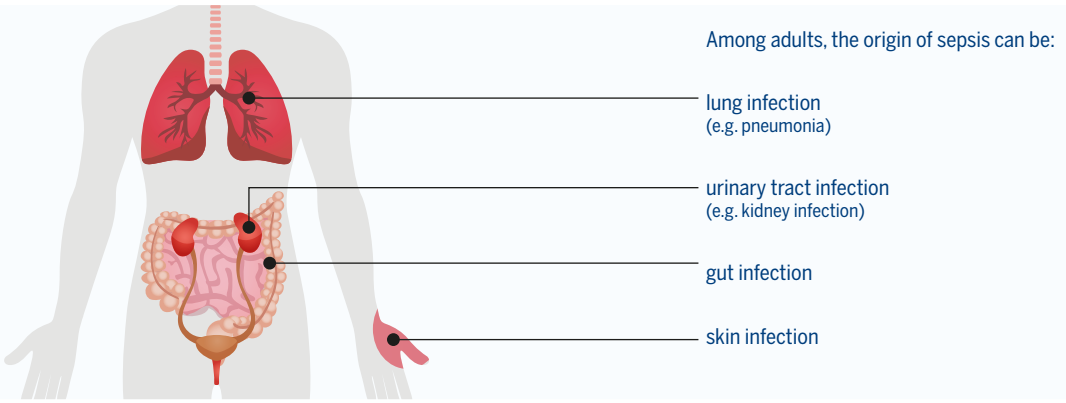


(A)Global sepsis-related deaths for all ages by infectious or non-infectious underlying cause. (B) Global sepsis-related deaths co-occurring with infectious causes by age group. (C) Global sepsis-related deaths co-occurring with non-infectious underlying causes by age group. Shaded areas indicate 95% uncertainty intervals. Neonatal=0–27 days. Post-neonatal=28–364 days.

Among bloodstream infections, the most frequent pathogens causing sepsis worldwide are ***Staphylococcus aureus*** and ***Escherichia coli*** [7][8]

Bacterial infection is the primary cause of sepsis.

Figure 3. Common infections can lead to sepsis [9]



Alongside common infections, bloodstream infection (BSI) is a distinct entity, frequently associated with sepsis and capable of progressing to septic shock.

Table 1. Pathogens that are consistently associated with high prevalence across cohorts in bloodstream infections

Reproduced with permission from: Holmes CL et al. Bloodstream infections mechanisms of pathogenesis and opportunities for intervention. Nat Rev Microbiol. 2025 Apr;23(4):210 224.

Pathogen	Frequency (%) [a]	Crude mortality (%) [a]	Common initial sites	Associated clinical syndromes	Preferred antimicrobial therapy [b]
Escherichia coli	5.6–26.9	12.1–22.4	Urinary tract, gut	Pyelonephritis, cholangitis, intra-abdominal abscess, CLABSI	β-Lactams (carbapenems if extended-spectrum β-lactamases present), fluoroquinolones, trimethoprim-sulfamethoxazole
Staphylococcus aureus	15.4–20.7	22.8–31.0	Skin, nares, indwelling device	CLABSI, endocarditis, vascular graft infection, skin and soft tissue infection	First-generation cephalosporins, antistaphylococcal penicillins, vancomycin, linezolid, daptomycin, ceftaroline
Coagulase-negative *Staphylococcus*	9.2–31.3	19.7–20.7	Skin, indwelling device	CLABSI, prosthetic valve endocarditis, vascular graft infection	First-generation cephalosporins, antistaphylococcal penicillins, vancomycin
Klebsiella species	4.8–13.2	17.6–34.7	Lungs, gut, urinary tract	Pyelonephritis, cholangitis, intra-abdominal abscess, CLABSI, pneumonia	β-Lactams (carbapenems if extended-spectrum β-lactamases present), fluoroquinolones, trimethoprim-sulfamethoxazole
Candida species	2.6–9.0	32.0–39.2	Skin, indwelling device, gut	CLABSI, intra-abdominal abscess, endocarditis	Echinocandins (azoles for step-down therapy)
Pseudomonas aeruginosa	3.4–8.9	24.7–48.9	Lung, indwelling device	Pneumonia, CLABSI	Variable (piperacillin-tazobactam, cefepime, carbapenems, ceftazidime-avibactam, ceftolozane-tazobactam, cefiderocol, plazomicin, fluoroquinolones)
Enterococcus species	2.8–9.4	23.6–49.5	Gut, urinary tract	Cholangitis, intra-abdominal abscess, CLABSI, endocarditis	Ampicillin (linezolid or daptomycin if ampicillin/vancomycin resistant)
Acinetobacter baumannii	1.3–12.5	34.0–52.1	Skin, indwelling device, lungs	Pneumonia, CLABSI	Variable (ampicillin-sulbactam, piperacillin-tazobactam, cefepime, carbapenems, cefiderocol, plazomicin, eravacycline, tetracyclines)
Enterobacter species	2.6–6.1	19.8–30.2	Gut	Pyelonephritis, cholangitis, intra-abdominal abscess, CLABSI	β-Lactams (cefepime or carbapenems if Enterobacter cloacae), fluoroquinolones, trimethoprim-sulfamethoxazole
Citrobacter species	~1.7%	Not available	Gut	Cholangitis, intra-abdominal abscess	β-Lactams (cefepime or carbapenems if Citrobacter koseri has been identified), fluoroquinolones, trimethoprim-sulfamethoxazole

CLABSI, central line-associated bloodstream infection.
[a] Data represent ranges for selected studies, when available. The selected studies included cohorts with nosocomial infections only or infections from multiple sources, including community, health care-associated and nosocomial origin.
[b] Preferred therapy may vary by region based on epidemiology and practice guidelines.

RISK FACTORS (2) (10)

- **Ages:** Advanced age is associated with a poorer prognosis in sepsis. Elderly and young individuals often have weaker immune systems and may have multiple comorbidities, making it harder for them to combat the infection.
- **Underlying conditions:** Preexisting conditions, such as diabetes, cancer, chronic lung diseases, kidney disease, loss of functional independence, or low BMI (≤18.5), are a risk factor developping sepsis. These conditions can significantly impact prognosis and weaken the body's ability to fight infections.
- **Healthcare-associated factors:** Postoperative infection, use of mechanical ventilation, history of hospitalization, history of emergency surgery, and previous history of sepsis.

SEPSIS PROGRESSION

Infection
Sepsis typically begins with an infection caused by bacteria, viruses, fungi, or parasites. This infection can occur anywhere in the body.

Dysregulated Immune Response
In sepsis, the body's immune system responds to the infection in an abnormal and harmful way. Instead of effectively fighting off the infection, the immune response triggers an excessive inflammatory reaction.

Systemic Inflammation
The inflammatory response in sepsis is not limited to the site of the infection but spreads throughout the bloodstream. This can lead to widespread inflammation and affect multiple organs and systems.

Organ Dysfunction
As a result of the systemic inflammation, organs may not function properly.
This can lead to a range of symptoms and complications such as organ failure.

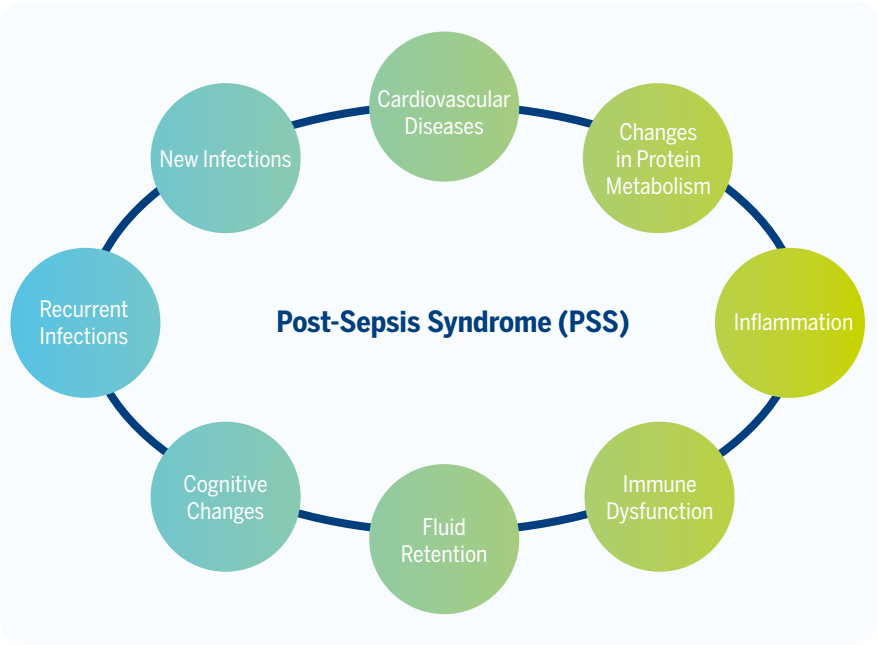
Not all bacteremia lead to sepsis

LONG-TERM CONSEQUENCES

Survivors of sepsis may experience long-term physical and psychological effects, a condition known as **Post-Sepsis Syndrome** (PSS).

These effects can include:

- Cognitive impairment
- Physical disabilities
- Mental health issues



Reproduced with permission from Gritte R, *et al.*, Why Septic Patients Remain Sick After Hospital Discharge? Front Immunol. 2021; 11:605666.

PATIENT MANAGEMENT

In addition to fluid resuscitation and hemodynamic monitoring (or "vasoactive drug monitoring") (refer to guidelines), appropriate patient management includes:

1 Severity assessment [11][12]

Several sepsis screening tools aim to facilitate early identification of sepsis, employing either manual methods or automated integration with electronic health records (EHR). Common screening variables include:

SOFA (Sequential Organ Failure Assessment):
- respiratory rate
- coagulation
- liver
- cardiovascular
- central nervous system
- renal systems

qSOFA* (quick Sequential Organ Failure Assessment):
- respiratory rate
- systolic blood pressure
- Glasgow Coma Score (GCS)

SIRS (Systemic Inflammatory Response Syndrome):
- temperature
- respiratory rate
- heart rate
- white blood cell count

NEWS (National Early Warning Score):
- temperature
- respiratory rate
- heart rate
- systolic blood pressure
- oxygen saturation
- level of consciousness
- oxygen saturation on room air (NEWS2)

MEWS (Modified Early Warning Score):
- respiratory rate
- heart rate
- systolic blood pressure

Numerous studies have produced contradictory results on the usefulness of these tools, showing that qSOFA is more specific but less sensitive than SIRS criteria for early identification of infection-induced organ dysfunction. [13]

*** In 2026, Surviving Sepsis Campaign guidelines strongly recommend against using qSOFA compared to SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock.** [13]

2 PATHOGEN IDENTIFICATION

- Blood culture: SSC 2026 recommend collecting blood cultures as soon as possible and ideally before the administration of antimicrobial therapy [13]
- Gram stain to **identify** broad category of pathogen
- Polymerase Chain Reaction (PCR) testing for **rapid pathogen identification** (ID) and detection of selected **genotypic antimicrobial resistance markers**
- MALDI-TOF or other automated identification testing on pathogen recovered from positive blood culture
- Antimicrobial Susceptibility Testing (AST) to determine the **phenotypic antimicrobial resistance** of the pathogen

3 IMAGING

- X-ray
- Ultrasound
- Computed Tomography (CT) scan

4 TREATMENT MONITORING

Inflammatory biomarkers: like C-reactive protein (CRP) and Procalcitonin (PCT) can be elevated in sepsis and may be used to monitor the inflammatory response to treatment.

SURVIVING SEPSIS CAMPAIGN GUIDELINES 2026

ANTIBIOTIC TREATMENT:

Possible Sepsis without Septic shock

- If infection, antibiotic treatment within **3 hours**.

Sepsis confirmed without Septic shock

- Antibiotic treatment started within **1 hour** of recognition.

Possible/probable or definite Septic shock

- Antibiotic treatment started within **1 hour** of recognition.

DIAGNOSTIC INVESTIGATION:

Confirmed Sepsis or Septic shock

- Use of **pathogen-specific rapid diagnostic tests**, in selected patients based on clinical features, local pathogen and resistance patterns, seasonality, and availability of tests and antibiotic stewardship guidance.
- "Strong recommendation": **de-escalation of antimicrobial therapy** over no de-escalation when a confirmed microbiological diagnosis and susceptibility profile is available.

GUIDELINES AND KEY RESOURCES

It's important to note that guidelines can vary by region and organization, the ones mentioned below are considered key references for healthcare professionals.

- **Surviving Sepsis Campaign (SSC)** [13]
- **Pediatric Sepsis Guidelines** [14]
- **JAMA Network** [15]
- **WHO sepsis** [16]
- **Global Sepsis Alliance** [17]

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