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Management of Sepsis in Hospitalized Patients

Sepsis is the leading cause of death worldwide. Mortality has improved in the past few decades but remains high, and survivors frequently have long-term complications. Initial diagnostic evaluation focuses on risk stratification and source and pathogen identification. Treatment includes intravenous fluids, vasopressors, steroids if shock is present, antimicrobial therapy targeting the most likely source of infection, and source control. Patients with shock or high-risk organ failure syndromes should be admitted early to an intensive care unit. After initial antimicrobials and resuscitation, care should focus on antimicrobial deescalation, volume management, and high-quality supportive care. Shared decision making about goals of care and transitions is important to support survivors after discharge.

Diagnosis

Treatment

Post-sepsis Outcomes

Practice Improvement

CME/MOC activity available at Annals.org.

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Sepsis—life-threatening organ dysfunction due to infection—results in 19 million hospitalizations and more than 5 million deaths each year, making it the costliest condition and the most common cause of in-hospital mortality in the United States (1–6). Nearly 50 million incident cases of sepsis and 11 million sepsis-related deaths occur annually, representing nearly 20% of all global deaths (1). Although changing definitions and coding practices in the United States affect sepsis epidemiology, sepsis incidence and mortality have both decreased over the past 30 years (1, 2). However, the incidence and mortality of sepsis show considerable global disparities, with the highest burden in sub-Saharan Africa and parts of Asia.

Sepsis is a syndrome that is defined by criteria set forth by expert consensus. In 1992, the first definition of sepsis (Sepsis-1) required presence of infection and 2 or more systemic inflammatory response syndrome (SIRS) criteria (abnormalities of temperature, heart rate, respiratory rate, or leukocyte count) (7). This original definition included 2 gradations of severity: severe sepsis, and septic shock. In 2016, the sepsis definition was updated (Sepsis-3) to require acute organ dysfunction caused by a dysregulated host response to infection, and SIRS was eliminated from the definition due to a widely recognized lack of specificity (8).

Diagnosis

What is the clinical presentation of sepsis?

The presentation of sepsis is heterogeneous. Patients may have symptoms specific to the site of infection (for example, urinary tract, pneumonia, skin and soft tissue) and general features of infection (such as fever, fatigue, or anorexia). Specific vital sign abnormalities might include hyperthermia, with a temperature exceeding 38 °C; hypothermia, with a temperature below 36 °C; tachycardia, with a heart rate exceeding 90 beats/min in adults; hypotension, with a systolic blood pressure less than 90 mm Hg; or tachypnea, with a respiratory rate exceeding 20 breaths/min in adults. Laboratory findings might include leukocytosis (leukocyte count >12 $\times$ 10^9 cells/L), leukopenia (leukocyte count <4 $\times$ 10^9 cells/L), or bandemia (>10% band forms on differential). Two or more abnormalities in temperature, heart rate, respiratory rate, and leukocyte count comprise SIRS, which has a pooled sensitivity of 88% but specificity of only 26% for identifying sepsis (3). Clinicians should be especially alert for signs and symptoms of acute organ dysfunction such as confusion, decreased urine output, or jaundice when considering a sepsis diagnosis.

Before developing hypotension, patients with sepsis may experience a decrease in systemic vascular resistance due to vasodilation. Alternatively, cardiac output may be elevated due to compensatory increases in heart rate or stroke volume. As sepsis progresses, patients may develop shock (defined as systolic blood pressure <90 mm Hg, mean arterial pressure [MAP] <70 mm Hg, or a decrease in systemic blood pressure >40 mm Hg below baseline) due to a decrease in stroke volume and cardiac output from myocardial depression and ongoing vasodilation (**Table 1**).

Unfortunately, no signs and symptoms can effectively confirm or rule out sepsis, and sepsis should be on the differential for all patients with severe illness without a definitive alternate diagnosis. Widespread implementation of electronic health records and advances in computational technology have catalyzed efforts to improve early detection of sepsis through electronic decision alerts. Evidence on the effectiveness of

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Table 1. **Hemodynamic Changes Associated With Sepsis and Septic Shock**

Hemodynamic Parameter	*Early Sepsis (Compensatory)*	*Septic Shock (Decompensated)**
Systemic vascular resistance	Decreased due to vasodilation	Decreased further
Stroke volume	Maintained or increased	Decreased due to poor preload
Cardiac output	Normal or elevated	Decreased in setting of impaired myocardial function
Pulse pressure	Normal or elevated	Decreased in setting of low cardiac output

** Treatment with fluid resuscitation and vasopressors affects presentation of septic shock.*

these tools is mixed. The widely used Epic Sepsis Model was shown to perform poorly in real-world settings (9), while a recent stepped-wedge randomized trial reported improved mortality during the electronic sepsis alert intervention period (10). Implementation factors such as the timing, type, and targeting of the alert are but a few aspects of electronic sepsis alerts that require further study (9).

How should clinicians approach the initial work-up for suspected sepsis?

Initial diagnostic work-up should focus on 2 goals: risk stratification and pathogen identification. Risk stratification for mortality is accomplished by evaluating hemodynamic status and organ function. Patients with a systolic blood pressure less than 90 mm Hg or a MAP less than 65 mm Hg despite receiving adequate fluid resuscitation are classified as having septic shock, which is associated with mortality of 30% to 40% (8). Organ dysfunction should be assessed using the Sequential Organ Failure Assessment (SOFA) score (4) or the quick SOFA (qSOFA) (5). The SOFA score evaluates organ dysfunction across 6 components: cardiovascular, respiratory, renal, hepatic, neurologic, and coagulation. Patients receive 0 to 4 points for each component, with higher scores indicating greater severity of illness. An increase in SOFA score of 2 or more indicates in-hospital mortality greater than 10%. The qSOFA is a simplified bedside clinical risk stratification tool, with poorer outcomes more likely with the presence of 2 or more of the following criteria: respiratory rate of 22 breaths/min or greater, altered mentation, or systolic blood pressure of 100 mm Hg or less. In contrast to SOFA, the qSOFA does not require laboratory testing; however, validation studies indicate poor sensitivity of qSOFA (3). Other general deterioration indices like the National Early Warning Score (NEWS) can be helpful in risk stratification (11). The NEWS is calculated from temperature, blood pressure, heart rate, respiratory rate, oxygenation, and level of consciousness and is one of the best-validated scores for sepsis (6–8). Measurement of serum lactate is recommended in all patients with suspected sepsis to identify occult shock (9). Lactate levels greater than 4 mmol/L are associated with in-hospital mortality (10).

In addition to risk stratification, clinicians should rapidly confirm and assess the source of infection. Blood cultures are recommended in most cases and should be drawn before antibiotic administration as sensitivity is reduced when they are drawn afterward (12). Testing for viral pathogens (for example, influenza viral testing) should be considered, particularly when patients present with signs and symptoms of respiratory infection. Imaging is often necessary (for example, chest radiography for pneumonia or computed tomography [CT] scan for abdominal source) and should be considered as soon as feasible. Imaging may also be needed early to identify a focus of infection that requires drainage. For example, CT may be considered to

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identify nephrolithiasis and hydronephrosis for a patient presenting with septic shock and kidney injury. Procalcitonin is not recommended to diagnose sepsis, as randomized controlled trial (RCT) data show no difference in mortality, duration of hospital or intensive care unit (ICU) stay, or effect on harm and costs (13).

What are established risk factors for sepsis?

Patients of any age and health status can develop sepsis, but older age and comorbid conditions are strong risk factors. Age greater than 65 years conveys 13.1-fold greater odds of developing sepsis compared with younger age and is a risk factor for mortality (11, 14). Comorbid conditions such as diabetes, chronic kidney or liver disease, HIV, and long-term use of immunosuppressive medications are risk factors due to impaired immune system function (15). Cancer increases risk for sepsis, and patients with cancer are more likely than patients without cancer to be hospitalized with sepsis after adjustment for age and gender (16). Hospitalization within the prior 3 months increases risk for sepsis by 3-fold, particularly if the index hospitalization was for sepsis (17). Growing evidence indicates that social elements, such as low socioeconomic status and neighborhood disadvantage, increase risk for sepsis and sepsis-attributable mortality (18, 19) (Table 2).

Table 2. **Risk Factors for Sepsis**

Category	*Risk Factors*
Demographic characteristics	Older age
Comorbid conditions	Diabetes Cancer Chronic kidney disease Chronic liver disease HIV Long-term use of immunosuppression medication
Health care use	Hospitalization within past 90 d Intensive care unit admission
Acute illness	Bacteremia Community-acquired pneumonia
Socioeconomic factors	Neighborhood socioeconomic status Race

Diagnosis... Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated response to infection. The clinical presentation of sepsis varies, and clinicians should include sepsis in the differential diagnosis for all patients presenting with severe illness. Risk factors include older age, immunosuppression, recent hospitalization, and pathogen virulence. Initial evaluation should include detailed history, physical examination, and targeted diagnostic evaluation for risk stratification and pathogen identification, including blood cultures in most cases.

CLINICAL BOTTOM LINE

Treatment

Sepsis and septic shock are medical emergencies requiring prompt treatment. The initial focus of treatment is to restore and maintain organ perfusion and to treat an underlying infectious cause. Thus, patients with suspected sepsis should receive a bundle of care that includes prompt intravenous fluids and vasopressors as needed to restore perfusion and treatment with antimicrobials to treat the underlying infection. Guidelines such as the Surviving Sepsis Campaign (SSC) and quality measures such as the Centers for Medicare & Medicaid Services (CMS) Severe Sepsis and Septic Shock Management Bundle (SEP-1) exist to help hospitals measure and improve

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Table 3. **Sepsis Resuscitation Early Care Bundles**

Care Bundle	*Hemodynamic Support*	*Antibiotics*	*Testing*
Centers for Medicare & Medicaid Services Severe Sepsis and Septic Shock Management Bundle (SEP-1)	Give weight-based fluid bolus (30 mL per kilogram of body weight) if hypotension is present or lactate level is ≥4.0 mmol/L within 3 hours of sepsis recognition Add vasopressors within 6 hours of sepsis presentation if hypotension persists	Administer antibiotics within 3 hours from sepsis recognition	Obtain blood cultures before administering antibiotics Measure lactate within 3 hours Repeat lactate measurement if initial level is >2.0 mmol/L Repeat volume status and tissue perfusion assessment
Surviving Sepsis Campaign guidelines (2021)	For patients with sepsis-induced hypoperfusion (mean arterial pressure <65 mm Hg or lactate level ≥4 mmol/L), give ≥30 mL of intravenous crystalloid per kilogram of body weight within first 3 hours (weak recommendation, low quality of evidence)	For adults with septic shock or high likelihood of sepsis, administer antimicrobials immediately, ideally within 1 hour of recognition (strong recommendation, low quality of evidence) For adults with possible sepsis without shock, recommend time-limited course of rapid investigation and administer antibiotics within 3 hours if concern about infection persists (weak recommendation, very low quality of evidence)	Rapid assessment for infection and lactate-guided resuscitation are recommended

performance in delivering optimal sepsis care (Table 3).

The SSC guidelines were first launched in 2002 as a global multisociety, multispecialty initiative to reduce sepsis mortality. In 2004, the first set of guidelines focused on early sepsis recognition and management. The guidelines regularly incorporate new research and evolving care practices, with updated versions published in 2008, 2012, 2016, and 2021.

What fluids should be administered to patients with suspected sepsis, and how should they be administered?

Initial treatment of sepsis includes fluid administration with the therapeutic goal of quickly reversing hypoperfusion (12). The SSC International Guidelines for Management of Sepsis and Septic Shock 2021 recommend at least 30 mL of intravenous crystalloid fluid per kilogram of body weight given within 3 hours in patients with sepsis-induced hypoperfusion or septic shock (weak recommendation given low quality of evidence) (13). The recommendation for 30 mL/kg was based on observational data suggesting that failure to receive this volume within 3 hours of sepsis onset increased odds of in-hospital mortality and length of ICU stay (14). In a single-center trial of early goal-directed therapy (16), a resuscitation protocol that included fluids, vasopressors, inotropes, and erythrocyte transfusion to reach prespecified resuscitation targets reduced mortality, and this practice was widely adopted (15). However, 3 subsequent multicenter RCTs of a protocol-based approach to early sepsis treatment—ProCESS in the United States, ARISE in Australasia, and ProMISe in the United Kingdom—found no survival benefit (17–19). Lack of mortality benefit between protocolized resuscitation and usual care in

Table 4. **Common Tests of Fluid Responsiveness in Sepsis**

Fluid Responsiveness Test	*Description*	*Considerations*
Passive leg raise	After starting with the head elevated to 45 degrees, rapidly reposition the patient by lowering the head and lifting the foot of the bed so the legs are elevated at 45 degrees for 2 minutes while cardiac output or related parameters are measured to determine fluid responsiveness (26–28)	Improvement in cardiac output or other parameters due to the "auto-bolus" induced by passive leg raise is a very useful marker of fluid responsiveness in a hemodynamically unstable patient (positive likelihood ratio, 11 [95% CI, 7.6 to 17]; pooled specificity, 92%; negative likelihood ratio, 0.13 [95% CI, 0.07 to 0.22]; pooled sensitivity, 88%)
Respiratory variation in inferior vena cava	Ultrasonographic assessment of size and degree of inspiratory collapse	Dependent on sonographer skill Correlates with central venous pressure; not a direct measure of fluid responsiveness
Capillary refill time	The examiner applies manual pressure to the ventral aspect distal phalanx nailbed until it blanches, holds for 10 seconds, and then releases, recording the number of seconds until normal color returns; a refill time >3 seconds is considered abnormal	Resuscitation targeting capillary refill time (compared with lactate-targeted resuscitation) was associated with lower mortality (34.9% vs. 43.4%; $P = 0.06$), less organ dysfunction, and lower treatment intensity (26)

these trials may be because early intravenous fluid resuscitation and antibiotics have become standard care.

Fluid therapy should be given in rapidly infused boluses (for example, 500 mL over 5 minutes, or 250 mL for patients at high risk for volume overload) with close assessment of hemodynamic response. Fluid boluses should be continued in the resuscitative phase of septic shock until the MAP no longer increases with small boluses, lactate improves, or complications suggesting overresuscitation occur (such as pulmonary edema) (12). Several tests of fluid responsiveness can be used to guide the decision to administer further intravenous fluids (**Table 4**).

Intravenous fluids are classified as crystalloid solutions containing water and electrolytes (for example, 0.9% sodium chloride or Ringer lactate) or colloid solutions that contain water, electrolytes, and a larger compound (such as albumin). Multiple RCTs have shown that resuscitation with albumin does not improve mortality compared with resuscitation with crystalloid (20).

A secondary analysis of patients with sepsis in a pragmatic trial of saline versus balanced crystalloids in patients in the ICU found that 30-day mortality was lower in patients receiving balanced crystalloid (such as Ringer lactate) compared with normal saline, although other RCTs did not replicate this finding (21–23). Most experts recommend using balanced crystalloid (Ringer lactate or Plasma-Lyte) over normal saline or albumin in patients with sepsis and septic shock (12, 20).

When should antimicrobials be given for patients with suspected sepsis?

Recommendations for how quickly antibiotics should be administered vary based on the severity of the patient's presentation (presence vs. absence of shock) and the likelihood that infection is present (possible or probable sepsis). Antimicrobials should be administered immediately (within 1 hour) for patients with septic shock, defined as persistent hypotension with MAP less than 65 mm Hg or lactate level above 2 mmol/L (5), regardless of the likelihood of infection (13). Antibiotics should

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also be administered within 1 hour for patients without shock but with a high likelihood of sepsis. These recommendations are supported by observational data showing mortality reduction with prompt antibiotic administration (24–26).

For patients with sepsis without shock, the relationship between time to antimicrobial therapy and mortality is less consistent, although mortality seems to increase with delays beyond 3 to 5 hours. Guidelines now recommend a 3-hour timing target for patients without shock and possible infection to allow additional time for diagnostic evaluation. A retrospective study of 166 559 hospitalized adult patients treated in the emergency department (ED) for suspected serious infection provided empirical support for the most recent guidelines aligning antibiotic timing targets with risk and likelihood of sepsis. In patients with possible sepsis without shock, mortality was low (2%) despite a conservative time to administration of antibiotics (median, 5.5 hours [interquartile range, 3.2 to 9.8 hours]) (27).

What antimicrobials should be given?

The most common sites of infection associated with sepsis are pulmonary (40% to 60% of cases), genitourinary (11% of cases in the critically ill population), and gastrointestinal (10% of cases in the critically ill population) (28, 29). The decision to use broad-spectrum antibiotics empirically should be based on presence of risk factors; evidence in community-onset sepsis indicates that drug-resistant organisms are isolated in less than 10% of patients treated with broad-spectrum agents (30). Guidelines provide recommendations for initial antimicrobials based on the most likely source of infection. Antibiogram data based on local, population-based infection rates should also be used to guide initial antimicrobial selection. Early consultation with an infectious diseases expert may be appropriate for patients with a history of infection with multidrug-resistant or particularly virulent organisms.

Antimicrobial coverage targeting methicillin-resistant *Staphylococcus aureus* (MRSA) should be part of empirical treatment for patients at high risk for MRSA infection, including those with a history of MRSA infection; receipt of intravenous antibiotics within 90 days; recurrent skin and soft tissue infections; invasive devices, such as indwelling venous catheters; hemodialysis; and hospitalization within 30 days (9). An antimicrobial with antipseudomonal coverage, such as cefepime or piperacillin–tazobactam, should be given to patients at risk for infection with resistant gram-negative bacteria (9). In the ACORN RCT comparing cefepime and piperacillin–tazobactam, treatment with piperacillin–tazobactam did not increase the incidence of acute kidney injury or death; however, treatment with cefepime resulted in more neurologic dysfunction (31).

In general, only one agent targeting gram-negative bacteria is needed, although local antibiotic resistance patterns and severity of illness should be considered. Double gram-negative coverage can be considered for patients with specific risk factors, such as severe immunosuppression or history of *Pseudomonas* infection, or in units with high local resistance patterns to gram-negative isolates (32). Therapy should be narrowed to a single agent once susceptibilities for the causative agent are determined. Empirical antifungal coverage should be considered only for patients at high risk for fungal infection (9). Risk factors for fungal infection include immunosuppression, total parenteral nutrition, longer ICU stays (generally >1 week), indwelling intravascular devices, and emergency gastrointestinal or hepatobiliary surgery (33).

What are the key components of source control in patients with sepsis?

Source control involves the identification and removal of an infection source

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to halt the systemic response and ongoing microbial contamination of a normally sterile organ, tissue, or body cavity via debridement, decompression, or drainage. The SSC guidelines recommend that source control measures be implemented within 12 hours after diagnosis, as delays are associated with increased mortality (34–37). Source control is commonly considered for abdominal infections but should be considered for all organs, including chest infections (empyema, lung abscess) or central nervous system infections (for example, brain abscesses or ventriculitis). Catheter-associated urine or bloodstream infections typically require removal of the catheter to obtain source control. If no clear source of sepsis is apparent based on physical examination and initial rapid diagnostic evaluation, cross-sectional imaging using CT should be ordered to identify foci of infection (38).

When should steroids be given for sepsis?

Sepsis can result in impairment of the hypothalamic–pituitary–adrenal axis and a "relative adrenal insufficiency." Multiple randomized trials have shown faster resolution of septic shock with administration of hydrocortisone (a glucocorticoid). For example, in the 2008 CORTICUS trial of 499 patients with septic shock, hydrocortisone administration was associated with faster reversal of shock (3.3 vs. 5.8 days) but no difference in 28-day mortality (39). In the larger 2018 ADRENAL trial of 3800 patients, hydrocortisone also resulted in faster resolution of shock with no difference in 28- or 90-day mortality (40). Two of 3 major randomized trials of hydrocortisone with the addition of fludrocortisone (a mineralocorticoid)—a French trial published in 2002 and the APROCCHSS trial published in 2018—demonstrated both faster resolution of shock and mortality benefit. A recent systematic review of 45 RCTs concluded that steroids may reduce mortality in sepsis and hasten reversal of septic shock but may also increase risk for hyperglycemia, hypernatremia, and neuromuscular weakness (41). The dose–response analysis suggested an optimal dose around 260 mg of hydrocortisone per day or equivalent (42).

In 2024, the Society for Critical Care Medicine provided a focused update on use of corticosteroids in sepsis, pneumonia, and acute respiratory distress syndrome (43). Drawing on results of APROCCHSS and the CAPE COD trial, in which hydrocortisone reduced 28-day mortality compared with placebo for patients with severe community-acquired pneumonia, a conditional recommendation for the use of steroids in patients with septic shock and a strong recommendation for the use of corticosteroids for severe community-acquired pneumonia were made (43, 44). The panel recommended against high-dose, short courses of corticosteroids (>400 mg hydrocortisone equivalent per day for <3 days) for adults with septic shock. No recommendation on the use of fludrocortisone was made due to limited evidence.

What vasopressors should be given in patients with septic shock, and when?

Vasopressors should be started when there is no further hemodynamic improvement with fluid administration (for example, MAP no longer increases with bolus) or a patient starts to develop complications (such as pulmonary edema) from fluids. In an RCT of 1563 patients, there was no mortality difference with a fluid-restrictive approach (less fluid and earlier use of vasopressors) versus a fluid-liberal approach for sepsis-induced hypotension that persisted after initial fluid resuscitation (45). Norepinephrine is the recommended first-line vasopressor for septic shock (strong recommendation in SSC guidelines). Norepinephrine is a potent α1- and β1-adrenergic

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receptor agonist, and its use results in vasoconstriction and an increase in MAP. Norepinephrine can be administered safely through a peripheral intravenous catheter with appropriate protocols in place and careful monitoring (46, 47). Reported rates of extravasation via peripheral administration are low, and tissue injury with extravasation is rare (48). Although protocols vary, peripheral vasopressors should only be administered when placement of the intravenous line is confirmed, ongoing monitoring for patency occurs, and an extravasation management plan is in place. For prolonged vasopressors (>48 hours) or high-dose vasopressors (for example, >15 mcg of norepinephrine per minute), placement of a central venous catheter should be considered.

The SSC guidelines recommend titrating vasopressors to target a MAP of 65 mm Hg during the initial resuscitation period. In a multicenter, open-label trial in 776 patients with septic shock (SEPSISPAM), targeting a higher MAP of 80 to 85 mm Hg did not result in a significant mortality difference compared with a target of 65 to 70 mm Hg; however, a prespecified subgroup analysis found less renal replacement therapy in patients with preexisting chronic hypertension who were randomly assigned to higher MAPs (49). An RCT of "permissive hypotension" (targeting a MAP of 60 to 65 mm Hg) compared with usual care in patients aged 65 years or older with septic shock found there was less exposure to vasopressors without a mortality difference in the permissive hypotension group (the mean MAP achieved in this group was 67 mm Hg) (50). Given the current evidence, we believe targeting a MAP of 65 mm Hg is reasonable for most patients with septic shock.

If the MAP remains inadequate after norepinephrine, vasopressin may be added as a second agent. Vasopressin is an endogenous peptide hormone that binds V1 receptors on vascular smooth muscle, resulting in vasoconstriction. It is administered as a fixed dose (usually 0.03 units/min) and is not titrated to achieve a goal MAP. The addition of vasopressin can reduce the dose of norepinephrine needed to maintain an adequate MAP. The VASST trial compared norepinephrine alone to norepinephrine with combination vasopressin therapy and found no difference in 28-day mortality (51). However, a mortality benefit was observed in the subgroup of patients who received lower doses of norepinephrine (<15 mcg/min). In clinical practice, the threshold for adding vasopressin varies and the optimal threshold remains an area of active investigation.

Angiotensin II is an endocrine hormone that plays a key role in the renin–angiotensin–aldosterone system and functions as a potent vasoconstrictor. In the ATHOS-3 trial, a synthetic formulation of angiotensin II increased blood pressure in patients with vasodilatory shock with no increase in adverse events. However, given limited evidence on outcomes and higher cost compared with vasopressin, angiotensin II is not recommended as a first-line agent, though it may be considered in refractory shock or as adjunctive therapy (9, 52).

When should patients with sepsis be admitted or transferred to the ICU?

Patients requiring vasopressors or mechanical ventilation should be admitted to the ICU as soon as a bed is available. Early admission to the ICU (within 3.3 hours of ED arrival) was associated with lower 28-day mortality in patients presenting to the ED with sepsis. Prolonged care in the ED while awaiting transfer to an inpatient bed (ED boarding) has been linked to increased mortality in observational studies of patients with sepsis (53). The association between timing of ICU admission and mortality is less clear in

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patients with hospital-onset sepsis, but SSC guidelines recommend transfer within 6 hours (54, 55). In facilities without capabilities to manage complex infections or organ failures, interhospital transfer should be considered in patients stable enough for transfer.

Predicting whether a patient who does not show clear indications for ICU admission could benefit from early admission to the ICU is challenging. In a study of 27 U.S. hospitals across 2 health systems from 2013 to 2018, initial admission to the ward, compared with the ICU, was associated with shorter length of stay and improved survival for patients with sepsis who did not require life support in the ED (56). Current evidence suggests that early ICU admission should be prioritized for patients with critical illness (need for vasopressors or ventilatory support) and may be less beneficial for patients not meeting this criterion. Future studies to determine optimal identification and targeting of patients who may benefit from early ICU transfer are needed.

What is the focus on sepsis treatment during the deescalation and stabilization phase?

Although prompt recognition of sepsis coupled with early administration of fluids, antibiotics, and vasopressors is the cornerstone of early sepsis care, outcomes after sepsis also depend on practices during the stabilization phase. The key components of treatment during this phase of sepsis care include daily assessment for deescalation of antimicrobials, diuresis in patients with volume overload, and implementation of tactics to reduce complications (**Box:** Hospital Management of Sepsis Beyond the First 6 Hours).

Antibiotic selection, dose, and duration should be reviewed daily. Once the infectious pathogen and resistance profile are known, broad-spectrum antibiotics should be discontinued to narrow the spectrum of coverage. Antimicrobial exposure is associated with the development of resistance at both the individual and societal levels and can be associated with adverse consequences in patients, such as *Clostridioides difficile* infection or acute kidney injury. There is mounting evidence that shorter courses of antimicrobials are as effective as the longer courses traditionally given for sepsis. For example, 8 days of antibiotics are generally as effective as 15 days for ventilator-associated pneumonia, and 7 days of antibiotics were not associated with worse outcomes compared with longer courses for patients with community-acquired pneumonia (57, 58). For patients with sepsis secondary to a urinary tract infection, 7 days of treatment has been shown to have clinical and microbiologic failure rates similar to those with longer courses of treatment (59).

Despite this evidence, patients with sepsis often receive excess antibiotic therapy (60). For this reason, procalcitonin has been studied as a biomarker to help guide discontinuation of antimicrobials. High serum procalcitonin levels are correlated with higher likelihood of positive blood culture results, and levels decrease with appropriate antimicrobials (61). Procalcitonin-guided antibiotic deescalation has been shown to decrease the duration of antimicrobial therapy without increasing the risk for complications in patients with acute respiratory infection (62, 63). Using procalcitonin to deescalate (not diagnose) sepsis has been shown to reduce antibiotic therapy safely in patients with sepsis (64). In the SAPS and PROGRESS randomized trials of procalcitonin-guided antibiotic deescalation, discontinuation of antibiotics was recommended when procalcitonin was reduced by at least 80% of the peak level or when the level was less than 0.5 mcg/L (monitored daily in SAPS and after day 5 in PROGRESS) (64, 65). The SSC guidelines therefore

Hospital Management of Sepsis Beyond the First 6 Hours

- Administer steroids for patients with septic shock
- Assess fluid responsiveness and administer ongoing fluids as needed
- Daily discussion of antibiotic scope and duration (antibiotic stewardship)
- Discussion of prognosis to develop shared understanding of goals of care
- Physical and occupational therapy for appropriate early mobility and preservation of function
- Delirium screening and mitigation
- Spontaneous breathing trials and awakening trials for ventilated patients
- Education of patient and family on sepsis presentation, treatment, and long-term complications

suggest using procalcitonin monitoring and clinical evaluation to guide discontinuation of antimicrobials (weak recommendation).

Given the potential consequences of too much fluid accumulation (such as pulmonary edema resulting in respiratory failure or peripheral edema leading to impaired physical function), active "deresuscitation" with diuretics should be considered in patients with volume overload. Evidence supporting active deresuscitation is limited. A systematic review and meta-analysis of 13 trials examining the effect of active deresuscitation in patients with septic shock did not find a difference in patient outcomes compared with usual care (66). A nonrandomized trial in patients with abdominal sepsis showed a reduction in duration of mechanical ventilation and duration of renal replacement therapy, suggesting a benefit in this patient population (67). Additional research using deresuscitation protocols with diuretics is needed to inform care.

Avoiding complications of hospitalization and sepsis therapy is also part of treatment in the stabilization phase. Careful attention is needed to ensure appropriate stress ulcer prophylaxis and thromboembolic prophylaxis. Hyperglycemia is common during sepsis and treatment with corticosteroids. The SSC guidelines recommend initiating insulin therapy at a glucose level of 180 mg/dL or higher and targeting a blood glucose range of 144 to 180 mg/dL (strong recommendation) (9). Out-of-bed mobility and early physical therapy should be delivered when feasible to all patients hospitalized with sepsis. For patients requiring admission to the ICU, best practices for ventilator liberation should be followed, including coordinating awakening and breathing trials, delirium screening, early mobility, and family engagement (referred to collectively as the ABCDEF bundle) (68, 69).

Treatment... Sepsis is a medical emergency. Prompt treatment aimed at restoring tissue perfusion and treating the underlying infection should be initiated alongside diagnostic testing. Guidelines recommend delivering a bundle of care to meet these goals, including intravenous fluids to restore tissue perfusion, antibiotics and source control targeting the most likely cause of infection, and vasopressors for patients with septic shock. In general, the initial target for volume of fluids should be 30 mL/kg. Norepinephrine is the recommended first-line vasopressor if hypotension persists after initial volume resuscitation. After the initial resuscitation phase, treatment should focus on deescalation of antimicrobials, diuresis in patients with volume overload, and prevention of complications.

CLINICAL BOTTOM LINE

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Post-sepsis Outcomes

What is known about outcomes for patients with sepsis?

Sepsis continues to have high short- and long-term mortality rates. Data from the Global Burden of Diseases, Injuries, and Risk Factors Study estimate that sepsis-related deaths represented 19.7% of deaths worldwide in 2017 (2). Mortality was highest in early childhood (age <5 years) and increased again among older adults. A meta-analysis of data from Europe, North America, and Australia found an average 30-day mortality rate of 35% for septic shock and a 90-day mortality rate of 39% (70). In a study using clinical data from 409 hospitals in the United States, 21% of patients with clinical indicators of sepsis died in the hospital or were discharged to hospice in 2014 (71). Mortality in sepsis varies widely across different sources of infection and types of organ dysfunction (72).

Survivors of sepsis often experience long-term complications, including functional decline, cognitive impairment, and mental health symptoms. The constellation of sequelae has been called post-sepsis syndrome or post-ICU syndrome in patients who required ICU admission. In older adults, hospitalization with sepsis is associated with the development of 1 or 2 new functional limitations, such as bathing or toileting independently (73), and a 10% absolute increase in moderate to severe cognitive impairment potentially due to vascular injury, neuroinflammation, and blood–brain barrier disruptions (74).

Impaired quality of life after sepsis can last as long as 5 years, although a patient's baseline status is an important determinant of postdischarge quality of life (75). Only half of patients with ICU-treated sepsis and one third of patients with ward-treated sepsis return to work at 2 years (76). Risk factors associated with poor long-term functional outcomes include chronic health conditions, delirium duration, vision or hearing impairment, immobility, frailty, older age, premorbid disability, prior nursing home care, severity of acute illness, and single marital status (77).

It is therefore unsurprising that patients with sepsis experience high risk for hospital readmission and late mortality after surviving to discharge. The most common reason for unplanned readmission after sepsis is new or recurrent infection (78). Sepsis is also an independent risk factor for cardiovascular events (myocardial infarction, stroke, fatal coronary heart disease), most often after pneumonia hospitalization (79). Health care facility (hospital, long-term acute care, or nursing facility) use in the year after a sepsis hospitalization is high, particularly for older survivors (80). A study using Medicare data reported that older patients spend a median of 10% (mean, 25%) of their days admitted to a health care facility in the year after a sepsis hospitalization (78).

More than 1 in 5 survivors experience death that is not explained by their health status before sepsis, and mortality remains elevated at least 2 years after sepsis hospitalization (81). Given high initial and longer-term mortality, conversations seeking to understand patients' goals of care and what treatments are acceptable are considered best practice in sepsis. Although the optimal timing of these conversations is uncertain, earlier conversations (within 72 hours of ICU admission) may improve perceived quality of communication and patient-centeredness of care (82).

What are best practices for care transitions and follow-up?

Given growing evidence of poor long-term outcomes after sepsis, a 2017 World Health Organization resolution

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Discharge Checklist After Hospitalization for Sepsis

- Medication reconciliation
- Home health and/or rehabilitation referral
- Early provider follow-up appointment
- Screening for unmet economic or social needs
- Screening for new cognitive or physical impairments
- Screening for impairments in activities of daily living or instrumental activities of daily living
- Palliative care assessment and referral as appropriate
- Discussion of signs and symptoms of new or unresolved infection with patient and family

called for greater attention to the recovery needs of sepsis survivors (83). In 2021, the SSC guidelines included "best practices" for transition and recovery, including discussing goals of care and prognosis, integrating principles of palliative care into the treatment plan, referral to peer support groups, screening and referrals for economic and social support, written and verbal sepsis education, and shared decision making in post-ICU and hospital discharge planning. Despite these suggestions, observational data suggest suboptimal delivery of these practices after hospitalization (84). This may be partly explained by the fact that most post-sepsis care practices are not yet supported by strong evidence. Cohort studies suggest that a combination of early home health nursing and a provider visit is associated with lower readmissions among sepsis survivors (85). A recent RCT found that a multicomponent Sepsis Transition and Recovery program delivered by a nurse navigator reduced the composite of readmission and mortality among high-risk sepsis survivors at both short- and long-term intervals (86, 87). In 2024, the Centers for Disease Control and Prevention added the code "Encounter for sepsis aftercare" (Z51.A) to the International Classification of Diseases, 10th Revision, to support epidemiologic monitoring after sepsis. A list of best practices for care after hospital discharge is provided (see **Box**: Discharge Checklist After Hospitalization for Sepsis).

Practice Improvement

The 2021 SSC guidelines recommend that all hospitals establish sepsis performance improvement programs. The Centers for Disease Control and Prevention has also released Hospital Sepsis Program Core Elements that outline structural and procedural components necessary to support optimal care of patients with sepsis (88).

CMS introduced SEP-1 in 2015. SEP-1 is a quality measure reporting adherence to 3- and 6-hour care bundles aligned with SSC guidelines (**Table 3**). Sepsis care bundles and quality improvement programs aim to facilitate early recognition of sepsis and prompt treatment within a specific time frame while reducing care variability. Despite widespread use of these care bundles, controversy surrounding specific recommendations remains, given the strength of evidence for individual components and different interpretations of major studies (89, 90). Some individual components of SEP-1, such as the 30-mL/kg fluid bolus and strict lactate measurement, continue to be debated, while other components, such as prompt antibiotic administration for patients with septic shock, have consensus support.

Compliance with SEP-1 is determined by manual chart abstraction and is currently reported as "all or none." Public reporting of hospital SEP-1 performance started in 2018 with no financial elements tied to performance. In 2023, CMS recommended that SEP-1 compliance become a pay-for-performance measure, with the adoption of SEP-1 compliance into hospital value-based purchasing beginning in 2026. The

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effect of SEP-1 bundle compliance on outcomes for patients with sepsis remains unclear; as such, its utility as a quality measure has been debated. In a cohort study of 117 150 patients admitted to 114 hospitals between 2013 and 2017, SEP-1 implementation was associated with an increase in lactate testing but no change in the outcome of in-hospital death or discharge to hospice (90). In contrast, Townsend and colleagues reported an association of SEP-1 bundle compliance with lower 30-day mortality in a propensity score–matched analysis of patient-level data reported to Medicare (91). In New York State, mandated protocolized sepsis care was associated with a greater decrease in sepsis mortality compared with sepsis mortality in states that did not implement regulations (92). A recent systematic review of 17 studies found no moderate- or high-level evidence to support that implementation of SEP-1 was associated with sepsis mortality (93). Because studies have failed to show an improvement in patient outcomes with SEP-1 compliance, and pay-for-performance for this metric may divert attention and resources from more effective sepsis care, multiple professional societies have recommended retiring SEP-1 and adopting alternate sepsis performance measures (94, 95). It is clear, however, that variation in sepsis care practices exists, and efforts to understand this variation and improve outcomes for patients with sepsis must remain a research and practice improvement priority (94).

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In the Clinic
Tool Kit

Management of Sepsis in Hospitalized Patients

Patient Information

https://medlineplus.gov/sepsis.html

Information on sepsis from the National Institutes of Health's MedlinePlus.

www.cdc.gov/sepsis

www.cdc.gov/sepsis/es/index.html

Information on sepsis in English and Spanish from the Centers for Disease Control and Prevention.

www.sepsis.org/education/resources

Patient resources on sepsis from the Sepsis Alliance.

Information for Health Professionals

www.sccm.org/clinical-resources/guidelines/guidelines/surviving-sepsis-guidelines-2021

Surviving Sepsis Campaign international guidelines for management of sepsis and septic shock.

www.cdc.gov/sepsis/hcp/communication-resources/index.html

Materials for health care professionals on how to help patients get ahead of sepsis from the Centers for Disease Control and Prevention.

www.who.int/activities/improving-the-prevention-diagnosis-and-clinical-management-of-sepsis

Guidance on improving the prevention, diagnosis, and clinical management of sepsis from the World Health Organization.

WHAT YOU SHOULD KNOW ABOUT SEPSIS

What Is Sepsis?

Sepsis is a serious medical condition that happens when the body has an extreme response to an infection. Instead of fighting the infection normally, the body's immune system overreacts and starts to damage its own tissues and organs. Sepsis can lead to organ failure, tissue damage, and even death if not treated quickly.

Sepsis can start from any infection, including pneumonia, urinary tract infections, skin infections, or infections from wounds. It is considered a medical emergency.

What Are the Symptoms?

- Fever, chills, or feeling very cold
- Confusion or disorientation
- Rapid heartbeat
- Rapid breathing
- Low blood pressure
- Extreme pain or discomfort
- Clammy or sweaty skin

If you or a loved one has an infection and suddenly starts to feel much worse or becomes more confused or sleepy, it's important to seek medical care right away.

What Are the Risk Factors?

Risk factors for sepsis include:

- Being aged 65 years or older
- Having chronic conditions like diabetes, cancer, or kidney disease
- Having a weakened immune system
- Recent surgery or hospitalization
- Having an invasive device like a catheter or a breathing tube
- Not being vaccinated against infections like pneumonia or the flu

How Is It Diagnosed?

- There is no one test to diagnose sepsis. Your doctor will make the diagnosis based on a number of clinical findings and tests.
- Your doctor will ask about your symptoms, medical history, and recent infections or hospital visits.
- Blood tests can help detect signs of infection and how well your organs are working.

- Imaging tests like a chest X-ray, a CT scan, or an ultrasound may be used to find the source of the infection.
- Other laboratory tests, such as urine tests or cultures from blood or wounds, can help identify the bacteria or virus causing the infection.

How Is It Treated?

- Sepsis is usually treated in the hospital as therapy requires many intravenous (IV) infusions that can only be given in an inpatient setting. Some patients with severe sepsis or septic shock may need care in the intensive care unit.
- Treatment usually includes antibiotics given through an IV to fight the infection.
- IV fluids are given to maintain blood pressure and support circulation.
- Other treatments, such as oxygen or medications to support organ function, may be needed depending on how the infection is affecting your body.
- The sooner treatment is started, the better the chance of recovery.

Questions for My Doctor

- How serious is my infection?
- What caused my sepsis?
- What treatments will I need in the hospital?
- Will I need follow-up care or rehab after I leave the hospital?
- How can I reduce my risk of getting sepsis again?

For More Information

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Centers for Disease Control and Prevention
www.cdc.gov/sepsis/hcp/core-elements/resources.html

Sepsis Alliance
www.sepsis.org/education/resources

Society of Critical Care Medicine
https://sccm.org/clinical-resources/sepsis-resources

Patient Information