Evaluation and management of suspected sepsis and septic shock in adults

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INTRODUCTION — Sepsis is a clinical syndrome characterized by systemic inflammation due to infection. There is a continuum of severity ranging from sepsis to septic shock. Although wide-ranging and dependent upon the population studied, mortality has been estimated to be ≥10 percent and ≥40 percent when shock is present [1,2].

In this topic review, the management of sepsis and septic shock is discussed. Our approach is consistent with 2016 guidelines issued by the Surviving Sepsis Campaign [3,4]. While we use the Society of Critical Care Medicine (SCCM)/European Society of Intensive Care Medicine (ESICM) definitions, such definitions are not unanimously accepted. For example, the Center for Medicare and Medicaid Services (CMS) still continues to support the previous definition of systemic inflammatory response syndrome, sepsis, and severe sepsis. In addition, the Infectious Diseases Society of America (IDSA) does not endorse the SCCM/ESICM 2016 guidelines for many reasons as outlined in several sections in this topic [5]. In particular the IDSA does not agree with “one size fits all” recommendations based upon varying definitions of sepsis that do not clearly differentiate between sepsis and septic shock stating that following the SCCM recommendations, while life-saving for those with shock, may lead to overtreatment with broad spectrum antibiotics for those with milder variants of sepsis. Definitions, diagnosis, pathophysiology, and investigational therapies for sepsis, as well as management of sepsis in the asplenic patient are reviewed separately. (See "Sepsis syndromes in adults: Epidemiology, definitions, clinical presentation, diagnosis, and prognosis" and "Pathophysiology of sepsis" and "Investigational and ineffective therapies for sepsis" and "Clinical features, evaluation, and management of fever in patients with impaired splenic function".)

IMMEDIATE EVALUATION AND MANAGEMENT — Securing the airway (if indicated) and correcting hypoxemia, and establishing venous access for the **early** administration of fluids and antibiotics are priorities in the management of patients with sepsis and septic shock [3,4].

Stabilize respiration — Supplemental oxygen should be supplied to all patients with sepsis and oxygenation should be monitored continuously with pulse oximetry. Intubation and mechanical ventilation may be required to support the increased work of breathing that typically accompanies sepsis, or for airway protection since encephalopathy and a depressed level of consciousness frequently complicate sepsis [6,7]. Techniques, and sedative and induction agents are discussed separately. (See "Induction agents for rapid sequence intubation in adults outside the operating room" and "Advanced emergency airway management in adults" and "Rapid sequence intubation for adults outside the operating room" and "The decision to intubate" and "Direct laryngoscopy and endotracheal intubation in adults".)

Establish venous access — Venous access should be established as soon as possible in patients with suspected sepsis. While peripheral venous access may be sufficient in some patients, particularly for initial resuscitation, the majority will require central venous access at some point during their course. However, the insertion of a central line should not delay the administration of resuscitative fluids and antibiotics. A central venous catheter (CVC) can be used to infuse intravenous fluids, medications (particularly vasopressors), and blood products, as well as to draw blood for frequent laboratory studies. While a CVC can be used to monitor the therapeutic response by measuring the central venous pressure (CVP) and the central venous oxyhemoglobin saturation ($ScvO_2$), evidence from randomized trials suggest that their value is limited [8-13]. (See "Complications of central venous catheters and their prevention" and 'Monitor response' below.)

Initial investigations — An initial brief history and examination, as well as laboratory, microbiologic, and imaging studies are often obtained simultaneously while access is being established and the airway stabilized. This brief assessment yields clues to the suspected source and complications of sepsis, and therefore, helps guide empiric therapy and additional testing (table 1). (See "Sepsis syndromes in adults: Epidemiology, definitions, clinical presentation, diagnosis, and prognosis", section on 'Clinical presentation' and 'Empiric antibiotic therapy (first hour)' below.).

Quickly obtaining the following is preferable (within 45 minutes of presentation) but should not delay the administration of fluids and antibiotics:

- Complete blood counts with differential, chemistries, liver function tests, and coagulation studies including D-dimer level. Results from these studies may support the diagnosis, indicate the severity of sepsis, and provide baseline to follow the therapeutic response.
- Serum lactate – An elevated serum lactate (eg, >2 mmol/L or greater than the laboratory upper limit of normal) may indicate the severity of sepsis and is used to follow the therapeutic response [3,4,14-16].
- Arterial blood gas (ABG) analysis – ABGs may reveal acidosis, hypoxemia, or hypercapnia.
- Peripheral blood cultures (aerobic and anaerobic cultures from at least two different sites), urinalysis, and microbiologic cultures from suspected sources (eg, sputum, urine, intravascular catheter, wound or surgical site, body fluids) from readily accessible sites. For patients with a central vascular catheter(s) suspected to be the source, blood should be obtained both from the catheter(s) and from peripheral sites.
- Imaging targeted at the suspected site of infection is warranted (eg, chest radiography, computed tomography of chest and/or abdomen).
- Procalcitonin – While the diagnostic value of procalcitonin in patients with sepsis is poorly supported by evidence, its value in deescalating antibiotic therapy is well established in populations other than those with sepsis, in particular, those with community acquired pneumonia and respiratory tracts infections. Measurement of procalcitonin to guide duration of antibiotic use is appropriate in those populations. Detailed evidence to support the use of procalcitonin is provided separately. (See "Diagnostic approach to community-acquired pneumonia in adults", section on 'Procalcitonin and CRP' and "Procalcitonin use in lower respiratory tract infections".)

INITIAL RESUSCITATIVE THERAPY — The cornerstone of initial resuscitation is the rapid restoration of perfusion and the early administration of antibiotics.

- Tissue perfusion is predominantly achieved by the aggressive administration of intravenous fluids (IVF), usually crystalloids (balanced crystalloids or normal saline) given at 30 mL/kg (actual body weight) within the first **three** hours following presentation.
- Empiric antibiotic therapy is targeted at the suspected organism(s) and site(s) of infection and preferably administered within the **first** hour.

Our approach is based upon several major randomized trials that used a protocol-based approach (ie, early goal-directed therapy [EGDT]) to treating sepsis [8-13]. Components of the protocols usually included the early administration of fluids and antibiotics (within one to six hours) using the following targets to measure the response: central venous oxyhemoglobin saturation ($ScvO_2$) ≥70 percent, central venous pressure (CVP) 8 to 12 mmHg, mean arterial pressure (MAP) ≥65 mmHg, and urine output ≥0.5 mL/kg/hour. Although all trials [9-11] (except for one [8]), did not show a mortality benefit to EGDT, it is thought that the lack of benefit was explained by an overall improved outcome in both control and treatment groups, and to improved clinical performance by trained clinicians in academic centers during an era that followed an aggressive sepsis education and management campaign. In support of this hypothesis is that central line placement was common (>50 percent) in control groups so it is likely that CVP and $ScvO_2$ were targeted in these patients. Furthermore, the mortality in studies that did not report a benefit to EGDT [9-11] approximated that of the treatment arm in the only study that reported benefit [8].

- One single center randomized trial of 263 patients with suspected sepsis reported a lower mortality in patients when $ScvO_2$, CVP, MAP, and urine output were used to direct therapy compared with those in whom only CVP, MAP, and urine output were targeted (31 versus 47 percent) [8]. Both groups initiated therapy, including antibiotics, within six hours of presentation. There was a heavy emphasis on the use of red cell transfusion (for a hematocrit >30) and dobutamine to reach the $ScvO_2$ target in this trial.

- Three subsequent multicenter randomized trials of patients with septic shock, ProCESS [9], ARISE [10], and ProMISE [11] and two meta-analyses [12,13] all reported no mortality benefit (mortality ranged from 20 to 30 percent), associated with an identical protocol compared with protocols that used some of these targets or usual care. In contrast, one meta-analysis of 13 trials reported a mortality benefit from early-goal directed therapy within the first six hours [17].

- A lack of benefit of resuscitation protocols has also been reported in low income settings. As an example, in a randomized trial of 212 patients with sepsis (defined as suspected infection plus two systemic inflammatory response syndrome criteria) and hypotension (systolic blood pressure ≤90 mmHg or mean arterial pressure <65 mmHg) in Zambia, a protocolized approach of aggressive fluid resuscitation, monitoring, blood, and vasopressor transfusion within the first six hours of presentation resulted in a higher rate of death (48 versus 33 percent) when compared with usual care [18]. However, several flaws including crude measurements of monitoring, lower than usual rates of lactate elevation, larger than typical volumes of fluid resuscitation, and use of dopamine (as opposed to norepinephrine) in a population with a high percentage of patients with human immune deficiency virus may have biased the results.

The importance of timely treatment, particularly with antibiotics, was illustrated in a database study of nearly 50,000 patients with sepsis and septic shock who were treated with various types of protocolized treatment bundles (that included fluids and antibiotics, blood cultures, and serum lactate measurements) [19]. Compared with those in whom a three-hour bundle (blood cultures before broad spectrum antibiotics, serum lactate level) was completed within the three-hour time frame, a higher in-hospital mortality was reported when a three-hour bundle was completed later than three hours (odds ratio [OR] 1.04 per hour). Increased mortality was associated with the delayed administration of antibiotics but not with a longer time to completion of a fluid bolus (as part of a six hour bundle) (OR 1.04 per hour versus 1.10 per hour).

Intravenous fluids (first three hours) — In patients with sepsis, intravascular hypovolemia is typical and may be severe, requiring rapid fluid resuscitation. (See "Treatment of hypovolemia or hypovolemic shock in adults".)

Volume — Intravascular hypovolemia is typical and may be severe in sepsis. Rapid, large volume infusions of IVF (30 mL/kg) are indicated as initial therapy for severe sepsis or septic shock, unless there is convincing evidence of significant pulmonary edema. This approach is based upon several randomized trials that reported no difference in mortality when mean infusion volumes of 2 to 3 liters were administered in the first three hours [9-11] compared with larger volumes of three to five liters, which was considered standard therapy at the time [8]. However, some patients may require higher than recommended volumes, particularly those who demonstrate clinical and/or hemodynamic indicators of fluid-responsiveness. (See 'Monitor response' below.)

Fluid therapy should be administered in well-defined (eg, 500 mL), rapidly infused boluses. The clinical and hemodynamic response and the presence or absence of pulmonary edema must be assessed before and after each bolus. Intravenous fluid challenges can be repeated until blood pressure and tissue perfusion are acceptable, pulmonary edema ensues, or fluid fails to augment perfusion.

Choice of fluid — Evidence from randomized trials and meta-analyses have found no convincing difference between using albumin solutions and crystalloid solutions (eg, normal saline, Ringer's lactate) in the treatment of sepsis or septic shock, but they have identified potential harm from using pentastarch or hydroxyethyl starch [20-29]. There is no role for hypertonic saline [30].

In our practice, we generally use a crystalloid solution instead of albumin solution because of the lack of clear benefit and higher cost of albumin. However, some experts administer albumin as an additive or maintenance fluid if there is a perceived need to avoid or treat the hyperchloremia that occurs when large volumes of crystalloid are administered, although the data to support this practice are weak.

Data discussing IVF choice among patients with sepsis include the following:

- **Crystalloid versus albumin** – Among patients with sepsis, several randomized trials and meta-analyses have reported no difference in mortality when albumin was compared with crystalloids, although one meta-analysis suggested benefit in those with septic shock [21,28,29]. In the Saline versus Albumin Fluid Evaluation (SAFE) trial performed in critically ill patients, there was no benefit to albumin compared with saline even in the subgroup with severe sepsis, who comprised 18 percent of the total group [20]. Among the crystalloids, there are no guidelines to suggest that one form is more beneficial than the other.

- **Crystalloid versus hydroxyethyl starch (HES)** – In the Scandinavian Starch for Severe Sepsis and Septic Shock (6S) trial, compared with Ringer's acetate, use of HES resulted in increased mortality (51 versus 43 percent) and renal replacement therapy (22 versus 16 percent) [22]. Similar results were found in additional trials of patients without sepsis.

- **Crystalloid versus** pentastarch – The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial compared pentastarch to modified Ringer's lactate in patients with severe sepsis and found no difference in 28-day mortality [23]. The trial was stopped early because there was a trend toward increased 90-day mortality among patients who received pentastarch.

- **Balanced salt solutions** – A retrospective study in the emergency department of 149 patients with sepsis, use of balanced salt solutions was associated with a lower odds of mortality compared with normal saline [31].

Data discussing IVF choice (including further discussion of balanced salt solutions) in non-septic patients are provided separately. (See "Treatment of hypovolemia or hypovolemic shock in adults", section on 'Choice of replacement fluid'.)

Treating metabolic acidosis — Whether metabolic acidosis associated with sepsis should be treated with bicarbonate is discussed separately. (See "Bicarbonate therapy in lactic acidosis".)

Empiric antibiotic therapy (first hour) — Prompt identification and treatment of the site(s) of infection is the primary therapeutic intervention, with most other interventions being purely supportive.

Identification of suspected source — Empiric antibiotics should be targeted at the suspected source(s) of infection which is typically identified from the initial brief history and preliminary laboratory findings and imaging (table 1) (see 'Initial investigations' above). However, additional diagnostic testing or interventions may be required to identify the anatomic site(s) of infection. (See 'Septic focus identification and source control' below.)

Timing — Once a presumed diagnosis of sepsis or septic shock has been made, optimal doses of appropriate intravenous antibiotic therapy should be initiated, preferably within one hour of presentation, after cultures have been obtained (see 'Initial investigations' above). The early administration of antimicrobials is challenging with several patient- and institutional-related factors that influence delay [32]. Institutional protocols should address timeliness as a quality improvement measure [33]. In keeping with this ideology, the Infectious Diseases Society of America (IDSA) criticized the Society of Critical Care Medicine (SCCM) for rigid time frames for antibiotic use and lack of specificity regarding the starting point. The IDSA favors removal of specific time frames for antibiotic administration stating that prompt administration once a presumed diagnosis of sepsis or shock has been made by the treating clinician is more appropriate [5].

Although the feasibility of a one hour target has not been assessed, the rationale for choosing it is based upon several observational studies that report poor outcomes with delayed (even beyond one hour), inadequately dosed, or inappropriate (ie, treatment with antibiotics to which the pathogen was later shown to be resistant in vitro) antimicrobial therapy [34-44].

- In a retrospective analysis of over 17,000 patient with sepsis and septic shock, delay in first antibiotic administration was associated with increased in-hospital mortality with a linear increase in the risk of mortality for each hour delay in antibiotic administration [42]. Similar results were reported in an emergency department cohort of 35,000 patients [44].

- A prospective cohort study of 2124 patients demonstrated that inappropriate antibiotic selection was surprisingly common (32 percent) [38]. Mortality was markedly increased in these patients compared with those who had received appropriate antibiotics (34 versus 18 percent).

Choosing a regimen — The choice of antimicrobials can be complex and should consider the patient's history (eg, recent antibiotics received, previous organisms), comorbidities (eg, diabetes, organ failures), immune defects (eg, human immune deficiency virus), clinical context (eg, community- or hospital-acquired), suspected site of infection, presence of invasive devices, Gram stain data, and local prevalence and resistance patterns [45-49]. The general principles and examples of potential empiric regimens are given in this section but antimicrobial choice should be **tailored to each individual**.

For most patients with sepsis without shock, we recommend empiric broad spectrum therapy with one or more antimicrobials to cover all likely pathogens. Coverage should be directed against both gram-positive and gram-negative bacteria and, if indicated, against fungi (eg, *Candida*) and rarely viruses (eg, influenza). Broad spectrum is defined as

therapeutic agent(s) with sufficient activity to cover a range of gram negative and positive organisms (eg, carbapenem, piperacillin-tazobactam). Many patients with septic shock, particularly those suspected to have gram negative sepsis, should receive combination therapy with at least two antimicrobials from two different classes (ie, combination therapy) depending on the organisms that are considered likely pathogens and local antibiotic susceptibilities. Combination therapy is defined as multiple antibiotics given with the intent of covering a known or suspected pathogen with more than one agent.

Among organisms isolated from patients with sepsis, the most common include *Escherichia coli*, *Staphylococcus aureus, Klebsiella pneumoniae,* and *Streptococcus pneumoniae,* such that coverage of these organisms should be kept in mind when choosing an agent [50].

However, when the organism is unknown, the clinician should be mindful of other potential pathogens when risk factors are present and consider the following:

- Methicillin-resistant *S. aureus* – There is growing recognition that methicillin-resistant *S. aureus* (MRSA) is a cause of sepsis not only in hospitalized patients, but also in community dwelling individuals without recent hospitalization [51,52]. For these reasons, we suggest empiric intravenous vancomycin (adjusted for renal function) be added to empiric regimens, particularly in those with shock or those at risk for MRSA. Potential alternative agents to vancomycin (eg, daptomycin for non-pulmonary MRSA, linezolid) should be considered for patients with refractory or virulent MRSA, or with a contraindication to vancomycin. (See "Methicillin-resistant Staphylococcus aureus (MRSA) in adults: Treatment of bacteremia", section on 'Bacteremia due to MRSA' and "Treatment of hospital-acquired and ventilator-associated pneumonia in adults", section on 'Methicillin-resistant Staphylococcus aureus'.)

  In our practice, if *Pseudomonas* is an unlikely pathogen, we favor combining vancomycin with one of the following:

  - Cephalosporin, 3rd generation (eg, ceftriaxone or cefotaxime) or 4th generation (cefepime), or
  - Beta-lactam/beta-lactamase inhibitor (eg, piperacillin-tazobactam, ticarcillin-clavulanate), or
  - Carbapenem (eg, imipenem or meropenem)

- *Pseudomonas* – Alternatively, if *Pseudomonas* is a likely pathogen, we favor combining vancomycin with two of the following, depending on local antibiotic susceptibility patterns (see "Principles of antimicrobial therapy of Pseudomonas aeruginosa infections"):

  - Antipseudomonal cephalosporin (eg, ceftazidime, cefepime), or
  - Antipseudomonal carbapenem (eg, imipenem, meropenem), or
  - Antipseudomonal beta-lactam/beta-lactamase inhibitor (eg, piperacillin-tazobactam, ticarcillin-clavulanate), or
  - Fluoroquinolone with good anti-pseudomonal activity (eg, ciprofloxacin), or
  - Aminoglycoside (eg, gentamicin, amikacin), or
  - Monobactam (eg, aztreonam)

- Non pseudomonal gram-negative organisms (eg, *E. coli*, *K. pneumoniae*) – Gram-negative pathogens have historically been covered with two agents from different antibiotic classes. However, several clinical trials and two meta-analyses have failed to demonstrate superior overall efficacy of combination therapy compared to monotherapy with a third generation cephalosporin or a carbapenem [38,53-57]. Furthermore, one meta-analysis found double coverage that included an aminoglycoside was associated with an increased incidence of adverse events (nephrotoxicity) [56,57]. For this reason, in patients with suspected gram negative pathogens, we recommend use of a single agent with proven efficacy and the least possible toxicity, except in patients who are either neutropenic or whose sepsis is due to a known or suspected *Pseudomonas* infection, where combination therapy can be considered [55]. (See "Pseudomonas aeruginosa bacteremia and endocarditis" and "Principles of antimicrobial therapy of Pseudomonas aeruginosa infections".)

- Invasive fungal infections – The **routine** administration of empirical antifungal therapy is not generally warranted in **non-neutropenic** critically-ill patients. Invasive fungal infections occasionally complicate the course of critical illness, especially when the following risk factors are present: surgery, parenteral nutrition, prolonged antimicrobial treatment or hospitalization (especially in the intensive care unit), chemotherapy, transplant, chronic liver or renal

failure, diabetes, major abdominal surgery, vascular devices, septic shock or multisite colonization with *Candida* spp. However, studies do not support the routine use of empiric antifungals in this population:

- In a meta-analysis of 22 studies (most often comparing fluconazole to placebo, but also using ketoconazole, anidulafungin, caspofungin, micafungin, and amphotericin B), untargeted empiric antifungal therapy possibly reduced fungal colonization and the risk of invasive fungal infection but did not reduce all-cause mortality [58].
- In a study of critically-ill patients ventilated at least five days, empiric antifungal treatment (mostly fluconazole) was not associated with a decreased risk of mortality or occurrence of invasive candidiasis [59].
- In a multicenter randomized trial (EMPIRICUS) of 260 non-neutropenic critically-ill patients with *Candida* colonization (at multiple sites), multiple organ failure, and ICU-acquired sepsis, empiric treatment for 14 days with micafungin did not result in improved infection-free survival at 28 days but did decrease the rate of new fungal infection [60].

However, if *Candida* or *Aspergillus* is strongly **suspected** or if neutropenia is present, echinocandin (for *Candida*) or voriconazole (for *Aspergillus*) are often appropriate. (See "Treatment and prevention of invasive aspergillosis" and "Management of candidemia and invasive candidiasis in adults".)

- Other – Other regimens should consider the inclusion of agents for specific organisms such as *Legionella* (macrolide or fluoroquinolone) or difficult to treat organisms (eg, *Stenotrophomonas*), or for specific conditions (eg, neutropenic bacteremia)

Dosing — Clinicians should pay attention to maximizing the dose in patients with sepsis and septic shock using a full "high-end" loading dose where possible. This strategy is based upon the known increased volume of distribution that can occur in patients with sepsis due to the administration of fluid [61-63] and that higher clinical success rates have been reported in patients with higher peak concentrations of antimicrobials [64-66]. Continuous infusions of antibiotics as compared with intermittent dosing regimens remains investigational at this time [67].

Location of admission — Whether patients should be admitted to an intensive care unit (ICU) or ward is unclear and likely varies with the individual presenting characteristics as well as available institutional services and policy, which vary from state to state and country to country. For example, patients with septic shock who require mechanical ventilation and vasopressors clearly require ICU admission while those without shock who quickly respond to fluid and antibiotics may be safely transferred to the floor. For those in between these extremes, close observation and a low threshold to admit to the ICU is prudent.

Use of a systematic approach to ICU admission has been studied. One study of 3037 critically ill French patients aged 75 years or older, randomized patients to hospitals that promoted a systematic approach to ICU admission (interventional group) or to hospitals that did not use this approach (usual care) [68]. Despite a doubling of the admission rate to the ICU and an increased risk of in-hospital death, there was no difference in mortality at six months after adjustment for age, illness severity, initial clinical diagnosis, seniority of the emergency department physician, time of intensive care unit admission, baseline functional status, living situation, and type of home support. However, several flaws including, higher severity of illness in the intervention group, lack of blinding, and a strategy that was underpowered to detect a mortality difference may have influenced these results. In addition, international differences in the care of patients with sepsis may also explain an opposing outcome reported by a US cohort [69].

MONITOR RESPONSE — After fluids and empiric antibiotics have been administered, the therapeutic response should be assessed frequently. We suggest that clinical, hemodynamic, and laboratory parameters be followed as outlined in the sections below. In our experience, most patients respond within the first 6 to 24 hours to initial fluid therapy, however, resolution can be protracted and take days or weeks. The response mostly influences further fluid management but can also affect antimicrobial therapy and source control.

Monitoring catheters — For many patients, a central venous catheter (CVC) and an arterial catheter are placed, although they are not always necessary. For example, an arterial catheter may be inserted if blood pressure is labile, sphygmomanometer readings are unreliable, restoration of perfusion is expected to be protracted (especially when vasopressors are administered), or dynamic measures of fluid responsiveness are selected to follow the hemodynamic response. A CVC may be placed if the infusion of large volumes of fluids or vasopressors are anticipated, peripheral access is poor, or the central venous pressure (CVP) or the central venous oxyhemoglobin saturation ($ScvO_2$) are chosen as methods of monitoring the hemodynamic response. (See "Arterial catheterization techniques for invasive

monitoring" and "Novel tools for hemodynamic monitoring in critically ill patients with shock" and "Overview of central venous access".)

We believe that pulmonary artery catheters (PACs) should **not** be used in the routine management of patients with sepsis or septic shock since they have not been shown to improve outcome [70-72]. PACs can measure the pulmonary artery occlusion pressure (PAOP) and mixed venous oxyhemoglobin saturation (SvO_2). However, the PAOP has proven to be a poor predictor of fluid responsiveness in sepsis and the SvO_2 is similar to the $ScvO_2$, which can be obtained from a CVC [73,74]. (See "Pulmonary artery catheterization: Indications, contraindications, and complications in adults".)

Clinical — All patients should be followed clinically for improved mean arterial pressure (MAP), urine output, heart rate, respiratory rate, skin color, temperature, pulse oximetry, and mental status. Among these, a MAP ≥65 mmHg (MAP = [(2 x diastolic) + systolic]/3) (calculator 1), and urine output ≥0.5 mL/kg per hour are common targets used in clinical practice. They have not been compared to each other nor have they been proven to be superior to any other target or to clinical assessment. Data supporting their use are discussed above. (See 'Initial resuscitative therapy' above.)

> The ideal target for MAP, is unknown. One trial that randomized patients to a target MAP of 65 to 70 mmHg (low target MAP) or 80 to 85 mmHg (high target MAP) reported no mortality benefit to targeting a higher MAP [75,76]. Patients with a higher MAP had a greater incidence of atrial fibrillation (7 versus 3 percent), suggesting that targeting a MAP >80 mmHg is potentially harmful. Another pilot randomized trial that compared a lower MAP target (60-65 mmHg) to a higher target (75-80 mmHg) reported that among patients aged 75 years or older, a higher MAP target was associated with increased hospital mortality (60 versus 13 percent) [76]. An analysis of data from both trials reported that targeting a higher MAP had no effect on mortality but was associated with a greater risk of supraventricular cardiac arrhythmias [77]. Another meta-analysis of the same trials reported increased mortality in those targeted at a higher MAP who were also treated with vasopressors for greater that six hours [78].

Hemodynamic — Static or dynamic predictors of fluid responsiveness should be employed in order to determine further fluid management. Guidelines state a preference for dynamic measures [3] since they are more accurate than static measures (eg, CVP) at predicting fluid responsiveness. However whether their use improved clinically impactful outcomes such as mortality remains unproven.

- **Static** – Traditionally, in addition to MAP, the following static CVC measurements were used to determine adequate fluid management:
  - CVP at a target of 8 to 12 mmHg
  - $ScvO_2$ ≥70 percent (≥65 percent if sample is drawn off a PAC)

  While one early trial of patients with septic shock reported a mortality benefit to these parameters in a protocol-based therapy, trials published since then (ProCESS, ARISE, ProMISe) have reported no mortality benefit in association with their use [8-11]. (See 'Initial resuscitative therapy' above.)

- **Dynamic** – Respiratory changes in the vena caval diameter, radial artery pulse pressure, aortic blood flow peak velocity, left ventricular outflow tract velocity-time integral, and brachial artery blood flow velocity are considered dynamic measures of fluid responsiveness. There is increasing evidence that dynamic measures are more accurate predictors of fluid responsiveness than static measures, as long as the patients are in sinus rhythm and passively ventilated with a sufficient tidal volume. For actively breathing patients or those with irregular cardiac rhythms, an increase in the cardiac output in response to a passive leg-raising maneuver (measured by echocardiography, arterial pulse waveform analysis, or pulmonary artery catheterization) also predicts fluid responsiveness. Choosing among these is dependent upon availability and technical expertise, but a passive leg raising maneuver may be the most accurate and broadly available. Future studies that report improved outcomes (eg, mortality, ventilator free days) in association with their use are needed. Further details are provided separately. (See "Novel tools for hemodynamic monitoring in critically ill patients with shock".)

Laboratory

- **Lactate clearance** – Although the optimal frequency is unknown, we follow serum lactate (eg, every six hours) in patients with sepsis until the lactate value has clearly fallen. While guidelines promote normalization of lactate [3], lactate-guided resuscitation has not been convincingly associated with improved outcomes.

The lactate clearance is defined by the equation [(initial lactate – lactate >2 hours later)/initial lactate] x 100. The lactate clearance and interval change in lactate over the first 12 hours of resuscitation has been evaluated as a potential marker for effective resuscitation [14,79-83]. One meta-analysis of five low quality trials reported that lactate–guided resuscitation resulted in a reduction in mortality compared with resuscitation without lactate [3]. Other meta-analyses reported modest mortality benefit when lactate clearance strategies were used compared with usual care or $ScvO_2$ normalization [82,83]. However, many of the included trials contain heterogeneous populations and varying definitions of lactate clearance as well as additional variables that potentially affected the outcome.

In addition, after the restoration of perfusion, lactate is a poor marker of tissue perfusion [84]. As a result, lactate values are generally unhelpful following restoration of perfusion, with one exception that a rising lactate level should prompt reevaluation of perfusion. (See "Venous blood gases and other alternatives to arterial blood gases".)

Newer point of care analyzers are commercially available that may allow clinicians to follow lactate levels at the bedside more readily [85-87].

- Arterial blood gases – It is prudent to follow arterial blood gas parameters including the arterial partial pressure of oxygen:fraction of inspired oxygen ratio as well as severity and type of acidosis (resolution of metabolic acidosis and avoidance of hyperchloremic acidosis). Worsening gas exchange may indicate pulmonary edema from fluid resuscitation or other complications including pneumothorax from central catheter placement, acute respiratory distress syndrome, or venous thromboembolism.

- Routine laboratories – Follow up laboratory studies, in particular platelet count, serum chemistries, and liver function tests are often performed (eg, every six hours) until values have reached normal or baseline. Hyperchloremia should be avoided, but if detected, switching to low chloride-containing (ie, buffered) solutions may be indicated. (See "Treatment of hypovolemia or hypovolemic shock in adults", section on 'Buffered crystalloid versus isotonic saline'.)

- Microbiology – Follow up indices of infection are also indicated, including complete blood count and additional cultures. Results should prompt alteration of antibiotic choice if a better regimen can be substituted and/or investigations directed toward source control. (See 'Septic focus identification and source control' below.)

SEPTIC FOCUS IDENTIFICATION AND SOURCE CONTROL — In our experience, a focused history and examination is the most valuable method for source detection. Following initial investigations and empiric antimicrobial therapy, further efforts aimed at identifying and controlling the source(s) of infection should be performed in **all** patients with sepsis. In addition, for those who fail despite therapy or those who fail having initially responded to therapy, further investigations aimed at adequacy of the antimicrobial regimen or nosocomial super infection should be considered.

- **Identification** – Additional investigations targeted at the suspected source(s) should be considered in patients with sepsis, within the first 12 hours. This may include imaging (eg, computed tomography, ultrasonography) and sample acquisition (eg, bronchoalveolar lavage, aspirating fluid collections or joints), and may incur risk if an intervention is involved and the patient remains unstable. If invasive *Candida* or *Aspergillus* infection is suspected, serologic assays for 1,3 beta-D-glucan, galactomannan, and anti-mannan antibodies, if available, may provide early evidence of these fungal infections. These assays are discussed separately. (See "Clinical manifestations and diagnosis of candidemia and invasive candidiasis in adults", section on 'Non-culture methods' and "Diagnosis of invasive aspergillosis", section on 'Galactomannan antigen detection' and "Diagnosis of invasive aspergillosis", section on 'Beta-D-glucan assay'.)

- **Source control** – Source control (ie, physical measures to eradicate a focus of infection and eliminate or treat microbial proliferation and infection) should be undertaken since undrained foci of infection may not respond to antibiotics alone (table 2). As examples, potentially infected vascular access devices should be removed (after other vascular access has been established). Other examples include removing other infected implantable devices/hardware, when feasible, abscess drainage (including thoracic empyema and joint), percutaneous nephrostomy, soft tissue debridement or amputation, colectomy (eg, for fulminant *Clostridium difficile*-associated colitis), and cholecystostomy.

  The optimal timing of source control is unknown but guidelines suggest no more than 6 to 12 hours after diagnosis since survival is negatively impacted by inadequate source control [3]. Although the general rule of thumb is that source control should occur as soon as possible [88-90], this is not always practical or feasible. In addition, the decision should take into consideration the risk of the intervention and its complications (eg, death, fistula formation) and the likelihood of success, particularly when there is diagnostic uncertainty regarding the source.

PATIENTS WHO FAIL INITIAL THERAPY — Patients having persistent hypoperfusion despite adequate fluid resuscitation and antimicrobial treatment should be reassessed for fluid responsiveness (see 'Hemodynamic' above) adequacy of the antimicrobial regimen and septic focus control (see 'Septic focus identification and source control' above) as well as the accuracy of the diagnosis and the possibility that unexpected complications or coexisting problems have occurred (eg, pneumothorax following CVC insertion) (see "Evaluation of and initial approach to the adult patient with undifferentiated hypotension and shock"). Other options including vasopressors, glucocorticoids, inotropic therapy, and blood transfusion are discussed in this section.

Vasopressors — Intravenous vasopressors are useful in patients who remain hypotensive despite adequate fluid resuscitation or who develop cardiogenic pulmonary edema. Based upon meta-analyses of small randomized trials and observational studies, a paradigm shift in practice has occurred such that most experts prefer to avoid dopamine in this population and favor norepinephrine as the first-choice agent (table 3 and table 4). Although guidelines suggest additional agents including vasopressin (up to 0.03 units/minute to reduce the dose of norepinephrine) or epinephrine (for refractory hypotension), practice varies considerably. Guidelines state a preference for central venous and arterial access especially when vasopressor administration is prolonged or high dose, or multiple vasopressors are administered through the same catheter [3]; while this is appropriate, waiting for placement should not delay their administration and the risks of catheter placement should also be taken into account.

- First agent – Data that support norepinephrine as the first-line single agent in septic shock are derived from numerous trials that have compared one vasopressor to another [91-97]. These trials included norepinephrine versus phenylephrine [98], norepinephrine versus vasopressin [99-102], norepinephrine versus terlipressin [103,104], norepinephrine versus epinephrine [105], and vasopressin versus terlipressin [106]. While some of the comparisons found no convincing difference in mortality, length of stay in the ICU or hospital, or incidence of kidney failure [102,107], two 2012 meta-analyses reported increased mortality among patients who received dopamine during septic shock compared with those who received norepinephrine (53 to 54 percent versus 48 to 49 percent) [94,108]. Although the causes of death in the two groups were not directly compared, both meta-analyses identified arrhythmic events about twice as often with dopamine than with norepinephrine.

  However, we believe the initial choice of vasopressor in patients with sepsis is often individualized and determined by additional factors including the presence of coexistent conditions contributing shock (eg, heart failure), arrhythmias, organ ischemia, or agent availability. For example, in patients with significant tachycardia (eg, fast atrial fibrillation, sinus tachycardia >160/minute), agents that completely lack beta adrenergic effects (eg, vasopressin) may be preferred if it is believed that worsening tachycardia may prompt further decompensation. Similarly, dopamine (DA) may be acceptable in those with significant bradycardia; but low dose DA should **not** be used for the purposes of “renal protection.”

  The impact of agent availability was highlighted by one study of nearly 28,000 patients from 26 hospitals, which reported that during periods of norepinephrine shortages, phenylephrine was the most frequent alternative agent chosen by intensivists (use rose from 36 to 54 percent) [109]. During the same period, mortality rates from septic shock rose from 36 to 40 percent. Whether this was directly related to phenylephrine use remains unknown.

- Additional agents – The addition of a second or third agent to norepinephrine may be required (eg, epinephrine, dobutamine, or vasopressin) with little data to support agent selection.

  - For patients with distributive shock from sepsis, vasopressin may be added. In a meta-analysis of 23 trials, the addition of vasopressin to catecholamine vasopressors (eg, epinephrine, norepinephrine) resulted in a lower rate of atrial fibrillation (relative risk 0.77; 95% CI 0.67-0.88) [110]. However, when including only studies at low risk of bias, no mortality benefit, reduced requirement for renal replacement therapy, or rate of myocardial injury, stroke, ventricular arrhythmias or length of hospital stay was reported. Although not studied, this effect is likely due to a reduced need for catecholamines which increase the risk of cardiac arrhythmias. This analysis is consistent with other meta-analyses that have demonstrated no mortality benefit from vasopressin in patients with septic shock [111,112].

  - For patients with refractory septic shock associated with a low cardiac output, an inotropic agent may be added. In a retrospective series of 234 patients with septic shock, among several vasopressor agents added to norepinephrine (dobutamine, dopamine, phenylephrine, vasopressin), inotropic support with dobutamine was associated with a survival advantage (epinephrine was not studied) [113]. (See "Use of vasopressors and inotropes", section on 'Epinephrine' and "Use of vasopressors and inotropes", section on 'Dobutamine'.)

Additional information regarding vasopressor use including angiotensin II is provided separately. (See "Use of vasopressors and inotropes".)

Additional therapies — Most physicians agree that additional therapies such as glucocorticoids, inotropic agents, or red blood cell (RBC) transfusion are not warranted routinely in those who present with sepsis or septic shock but can be reserved for refractory cases or special circumstances.

Glucocorticoids — Guidelines recommend against the routine use of glucocorticoids in patients with sepsis. However, corticosteroid therapy is appropriate in patients with septic shock that is refractory to adequate fluid resuscitation and vasopressor administration. This topic is discussed in detail separately. (See "Glucocorticoid therapy in septic shock".)

Inotropic therapy — A trial of inotropic therapy may be warranted in patients who fail to respond to adequate fluids and vasopressors, particularly those who also have diminished cardiac output (table 4) [8,114-116]. Inotropic therapy should not be used to increase the cardiac index to supranormal levels [117]. Dobutamine is a suitable first-choice agent; epinephrine is a suitable alternative. (See "Use of vasopressors and inotropes", section on 'Dobutamine'.)

Red blood cell transfusions — Based upon clinical experience, randomized studies, and guidelines on transfusion of blood products in critically ill patients, we typically reserve red blood cell transfusion for patients with a hemoglobin level ≤7 g per deciliter. Exceptions include suspicion of concurrent hemorrhagic shock or active myocardial ischemia.

Support for a restrictive transfusion strategy (goal hemoglobin >7 g/dL) is derived from direct and indirect evidence from randomized studies of patients with septic shock:

- One multicenter randomized study of 998 patients with septic shock reported no difference in 28-day mortality between patients who were transfused when the hemoglobin was ≤7 g/dL (restrictive strategy) and patients who were transfused when the hemoglobin was ≤9 g/dL (liberal strategy) [118]. The restrictive strategy resulted in 50 percent fewer red blood cell transfusions (1545 versus 3088 transfusions) and did not have any adverse effect on the rate of ischemic events (7 versus 8 percent).

- One randomized trial initially reported a mortality benefit from a protocol that included transfusing patients to a goal hematocrit >30 (hemoglobin level 10 g/dL) [8]. However, similarly designed studies published since then reported no benefit to this strategy [9-11]. These studies are discussed below.

In further support of a restrictive approach to transfusion in patients with septic shock is the consensus among experts that transfusing to a goal of >7 g/dL is also preferred in critically ill patients without sepsis [119-121], the details of which are provided separately. (See "Use of blood products in the critically ill", section on 'Red blood cells'.)

PATIENTS WHO RESPOND TO THERAPY — Once patients have demonstrated a response to therapy, attention should be directed towards continuing to control the septic focus, and de-escalation of fluids and antibiotics, as appropriate. This may occur within hours or days, depending upon the indicators of response and the individual patient. (See 'Clinical' above and 'Hemodynamic' above and 'Laboratory' above.)

Identification and control of the septic focus — Following initial investigations and empiric antimicrobial therapy, further efforts aimed at identifying and controlling the source of infection should be performed in all patients with sepsis. (See 'Septic focus identification and source control' above.)

De-escalation fluids — Patients who respond to therapy (ie, clinical hemodynamic and laboratory targets are met; usually hours to days) should have the rate of fluid administration reduced or stopped, vasopressor support weaned, and, if necessary, diuretics administered. While early fluid therapy is appropriate in sepsis, fluids may be unhelpful or harmful when the circulation is no longer fluid responsive. Careful and frequent monitoring is essential because patients with sepsis may develop cardiogenic and noncardiogenic pulmonary edema (ie, acute respiratory distress syndrome [ARDS]).

In patients with ARDS or sepsis, a restrictive approach to intravenous fluid administration has been shown to decrease the duration of mechanical ventilation and ICU stay, compared to a more liberal approach [122,123]. In addition, small retrospective studies have reported that fluid overload is common in patients with sepsis and is associated with the increased performance of medical interventions (eg, diuresis, thoracentesis); the effect of fluid overload and such interventions on mortality and functional recovery in sepsis is unclear [124-126]. (See "Acute respiratory distress syndrome: Supportive care and oxygenation in adults", section on 'Fluid management'.)

De-escalation and duration of antibiotics — It is appropriate that de-escalation and duration of antimicrobial agents be assessed daily [127]. When uncertain, it is also appropriate to obtain an infectious diseases consultation to facilitate good antimicrobial stewardship.

- **De-escalation** – Once pathogen identification and susceptibility data return and/or patients clinically improve, we recommend that antimicrobial therapy be narrowed (typically a few days). When possible, antimicrobial therapy should also be pathogen- and susceptibility-directed (also known as targeted/definitive therapy). However, since no pathogen is identified in approximately 50 percent of patients, de-escalation of empiric therapy requires a component of clinical judgement. For example, vancomycin is typically discontinued, if no *Staphylococcus* is cultured.

  While there is no consensus on de-escalation criteria, most experts use follow-up clinical (improved vital signs), laboratory and imaging data, and a fixed course of broad-spectrum therapy (eg, 3 to 5 days).

  There are no high quality trials testing safety of de-escalation of antibiotic therapy in adult patients with sepsis or septic shock [128-131]. However, most observational trials report equivalent or improved outcomes with this strategy.

- **Duration** – The duration of antibiotics should be individualized. For most patients, the duration of therapy is typically 7 to 10 days [132-135]. However, longer courses are appropriate in patients who have a slow clinical response, an undrainable focus of infection, bacteremia with *S. aureus*, some fungal (eg, deep *Candida* infections) or viral infections (eg, herpes or cytomegalovirus), endocarditis, osteomyelitis, large abscesses, highly resistant gram-negative pathogens with marginal or limited sensitivities, neutropenia, or immunologic deficiencies [136-141]. Similarly, shorter courses may be acceptable in patients with negative cultures and rapid resolution of sepsis and laboratory studies. In patients who are neutropenic, antibiotic treatment should continue until the neutropenia has resolved or the planned antibiotic course is complete, whichever is longer. In non-neutropenic patients in whom infection is thoroughly excluded, antibiotics should be discontinued as early as is feasible to minimize colonization or infection with drug-resistant microorganisms and superinfection with other pathogens. Occasionally, shorter courses may be appropriate (eg, patients with pyelonephritis, urinary sepsis, or peritonitis who have rapid resolution of source control) [142-145].

- **Role of procalcitonin** – Although many institutions and guidelines support the use of procalcitonin to limit antibiotic (empiric or therapeutic) use in critically ill patients with suspected infection or documented infection, the evidence to support this practice is limited. While one randomized open-label trial of critically ill patients with infection reported a mortality benefit when the duration of antibiotic use was guided by normalization of procalcitonin levels [146], several randomized trials and meta-analyses found that using procalcitonin-guided algorithms to guide antimicrobial de-escalation did not result in any mortality benefit [147-152]. However, most trials report a reduction in the duration of antibiotic therapy (on average one day). Another retrospective analysis suggested that use of procalcitonin was associated with lower hospital and ICU length of stay, but no clinically meaningful outcomes were measured in this study [153]. Other studies suggest that procalcitonin may distinguish infectious from noninfectious conditions and may therefore facilitate the decision to de-escalate empiric therapy [147,154-156]. However, procalcitonin's greatest utility is in guiding antibiotic discontinuation in patients with known community-acquired pneumonia and acute bronchitis; thus measuring procalcitonin in these populations is appropriate. (See "Procalcitonin use in lower respiratory tract infections".)

SUPPORTIVE THERAPIES — Details regarding supportive therapies needed for the care of critically ill patients, including those with sepsis are provided separately:

- Blood product infusion (see "Use of blood products in the critically ill")
- Nutrition (see "Nutrition support in critically ill patients: An overview")
- Stress ulcer prophylaxis (see "Stress ulcer prophylaxis in the intensive care unit")
- Neuromuscular blocking agents (see "Clinical use of neuromuscular blocking agents in critically ill patients")
- Venous thromboembolism prophylaxis (see "Prevention of venous thromboembolic disease in acutely ill hospitalized medical adults")
- Intensive insulin therapy (see "Glycemic control and intensive insulin therapy in critical illness")

- External cooling or antipyretics (see "Fever in the intensive care unit", section on 'Management')
- Mechanical ventilation, sedation, weaning (see "Mechanical ventilation of adults in acute respiratory distress syndrome" and "Sedative-analgesic medications in critically ill adults: Selection, initiation, maintenance, and withdrawal" and "Methods of weaning from mechanical ventilation")
- Investigational therapies for sepsis and acute respiratory distress syndrome (eg, intravenous immune globulin, antithrombin, thrombomodulin, heparin, cytokine and toxin inactivators, as well as hemofiltration, statins, beta-2 agonists, beta blockade, and vitamin C/thiamine/hydrocortisone combination) (see "Investigational and ineffective therapies for sepsis" and "Acute respiratory distress syndrome: Investigational or ineffective therapies in adults")

PREGNANCY — There are no specific guidelines on how to manage sepsis in pregnancy but most experts treat using the same principles as outlined in this topic being cognizant of the altered hemodynamics of pregnancy. Guidelines have been proposed but have not been validated [157]. Further details regarding the management of critically ill pregnant patients are provided separately. (See "Critical illness during pregnancy and the peripartum period".)

SOCIETY GUIDELINE LINKS — Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Sepsis in children and adults".)

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Sepsis in adults (The Basics)")

SUMMARY AND RECOMMENDATIONS

- For patients with sepsis and septic shock, therapeutic priorities include securing the airway, correcting hypoxemia, and establishing vascular access for the early administration of fluids and antibiotics. Simultaneously obtaining the following is preferable (within 45 minutes) but should not delay the administration of fluids and antibiotics: routine laboratory studies, serum lactate, arterial blood gases, blood cultures (aerobic and anaerobic) from two distinct venipuncture sites and from all indwelling vascular access devices, cultures from easily accessible sites (eg, sputum, urine), and imaging of suspected sources. (See 'Immediate evaluation and management' above.)
- For patients with sepsis and septic shock, we recommend the infusion of intravenous fluids (30mL/kg) within the first three hours of presentation, rather than vasopressors, inotropes, or red blood cell transfusions (**Grade 1B**). Fluid boluses are the preferred method of administration and should be repeated until blood pressure and tissue perfusion are acceptable, pulmonary edema ensues, or there is no further response. Crystalloid solutions (eg, normal saline or Ringer's lactate) are our preferred resuscitation fluid. We recommend that a hyperoncotic starch solution NOT be administered (**Grade 1A**). (See 'Initial resuscitative therapy' above and 'Intravenous fluids (first three hours)' above.)
- For patients with sepsis, we recommend that optimal doses of empiric broad spectrum intravenous therapy with one or more antimicrobials be administered, in a prompt fashion (eg, within one hour) of presentation (**Grade 1B**). Broad spectrum is defined as therapeutic agent(s) with sufficient activity to cover a broad range of gram negative and positive organisms and, if suspected, against fungi and viruses. For patients with septic shock, particularly that associated with likely gram negative sepsis, we suggest combination therapy, defined as multiple antibiotics (at least two) from different classes given with the intent of covering a known or suspected pathogen with more than one antibiotic. Agent selection depends upon patient's history, comorbidities, immune defects, clinical context, suspected site of infection, presence of invasive devices, Gram stain data, and local prevalence and resistance patterns. The routine administration of antifungal therapy is not warranted in non-neutropenic patients. (See 'Empiric antibiotic therapy (first hour)' above and 'Initial resuscitative therapy' above.)

- For most patients with sepsis and septic shock, we recommend that fluid management be guided using clinical targets including mean arterial pressure 65 mmHg to 70 mmHg (calculator 1) and urine output ≥0.5 mL/kg/hour (**Grade 1B**). In addition, while dynamic measures of fluid responsiveness (eg, respiratory changes in the radial artery pulse pressure) are preferred, static measures of determining adequacy of fluid administration (eg, central venous pressure 8 to 12 mmHg or central venous oxygen saturation ≥70 percent) may be more readily available. Serum lactate should be followed (eg, every six hours), until there is a definitive clinical response. It is prudent that other measures of the overall response to infection also be followed (eg, routine laboratory studies, arterial blood gases, microbiology studies). (See 'Monitor response' above.)

- For patients with sepsis who remain hypotensive despite adequate fluid resuscitation (eg, 3L in first three hours), we recommend vasopressors (**Grade 1B**); the preferred initial agent is norepinephrine (table 4). For patients who are refractory to intravenous fluid and vasopressor therapy, additional therapies, such as glucocorticoids, inotropic therapy, and blood transfusions, can be administered on an individual basis. We typically reserve red blood cell transfusion for patients with a hemoglobin level <7 g per deciliter. (See 'Additional therapies' above and "Use of vasopressors and inotropes", section on 'Choice of agent in septic shock'.)

- Following initial investigations and empiric antimicrobial therapy, further efforts aimed at identifying and controlling the source(s) of infection (ideally within 6 to 12 hours) should be performed in **all** patients with sepsis (table 2 and table 1). In addition, for those who fail despite therapy or those who fail having initially responded to therapy, further investigations aimed at removal of devices suspected to be infected, adequacy of the antimicrobial regimen, or nosocomial super infection should be considered. (See 'Septic focus identification and source control' above.)

- For patients with sepsis who have demonstrated a response to therapy, we suggest that the rate of fluid administration should be reduced or stopped, vasopressor support weaned, and if necessary diuretics administered. We also recommend that antimicrobial therapy be narrowed once pathogen identification and susceptibility data return. Antimicrobial therapy should be pathogen- and susceptibility-directed for a total duration of 7 to 10 days, although shorter or longer courses are appropriate for select patients. (See 'Patients who respond to therapy' above.)

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Topic 1613 Version 105.0

GRAPHICS

Initial evaluation of common sources of sepsis

Suspected site	Symptoms/signs*	Initial microbiologic evaluation¶
Upper respiratory tract	Pharyngeal inflammation plus exudate ± swelling and lymphadenopathy	Throat swab for aerobic culture
Lower respiratory tract	Productive cough, pleuritic chest pain, consolidative auscultatory findings	Sputum of good quality, rapid influenza testing, urinary antigen testing (eg, pneumococcus, legionella; not recommended in children), quantitative culture of protected brush or bronchoalveolar lavage
Urinary tract	Urgency, dysuria, loin, or back pain	Urine culture and microscopy showing pyuria
Vascular catheters: arterial, central venous	Redness or drainage at insertion site	Culture of blood (from the catheter and a peripheral site), culture catheter tip (if removed)
Indwelling pleural catheter	Redness or drainage at insertion site	Culture of pleural fluid (through catheter), culture of catheter tip (if removed)
Wound or burn	Inflammation, edema, erythema, discharge of pus	Gram stain and culture of draining pus, wound culture not reliable
Skin/soft tissue	Erythema, edema, lymphangitis	Culture blister fluid or draining pus; role of tissue aspirates not proven
Central nervous system	Signs of meningeal irritation	CSF cell count, protein, glucose, Gram stain, and culture$^{\Delta}$
Gastrointestinal	Abdominal pain, distension, diarrhea, and vomiting	Stool culture for Salmonella, Shigella, Campylobacter, and Clostridium difficile
Intra-abdominal	Specific abdominal symptoms/signs	Aerobic and anaerobic culture of percutaneously or surgically drained abdominal fluid collections
Peritoneal dialysis (PD) catheter	Cloudy PD fluid, abdominal pain	Cell count and culture of PD fluid
Genital tract	Women: Low abdominal pain, vaginal discharge Men: Dysuria, frequency, urgency, urge incontinence, cloudy urine, prostatic tenderness	Women: Endocervical and high vaginal swabs onto selective media Men: Urine Gram stain and culture
Bone	Pain, warmth, swelling, decreased use	Blood cultures, MRI, bone cultures at surgery or by interventional radiology
Joint	Pain, warmth, swelling, decreased range of motion	Arthrocentesis with cell counts, Gram stain, and culture

CSF: cerebrospinal fluid; PD: peritoneal dialysis; MRI: magnetic resonance imaging.
*Fever is frequently seen with all conditions.
¶ Suggested initial tests are not considered to be comprehensive. Additional testing and infectious disease consultation may be warranted.
$^{\Delta}$Bacterial antigen and/or molecular testing may also be appropriate in selected patients. Refer to UpToDate topics on diagnostic testing for meningitis.

Adapted from: Cohen J. Microbiologic requirements for studies of sepsis. In: Clinical Trials for the Treatment of Sepsis, Sibbald WJ, Vincent JL (eds), Springer-Verlag, Berlin 1995.

Graphic 59769 Version 12.0

Source control methods for common ICU infections

Source	Interventions
Pneumonia	Chest physiotherapy, suctioning
Urinary tract	Drainage of abscesses, relief of obstruction, removal or changing of infected catheters
Catheter-related bacteremia	Removal of catheter
Peritonitis	Resection, repair, or diversion of ongoing sources of contamination, drainage of abscesses, debridement of necrotic tissue
Pancreatic infection	Drainage or debridement
Soft tissue infection	Debridement of necrotic tissue and drainage of discrete abscesses
Septic arthritis	Joint drainage and debridement
Endocarditis	Valve replacement
Prosthetic device infection	Device removal
Empyema	Drainage, decortication
Sinusitis	Surgical decompression of the sinuses
Cholangitis	Bile duct decompression

Adapted from: Marshall JC, Lowry SF. Evaluation of the adequacy of source control. In: Clinical Trials for the Treatment of Sepsis, Sibbald WJ, Vincent JL (Eds), Springer-Verlag, Berlin 1995.

Graphic 58257 Version 2.0

Vasoactive agents in septic shock

Drug	Effect on heart rate	Effect on contractility	Arterial constriction effects
Dobutamine	+	+++	- (dilates)
Dopamine	++	++	++
Epinephrine	+++	+++	++
Norepinephrine	++	++	+++
Phenylephrine	0	0	+++

Graphic 74872 Version 2.0

Vasopressors and inotropes in treatment of acute hypotensive states and shock: Adult dose and selected characteristics

Agent	US trade name	Initial dose	Usual maintenance dose range	Range of maximum doses used in refractory shock	Role in therapy and selected characteristics
Vasopressors (alpha-1 adrenergic)					
Norepinephrine (noradrenaline)	Levophed	8 to 12 mcg/minute (0.1 to 0.15 mcg/kg/minute) A lower initial dose of 5 mcg/minute may be used, eg, in older adults	2 to 4 mcg/minute (0.025 to 0.05 mcg/kg/minute)	35 to 100 mcg/minute (0.5 to 0.75 mcg/kg/minute; up to 3.3 mcg/kg/minute has been needed rarely)	▪ Initial vasopressor of choice in septic, cardiogenic, and hypovolemic shock. ▪ Wide range of doses utilized clinically. ▪ Must be diluted; eg, a usual concentration is 4 mg in 250 mL of D5W or NS (16 micrograms/mL).
Epinephrine (adrenaline)	Adrenalin	1 mcg/minute (0.014 mcg/kg/minute)	1 to 10 mcg/minute (0.014 to 0.14 mcg/kg/minute)	10 to 35 mcg/minute (0.14 to 0.5 mcg/kg/minute)	▪ Initial vasopressor of choice in anaphylactic shock. ▪ Typically an add-on agent to norepinephrine in septic shock when an additional agent is required to raise MAP to target and occasionally an alternative first-line agent if norepinephrine is contraindicated. ▪ Increases heart rate; may induce tachyarrhythmias and ischemia. ▪ Elevates lactate concentrations during initial administration (ie, may preclude use of lactate clearance goal); may decrease mesenteric perfusion. ▪ Must be diluted; eg, a usual concentration is 1 mg in 250 mL D5W (4 micrograms/mL).
Phenylephrine	Neo-Synephrine, Vazculep	100 to 180 mcg/minute until stabilized (alternatively, 0.5 to 2 mcg/kg/minute)	20 to 80 mcg/minute (0.25 to 1.1 mcg/kg/minute)	80 to 360 mcg/minute (1.1 to 6 mcg/kg/minute); Doses >6 mcg/kg/minute do not increase efficacy according to product information in	▪ Pure alpha-adrenergic vasoconstrictor. ▪ Initial vasopressor when tachyarrhythmias preclude use of norepinephrine. ▪ Alternative vasopressor for patients with septic shock who: (1) develop tachyarrhythmias on norepinephrine,

				the United States	epinephrine, or dopamine, (2) have persistent shock despite use of two or more vasopressor/inotropic agents including vasopressin (salvage therapy), or (3) high cardiac output with persistent hypotension. ▪ May decrease stroke volume and cardiac output in patients with cardiac dysfunction. ▪ May be given as bolus dose of 50 to100 micrograms to support blood pressure during rapid sequence intubation. ▪ Must be diluted; eg, a usual concentration is 10 mg in 250 mL D5W or NS (40 micrograms/mL).
Dopamine	Inotropin	2 to 5 mcg/kg/minute	5 to 20 mcg/kg/minute	20 to >50 mcg/kg/minute	▪ An alternative to norepinephrine in septic shock in highly selected patients (eg, with compromised systolic function or absolute or relative bradycardia and a low risk of tachyarrhythmias). ▪ More adverse effects (eg, tachycardia, arrhythmias particularly at doses ≥20 mcg/kg/minute) and less effective than norepinephrine for reversing hypotension in septic shock. ▪ Lower doses (eg, 1 to 3 mcg/kg/minute) should not be used for renal protective effect and can cause hypotension during weaning. ▪ Must be diluted; eg, a usual concentration is 400 mg in 250 mL D5W (1.6 mg/mL); use of a commercially available pre-diluted solution is preferred.
Antidiuretic hormone					
Vasopressin (arginine-vasopressin)	Pitressin, Vasostrict	0.03 units per minute (alternatively 0.01 to 0.03	0.03 to 0.04 units per minute (not titrated)	0.04 to 0.07 units/minute;	▪ Add-on to norepinephrine to raise blood pressure to target MAP or

		units/minute initially)		Doses >0.04 units/minute can cause cardiac ischemia and should be reserved for salvage therapy	decrease norepinephrine requirement. Not recommended as a replacement for a first-line vasopressor. ▪ Pure vasoconstrictor; may decrease stroke volume and cardiac output in myocardial dysfunction or precipitate ischemia in coronary artery disease. ▪ Must be diluted; eg, a usual concentration is 25 units in 250 mL D5W or NS (0.1 units/mL).
Inotrope (beta$_1$ adrenergic)					
Dobutamine	Dobutrex	0.5 to 1 mcg/kg/minute (alternatively, 2.5 mcg/kg/minute in more severe cardiac decompensation)	2 to 20 mcg/kg/minute	20 to 40 mcg/kg/minute; Doses >20 mcg/kg/minute are not recommended in heart failure and should be reserved for salvage therapy	▪ Initial agent of choice in cardiogenic shock with low cardiac output and maintained blood pressure. ▪ Add-on to norepinephrine for cardiac output augmentation in septic shock with myocardial dysfunction (eg, in elevated left ventricular filling pressures and adequate MAP) or ongoing hypoperfusion despite adequate intravascular volume and use of vasopressor agents. ▪ Increases cardiac contractility and rate; may cause hypotension and tachyarrhythmias. ▪ Must be diluted; a usual concentration is 250 mg in 500 mL D5W or NS (0.5 mg/mL); use of a commercially available pre-diluted solution is preferred.
Inotrope (nonadrenergic, PDE$_3$ inhibitor)					
Milrinone	Primacor	Optional loading dose: 50 mcg/kg over 10 minutes (usually not given)	0.125 to 0.75 mcg/kg/minute		▪ Alternative for short-term cardiac output augmentation to maintain organ perfusion in cardiogenic shock refractory to other agents. ▪ Increases cardiac contractility and modestly increases heart rate at high doses; may cause

					peripheral vasodilation, hypotension, and/or ventricular arrhythmia. ▪ Renally cleared; dose adjustment in renal impairment needed. ▪ Must be diluted; eg, a usual concentration is 40 mg in 200 mL D5W (200 micrograms/mL); use of a commercially available pre-diluted solution is preferred.

- All doses shown are for intravenous (IV) administration in adult patients. The initial doses shown in this table may differ from those recommended in immediate post-cardiac arrest management (ie, advanced cardiac life support). For details, refer to the UpToDate topic review of post-cardiac arrest management in adults, section on hemodynamic considerations.
- Vasopressors can cause life-threatening hypotension and hypertension, dysrhythmias, and myocardial ischemia. They should be administered by use of an infusion pump adjusted by clinicians trained and experienced in dose titration of intravenous vasopressors using continuous noninvasive electronic monitoring of blood pressure, heart rate, rhythm, and function. Hypovolemia should be corrected prior to the institution of vasopressor therapy. Reduce infusion rate gradually; avoid sudden discontinuation.
- Vasopressors can cause severe local tissue ischemia; central line administration is preferred. When a patient does not have a central venous catheter, vasopressors can be temporarily administered in a low concentration through an appropriately positioned peripheral venous catheter (ie, in a large vein) until a central venous catheter is inserted. The examples of concentrations shown in this table are useful for peripheral (short-term) or central line administration. Closely monitor catheter site throughout infusion to avoid extravasation injury. In event of extravasation, prompt local infiltration of an antidote (eg, phentolamine) may be useful for limiting tissue ischemia. Stop infusion and refer to extravasation management protocol.
- Vasopressor infusions are high-risk medications requiring caution to prevent a medication error and patient harm. To reduce the risk of making a medication error, we suggest that centers have available protocols that include steps on how to prepare and administer vasopressor infusions using a limited number of standardized concentrations. Examples of concentrations and other detail are based on recommendations used at experienced centers; protocols can vary by institution.

D5W: 5% dextrose water; MAP: mean arterial pressure; NS: 0.9% saline.

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1. *Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017; 45:486.*
2. *Hollenberg SM. Vasoactive drugs in circulatory shock. Am J Respir Crit Care Med 2011; 183:847.*
3. *Lexicomp Online. Copyright © 1978-2018 Lexicomp, Inc. All Rights Reserved.*

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