IHI Severe Sepsis Bundles
The Severe Sepsis Bundles have been revised in conjunction with the updated 2012 International Guidelines for Management of Severe Sepsis and Septic Shock. As a result:

- The previous version of the Sepsis Resuscitation Bundle has been modified into two bundles: the **Severe Sepsis 3-Hour Resuscitation Bundle** and the **6-Hour Septic Shock Bundle**
- The Sepsis Management Bundle — part of the previous version of the Severe Sepsis Bundles — has been eliminated, and **Other Supportive Therapies** have been added

**Overview: Severe Sepsis 3-Hour Resuscitation Bundle and 6-Hour Septic Shock Bundle**

**Severe Sepsis 3-Hour Resuscitation Bundle**: Evidence-based goals that must be completed within 3 hours for patients with severe sepsis.

The Severe Sepsis 3-Hour Resuscitation Bundle contains the following elements, to be completed within 3 hours of the time of presentation²:

1. Measure Lactate Level
2. Obtain Blood Cultures Prior to Administration of Antibiotics
3. Administer Broad Spectrum Antibiotics
4. Administer 30 mL/kg Crystalloid for Hypotension or Lactate ≥4 mmol/L

**6-Hour Septic Shock Bundle**: Evidence-based goals that must be completed within 6 hours for patients with severe sepsis.

The 6-Hour Septic Shock Bundle contains the following elements, to be completed within 6 hours of the time of presentation²:

1. Apply Vasopressors (for Hypotension That Does Not Respond to Initial Fluid Resuscitation to Maintain a Mean Arterial Pressure (MAP) ≥65 mm Hg)
2. In the Event of Persistent Arterial Hypotension Despite Volume Resuscitation (Septic Shock) or Initial Lactate ≥4 mmol/L (36 mg/dL):
   a. Measure Central Venous Pressure (CVP)³
   b. Measure Central Venous Oxygen Saturation (ScvO2)³
3. Remeasure Lactate If Initial Lactate Was Elevated³

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² “Time of presentation” is defined as the time of triage in the emergency department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of severe sepsis or septic shock ascertained through chart review.
³ Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, ScvO2 of ≥70%, and lactate normalization.
Some bundle elements may not be completed if the clinical conditions described in the bundle do not prevail, but clinicians must assess for those conditions and make a determination. The intention in applying the bundle is to perform all indicated tasks 100 percent of the time within the first 6 hours of identification of severe sepsis.

**Background**
The Severe Sepsis 3-Hour Resuscitation Bundle and the 6-Hour Septic Shock Bundle represent a distillation of the concepts and recommendations found in the practice guidelines published by the Surviving Sepsis Campaign. The bundles are designed to allow teams to follow the timing, sequence, and goals of the individual elements of care.

Individual hospitals should use the bundles to create customized protocols and pathways specific to their institutions. However, we recommend that each of the elements in the bundles should be incorporated in those protocols. These bundles have been approved by the National Quality Forum (NQF) as the first scientifically sound, valid, and reliable elements for care of severely septic patients. The addition of other strategies not found in the bundles may be found in the Surviving Sepsis Campaign Guidelines, but are not part of the NQF measure at this time. In your hospital, the bundles will directly inform the measurements that your improvement team may use to follow their progress as they progressively make changes intended to improve care.

**Related Measures**
[Reliability: Severe Sepsis Bundles](#)
[Compliance with Severe Sepsis Bundles](#) (with the Goal of Reducing Mortality)

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**Severe Sepsis 3-Hour Resuscitation Bundle**

1. **Measure Lactate Level**

**Background**
Hyperlactatemia is typically present in patients with severe sepsis or septic shock and may be secondary to anaerobic metabolism due to hypoperfusion or other complex factors. The prognostic value of raised blood lactate levels has been well established in septic shock patients [1], particularly if the high levels persist. [2,3] In addition, blood lactate levels have been shown to have greater prognostic value than oxygen-derived variables. [4] Obtaining a lactate level is essential to identifying tissue hypoperfusion in patients who are not yet hypotensive but who are at risk for septic shock.
Limitations
The interpretation of blood lactate levels in septic patients is not always straightforward. A number of studies have suggested that elevated lactate levels may result from cellular metabolic failure in sepsis rather than from global hypoperfusion. Elevated lactate levels can also result from decreased clearance by the liver. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation.

Implications
Given the high risk for septic shock, all patients with elevated lactate ≥4 mmol/L (36 mg/dL) enter the early goal-directed therapy portion of the 6-Hour Septic Shock Bundle, regardless of blood pressure. Mortality is high in septic patients with both hypotension and lactate ≥4 mmol/L (46.1 percent). Mortality is also increased in severely septic patients with hypotension alone (36.7 percent) and lactate ≥4 mmol/L alone (30 percent). [5] This approach is consistent with the trial that established the value of early goal-directed therapies. [6]

Turnaround Time
Lactate levels must be available in your institution with rapid turnaround time (within minutes) to effectively treat severely septic patients. An arterial blood gas analyzer located in the clinical laboratories usually satisfies this requirement. However, any means of rapid turnaround time is acceptable. In some cases, it will be essential for hospitals to invest in adequate equipment in order to meet present standards of care for septic patients.

The technique of obtaining lactate by venipuncture typically carries a 24- to 48-hour turnaround time and will not be suitable to care for septic patients. This technique also requires special collection conditions, such as without the use of tourniquet, which will likely hinder proper clinical care.

Arterial vs. Venous Lactate
The question has been raised several times as to whether an arterial or venous lactate sample is required. While there is no consensus of settled literature on this question, an elevated lactate of any variety is typically abnormal and must be explained. Either collection is appropriate for bundle compliance. Lactate elevations may be influenced by other conditions such as a variety of medications, hepatic insufficiency, or hyperlactatemia due to primarily cardiac causes of hypoperfusion.

Grading the Evidence [See Ranking the Evidence]
- The use of lactate as a method to detect severe sepsis and septic shock and as a rationale for further therapies was evaluated as part of the larger recommendation on initial resuscitation in the 2012 Surviving Sepsis Campaign Guidelines. There, the guidelines committee recommended the protocolized, quantitative resuscitation of a
patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration equal to or greater than 4 mmol/L).

Evidence Grade 1C: This is a strong recommendation for care based on a number of qualitative considerations. “C” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies.

- The strategy of clearing lactate to normal values was also assessed in the 2012 Surviving Sepsis Campaign Guidelines. The Campaign suggests targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion.

Evidence Grade 2C: This is a suggestion for care based on a number of qualitative considerations. “C” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. [7]

References

Content adapted extensively from:
Tips
1. If serum lactate is not rapidly available in your institution, invest in equipment to make rapid assessment possible. This should be presented to hospital and laboratory administration as a present standard of care.
2. Create a standardized protocol to manage severe sepsis that includes measurement of lactate.
3. Include a prompt on arterial blood gas requisitions or physician order entry to prompt users to order lactate for suspected severe sepsis.

Severe Sepsis 3-Hour Resuscitation Bundle

2. Obtain Blood Cultures Prior to Administration of Antibiotics

Related Measures
Timming of Blood Cultures

Background
The incidence of sepsis and bacteremia in critically ill patients has been increasing in the past two decades. [8,9] Thirty percent to 50 percent of patients presenting with a clinical syndrome of severe sepsis or shock have positive blood cultures. Therefore, blood should be obtained for culture in any critically ill septic patient.

Collecting blood cultures prior to antibiotic administration offers the best hope of identifying the organism that caused severe sepsis in an individual patient. Failure to check blood cultures prior to antibiotic infusion will perhaps affect the growth of any blood borne bacteria and prevent a culture from becoming positive later.

Collection Strategy
Two or more blood cultures are recommended with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently inserted (<48 hours). [1,2] In patients with suspected catheter-related infection, a pair of blood cultures obtained through the catheter hub and a peripheral site should be obtained simultaneously. Cultures of other sites (preferably quantitative, where appropriate), such as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection should also be obtained before antimicrobial therapy. [2] If the same organism is recovered from both cultures, the likelihood that the organism is causing the severe sepsis is enhanced. In addition, if the culture drawn through the vascular access device is positive much earlier than the peripheral blood culture (i.e., >2 hours earlier), it may offer support that the vascular access device is the source of the infection. [3] Volume of blood may also be important. [4]
Indications
Fever, chills, hypothermia, leukocytosis, left shift of neutrophils, neutropenia, and the development of otherwise unexplained organ dysfunction (e.g., renal failure or signs of hemodynamic compromise) are specific indications for obtaining blood for culture. Blood cultures should be taken as soon as possible after the onset of fever or chills.

While it remains difficult to predict bacteremia in patients with sepsis [5], a number of clinical and laboratory parameters are independently correlated with the presence of bacteria in the blood of patients when infection is suspected. These include chills, hypoalbuminemia, the development of renal failure, and a diagnosis of urinary tract infection [5,6]; other criteria are new fever, hypothermia, leukocytosis and left shift of neutrophils, neutropenia, and signs of hemodynamic compromise. [7] Peaking fever appears to be more sensitive than leukocytosis to predict bacteremia [8]; however, fever and low-grade bacteremia can be continuous, such as in endocarditis.

Grading the Evidence [See Ranking the Evidence]
The 2012 Surviving Sepsis Campaign Guidelines recommend obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay in antibiotic administration.

Evidence Grade 1C: This is a strong recommendation for care based on a number of qualitative considerations. The quality of the evidence generally derives from well-done observational or cohort studies with controls.

References

Content adapted extensively from:

**Tips**

1. Create a standardized protocol to manage severe sepsis that includes reminders to draw blood cultures before administering antibiotics.
2. Place prompts in locations near antibiotic storage querying staff regarding whether blood cultures have been drawn.
3. Store first dose antibiotics in automated dispensing system on unit.

**Severe Sepsis 3-Hour Resuscitation Bundle**

**3. Administer Broad Spectrum Antibiotics**

**Related Measures**

*Timing of Antibiotics*

**Background**

Once severe sepsis is identified, antibiotics must be started rapidly to treat the underlying infection. Although early antibiotic administration seems to be an intuitive approach, administration of effective therapies is often delayed. Evidence supports that for patients with septic shock, the duration of hypotension prior the administration of antibiotics is a critical determinant in the survival of septic shock. [1]

The balance of evidence unwaveringly suggests that early administration of appropriate antibiotics reduces mortality in patients with Gram-positive and Gram-negative bacteremias. Some of the evidence supporting early administration is based on the assumption that patients who fail to receive appropriate antibiotics essentially represent a set of patients for whom delay has occurred in antibiotic delivery. Several studies have confirmed the mortality benefit...
associated with appropriate antimicrobials in patients with severe infections due to Gram-
negative and Gram-positive bacteria. [2-4]

In addition, the major sources of infection in severe sepsis or shock are pneumonia and intra-
abdominal infections [5,6] and other sources generally account for <5 percent of cases. The
prevalence of pneumonia as a cause of sepsis lends support to the case for treating severe
sepsis with early antibiotic administration. In a study of ventilator-acquired pneumonia, patients
with significant organ dysfunction (required criteria for severe sepsis) who received antibiotics
later had far greater ICU mortality: 37 percent vs. 7 percent (p=0.006); hospital mortality: 44
percent vs. 15 percent (p=0.01). [7]

**Choice of Antibiotics**
The choice of antibiotics should be guided by the susceptibility of likely pathogens in the
community and the hospital, as well as any specific knowledge about the patient, including drug
intolerance, underlying disease, the clinical syndrome. The regimen should cover all likely
pathogens since there is little margin for error in critically ill patients. There is ample evidence
that failure to initiate appropriate therapy promptly (i.e., therapy that is active against the
causative pathogen) has adverse consequences on outcome. [2-4]

Although restricting the use of antibiotics, and particularly broad spectrum antibiotics, is
important for limiting superinfection and for decreasing the development of antibiotic
resistant pathogens, patients with severe sepsis or septic shock warrant broad spectrum
therapy until the causative organism and its antibiotic susceptibilities are defined.

**Availability**
Establishing a supply of premixed antibiotics in an emergency department or critical care unit for
such urgent situations is an appropriate strategy for enhancing the likelihood that antimicrobial
agents will be infused promptly. Staff should be cognizant that some agents require more
lengthy infusion time, whereas others can be rapidly infused or even administered as a bolus.

**48- to 72-Hour Re-evaluation**
Once the causative agent and antibiotic susceptibilities have been identified, restriction of the
number of antibiotics and narrowing the spectrum of antimicrobial therapy is an important and
responsible strategy for minimizing the development of resistant pathogens and for containing
costs.

The antimicrobial regimen should always be reassessed after 48 to 72 hours on the basis of
microbiological and clinical data, with the aim of using a narrow-spectrum antibiotic to prevent
the development of resistance, to reduce toxicity, and to reduce costs. Empiric combination
therapy should not be administered for more than 3 to 5 days. [12-16] Once a causative
pathogen is identified, there is no evidence that combination therapy is more effective than
monotherapy. The duration of therapy should typically be 7 to 10 days and guided by clinical response. Longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with S. aureus, some fungal and viral infections, or immunologic deficiencies, including neutropenia. [17]

**Dosing**

All patients should receive a full loading dose of each antimicrobial. However, patients with sepsis or septic shock often have abnormal renal or hepatic function and may have abnormal volumes of distribution due to aggressive fluid resuscitation. The ICU pharmacist should be consulted to ensure that serum concentrations are attained that maximize efficacy and minimize toxicity. [8-11]

**Grading the Evidence** [See Ranking the Evidence]

The Grade 1 recommendations below reflect strong evidence for care based on a number of qualitative considerations. The Grade 2 suggestions below are weaker recommendations for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects case series data or expert opinion. “UG” level evidence is ungraded.

- Administer effective intravenous antimicrobials within the first hour of recognition of septic shock (Grade 1B) and severe sepsis without septic shock (Grade 1C) as the goal of therapy.
- Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (Grade 1B) should be employed.
- Antimicrobial regimen should be reassessed daily for potential deescalation (Grade 1B).
- Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (Grade 2C).
- Combination empirical therapy for neutropenic patients with severe sepsis (Grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas* spp. (Grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for *P. aeruginosa* bacteremia (Grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (Grade 2B).
• Empiric combination therapy should not be administered for more than 3 to 5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (Grade 2B).
• Duration of therapy is typically 7 to 10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus*, some fungal and viral infections, or immunologic deficiencies, including neutropenia (Grade 2C).
• Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (Grade 2C).
• Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG).

References


Content adapted extensively from:

Tips
1. Establish a standardized clinical protocol that includes the empiric administration of antibiotics in severe sepsis within 1 hour of presentation.
2. Establish a pre-mixed quantity of broad spectrum antibiotics available in the emergency department and ICU, in order to avoid delays involving pharmacy acquisition of the antibiotic.
3. Infuse antibiotics through multiple lines as available in order to speed delivery of agents.
4. Cover both Gram-positive and Gram-negative organisms.
5. Consider specific knowledge about the patient’s past organism burden, if available (including fungal infection); the setting from which the patient arrived in the emergency department (e.g., another institution that may harbor resistant organism); and community and hospital resistance patterns in making choices.

Severe Sepsis 3-Hour Resuscitation Bundle

4. Administer 30 mL/kg Crystalloid for Hypotension or Lactate ≥4 mmol/L

In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or lactate ≥4 mmol/L (36 mg/dL):
- Measure central venous pressure (CVP)*
- Measure central venous oxygen saturation (ScvO₂)*
*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, ScvO2 of ≥70 percent, and lactate normalization.

Background
Patients with severe sepsis and septic shock may experience ineffective arterial circulation due to the vasodilatation associated with infection or impaired cardiac output. Poorly perfused tissue beds result in global tissue hypoxia, which is often found in association with an elevated serum lactate level. A serum lactate value greater than 4 mmol/L (36 mg/dL) is correlated with increased severity of illness and poorer outcomes even if hypotension is not yet present. As such, patients who are hypotensive or have a lactate greater than 4 mmol/L (36 mg/dL) require intravenous fluids to expand their circulating volume and effectively restore perfusion pressure.

Initial Fluid Administration
The Severe Sepsis 3-Hour Resuscitation Bundle calls for an initial administration of 30 mL/kg of crystalloid as a fluid challenge in cases of suspected hypovolemia or actual cases of serum lactate greater than 4 mmol/L (36 mg/dL).

Fluid resuscitation should be commenced as early as possible in the course of septic shock (even before intensive care unit admission). Requirements for fluid infusion are not easily determined so that repeated fluid challenges should be performed.

The targets for quantitative resuscitation provided in the guidelines are CVP of ≥8 mm Hg, ScvO2 of ≥70 percent, and normalization of lactate.

Fluid Challenge vs. Increase in Maintenance Fluids
An increase in maintenance fluid administration must be distinguished from fluid challenge. Fluid challenge is a term used to describe the initial volume expansion period in which the response of the patient to fluid administration is carefully evaluated. During this process, large amounts of fluids may be administered over a short period of time under close monitoring to evaluate the patient’s response.

Fluid challenges require the definition of four components: 1) the type of fluid to be administered; 2) the rate of fluid infusion (e.g., 500 mL to 1,000 mL over 30 minutes); 3) the end points (e.g., mean arterial pressure of >65 mm Hg, heart rate of <110 beats per minute); and 4) the safety limits (e.g., development of pulmonary edema). Maintenance fluid increases typically alter only the rate of administration of continuous fluids.

Crystalloid vs. Colloid
Although prospective studies of choice of fluid resuscitation in patients with septic shock only are lacking, a prospective, controlled, randomized, double-blind study comparing 4 percent human albumin solution with 0.9 percent sodium chloride (saline) in critically ill patients requiring
fluid resuscitation (SAFE study) has been completed. The results of this study showed identical mortality rates in patients receiving albumin or 0.9 percent sodium chloride. Subgroup analysis revealed that albumin might have some (albeit not statistically significant) benefit in patients with severe sepsis. [1]

In addition, meta-analyses of clinical studies comparing crystalloid and colloid resuscitation in general and surgical patient populations indicate no clinical outcome difference between colloids and crystalloids and would appear to be generalizable to sepsis populations. [2-4] As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same goals and results in more edema.

**End Points of Fluid Resuscitation**

For the Severe Sepsis 3-Hour Resuscitation Bundle, a minimum fluid challenge is defined in an effort to avoid hypotension. The bundle does not restrict additional fluids. If, however, the patient should enter the early goal-directed phases of the 6-Hour Septic Shock Bundle, either for hypotension not responding to fluid challenges or a lactate ≥4 mmol/L (36 mg/dL), targets for central venous pressure as well as central and mixed venous oxygen saturation have been defined. These targets are not arbitrary. They are based on specifications defined in the best available literature, [5] and a recent analysis supporting a 65 percent SvO2 saturation as similar to a 70 percent ScvO2. [6]

In Rivers et al., hospital mortality was 30.5 percent in the group assigned to early goal-directed therapy, compared with 46.5 percent in the standard therapy group (p=0.009). [5] Rivers et al. used restoration of a central venous oxygen saturation of >70 percent as one of their goals, and this was met in 95 percent of the early goal-directed group, compared with just 60 percent of the standard treatment group (p<0.001). Patients in the early goal-directed treatment groups received more fluids (5 vs. 3.5 L, p<0.001) and more were given red cell transfusions (64 vs. 18.5 percent, p<0.001) in the first 6 hours than in the standard treatment group, emphasizing the importance of early and adequate fluid resuscitation in patients with severe sepsis.

However, considerable debate remains on these thresholds largely because of problems in monitoring the regional microcirculation and oxygenation. Changes may persist at a local level while systemic hemodynamic and oxygenation variables seem to have stabilized. Each end point must be considered in its context, and the combination of clinical variables (mean arterial pressure, urine output, apparent skin perfusion, level of consciousness) along with serum lactate values may be helpful to the clinician despite a lack of randomized trials to establish this point.

**Safety Margins**

Patients should be carefully observed for evidence of pulmonary and systemic edema during fluid resuscitation. The degree of intravascular volume deficit in patients with severe sepsis
varies. With venodilation and ongoing capillary leak, most patients require continuing aggressive fluid resuscitation during the first 24 hours of management. Input is typically much greater than output, and input/output ratio is of no utility to judge fluid resuscitation needs during this time.

**Grading the Evidence** [See *Ranking the Evidence*]
The Grade 1 recommendations below are based on strong evidence for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence. “UG” level evidence is ungraded.

- The 2012 *Surviving Sepsis Campaign Guidelines* recommend fluid resuscitation with crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (Grade 1B). The absence of any clear benefit following the administration of colloid solutions compared to crystalloid solutions, together with the expense associated with colloid solutions, supports a high-grade recommendation for the use of crystalloid solutions in the initial resuscitation of patients with severe sepsis and septic shock.

- The *Surviving Sepsis Campaign* recommends fluid resuscitation initially target a CVP of at least 8 mm Hg (12 mm Hg in mechanically ventilated patients). Further fluid therapy is often required (Grade 1C).

- The *Surviving Sepsis Campaign* recommends that a fluid challenge technique be applied, wherein fluid administration is continued as long as the hemodynamic improvement (e.g., arterial pressure, heart rate, urine output) continues (UG). The *Surviving Sepsis Campaign* recommends fluid challenge in patients with suspected hypovolemia be started with at least 30 mL/kg of crystalloids (a portion of this may be albumin equivalent) over 30 minutes. More rapid administration and greater amounts of fluid may be needed in patients with sepsis induced tissue hypoperfusion (Grade 1C). The *Surviving Sepsis Campaign* recommends the rate of fluid administration be reduced substantially when cardiac filling pressures (CVP or pulmonary artery balloon-occluded pressure) increase without concurrent hemodynamic improvement (Grade 1D).

**References**


Content adapted extensively from:

6-Hour Septic Shock Bundle

1. Apply Vasopressors (for Hypotension That Does Not Respond to Initial Fluid Resuscitation) to Maintain a Mean Arterial Pressure (MAP) ≥65 mm Hg

Background
Adequate fluid resuscitation is a prerequisite for the successful and appropriate use of vasopressors in patients with septic shock. In general, the end points of fluid resuscitation are the same as those for the use of pharmacologic hemodynamic support (i.e., MAP ≥65 mm Hg). Sometimes, fluid resuscitation alone may suffice.

When an appropriate fluid challenge fails to restore an adequate arterial pressure and organ perfusion, therapy with vasopressor agents should be started. Vasopressor therapy may also be required transiently to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not been resolved or when a fluid challenge is in progress.

Cautions
Although all the vasopressor agents generally result in an increase in blood pressure, concerns remain in clinical practice about their potentially inappropriate or detrimental use.
- The most obvious of these relates to the inadequately volume-resuscitated patient, in whom vasopressor use may worsen already inadequate organ perfusion.
• Even when volume resuscitation has been performed, discussion continues as to whether vasopressor agents may raise blood pressure at the expense of the perfusion of vulnerable organs, most particularly the kidneys and the gut.
• A further concern relates to the possibility that overenthusiastic use, especially if an unnecessarily high blood pressure is targeted, may increase left ventricular work to an unsustainable degree and so worsen cardiac output and end-organ perfusion. This may be especially harmful in patients with pre-existing heart disease.

Monitoring
Because hypotension is a primary feature of septic shock and improving blood pressure is a therapeutic goal, accurate and continuous measurement of blood pressure is essential. It is therefore customary to use an arterial catheter to enable continuous invasive blood pressure monitoring. The radial artery is the site most frequently chosen, but the femoral artery is also often used. It is important to note that there may be marked differences in the blood pressure recordings at the two sites, especially in patients who are in shock, receiving vasopressors, and still hypovolemic.

Choice of Vasopressors
Norepinephrine (through an arterial catheter as soon as placement is possible) is the first-choice vasopressor agent to correct hypotension in septic shock (Grade 1B).

Epinephrine (added to and potentially substituted for norepinephrine) may be used when an additional agent is needed to maintain adequate blood pressure (Grade 2B). [1-3]

Phenylephrine should not be used as a first-line vasopressor as part of the treatment of septic shock. Phenylephrine was reported to reduce splanchnic blood flow and oxygen delivery in septic shock patients. [4]

Vasopressin use may be considered in patients with refractory shock despite adequate fluid resuscitation and high-dose conventional vasopressors. Pending the outcome of ongoing trials, it is not recommended as a replacement for norepinephrine or dopamine as a first-line agent.

Dopamine
Dopamine may be used as an alternative vasopressor agent to norepinephrine only in highly selected patients (e.g., a patient with low risk of tachyarrhythmias and absolute or relative bradycardia). Dopamine increases mean arterial pressure primarily by increasing cardiac index with minimal effects on systemic vascular resistance. The increase in cardiac index is due to an increase in stroke volume and, to a lesser extent, to increased heart rate. [5,6]

Splanchnic perfusion and the integrity of the gut mucosa may play an important role in the pathogenesis of multiple organ failure. The effect of dopamine on gastric tonometric and
splanchnic variables has been evaluated with mixed results. At low doses, dopamine increases splanchnic oxygen delivery by 65 percent but splanchnic oxygen consumption by only 16 percent. Despite this, dopamine may decrease pH, perhaps by a direct effect on the gastric mucosal cell. The effects of dopamine on cellular oxygen supply in the gut remain incompletely defined.

Studies have shown that dopamine may alter the inflammatory response in septic shock by decreasing the release of a number of hormones, including prolactin. [7] Other potentially harmful endocrine effects have been demonstrated in trauma patients. [8-11] In a study of 12 stable mechanically ventilated patients, Dive et al. used intestinal manometry to demonstrate that dopamine resulted in impaired gastroduodenal motility. [12] Concerns remain that these and other poorly understood biological effects of dopamine might potentially have harmful effects in patients with septic shock.

**Norepinephrine**

Norepinephrine is a potent α-adrenergic agonist with some β-adrenergic agonist effects. Norepinephrine therapy usually causes a statistically and clinically significant increase in mean arterial pressure due to the vasoconstrictive effects, with little change in heart rate or cardiac output, leading to increased systemic vascular resistance. [13-15]

In open-label trials, norepinephrine has been shown to increase mean arterial pressure in patients with hypotension resistant to fluid resuscitation and dopamine. In the past, there was concern that norepinephrine may have negative effects on blood flow in the splanchnic and renal vascular beds, with resultant regional ischemia. This meant that in the past norepinephrine was commonly reserved for use as a last resort, with predictably poor results. However, recent experience with the use of norepinephrine in patients with septic shock suggests that it can successfully increase blood pressure without causing the feared deterioration in organ function. Norepinephrine seems to be more effective than dopamine at reversing hypotension in septic shock patients. [16]

Concern is frequently expressed with regard to the effect of norepinephrine on the kidney. In patients with hypotension and hypovolemia during hemorrhagic shock, for example, norepinephrine and other vasoconstrictor agents may have severe detrimental effects on renal hemodynamics. Despite the improvement in blood pressure, renal blood flow does not increase, and renal vascular resistance continues to rise. [17] However, in hyperdynamic septic shock, during which urine flow is believed to decrease mainly because of lowered renal glomerular perfusion pressure, the situation is different. [18] Norepinephrine markedly improves mean arterial pressure and glomerular filtration. This is particularly true in the high-output, low-resistance state of many septic shock patients. After restoration of systemic hemodynamics, urine flow reappears in most patients and renal function improves. This fact supports the hypothesis that the renal ischemia observed during hyperdynamic septic shock is not worsened...
by norepinephrine infusion and even suggests that this drug may be effective in improving renal blood flow and renal vascular resistance. [19-22]

**Combination Therapies**

The effects of dopamine on cellular oxygen supply in the gut remain incompletely defined, and the effects of norepinephrine alone on splanchnic circulation may be difficult to predict. [23-25] The combination of norepinephrine and dobutamine seems to be more predictable and more appropriate to the goals of septic shock therapy than norepinephrine with dopamine or dopamine alone. [26, 27]

**Grading the Evidence** [See Ranking the Evidence]

The Grade 1 recommendations below are based on strong evidence for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

- The **2012 Surviving Sepsis Campaign Guidelines** recommend mean arterial pressure (MAP) be maintained ≥65 mm Hg (Grade 1C).

  Vasopressor therapy is required to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not yet been resolved. Below a certain mean arterial pressure, autoregulation in various vascular beds can be lost, and perfusion can become linearly dependent on pressure. Thus, some patients may require vasopressor therapy to achieve a minimal perfusion pressure and maintain adequate flow. [28, 29] The titration of norepinephrine to as low as MAP of 65 mm Hg has been shown to preserve tissue perfusion. [29] In addition, pre-existing comorbidities should be considered as to most appropriate MAP target. For example, a MAP of 65 mm Hg might be too low in a patient with severe uncontrolled hypertension, and in a young previously normotensive patient, a lower MAP might be adequate. Supplementing end points such as blood pressure with assessment of regional and global perfusion, such as blood lactate concentrations and urine output, is important. Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock, and should ideally be achieved before vasopressors and inotropes are used, but using vasopressors early as an emergency measure in patients with severe shock is frequently necessary. When that occurs great effort should be directed to weaning vasopressors with continuing fluid resuscitation.

- The Surviving Sepsis Campaign also recommends norepinephrine as the first choice vasopressor agent to correct hypotension in septic shock, administered through a central catheter as soon as one is available (Grade 1B).
The Grade 2 suggestions below are weaker recommendations for care based on a number of qualitative considerations. “D” level evidence generally reflects Downgraded controlled studies or expert opinion based on other evidence. “UG” level evidence is ungraded.

- The Surviving Sepsis Campaign suggests that epinephrine, phenylephrine, or vasopressin should not be administered as the initial vasopressor in septic shock (Grade 2C). Vasopressin 0.03 units/minute may be subsequently added to norepinephrine with anticipation of an effect equivalent to norepinephrine alone (UG). The Surviving Sepsis Campaign suggests that epinephrine be the first chosen alternative agent in septic shock that is poorly responsive to norepinephrine (Grade 2B).

There is no high-quality primary evidence to recommend one catecholamine over another. Much literature exists that contrasts the physiologic effects of choice of vasopressor and combined inotrope/vasopressors in septic shock. Human and animal studies suggest some advantages of norepinephrine and dopamine over epinephrine (the latter with the potential for tachycardia as well as disadvantageous effects on splanchnic circulation and hyperlactemia) and phenylephrine (decrease in stroke volume). There is, however, no clinical evidence that epinephrine results in worse outcomes, and it should be the first chosen alternative to dopamine or norepinephrine. Phenylephrine is the adrenergic agent least likely to produce tachycardia, but as a pure vasopressor would be expected to decrease stroke volume. Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Either may be used as a first-line agent to correct hypotension in sepsis. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function, but causes more tachycardia and may be more arrhythmogenic. [30] It may also influence the endocrine response via the hypothalamic-pituitary axis and have immunosuppressive effects.

Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state. [31] Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors, and may have other potential physiologic benefits. [32-37] Terlipressin has similar effects but is long lasting. [38] Studies show that vasopressin concentrations are elevated in early septic shock, but with continued shock, concentration decreases to normal range in the majority of patients between 24 and 48 hours. [39] This has been called “relative vasopressin deficiency” because in the presence of hypotension, vasopressin would be expected to be elevated. The significance of this finding is unknown. The recent VASST trial, a randomized, controlled trial comparing norepinephrine alone to norepinephrine plus vasopressin at 0.03
units/minute showed no difference in outcome in the intent to treat population. An a priori defined subgroup analysis showed that the survival of patients receiving less than 15 µg/min norepinephrine at the time of randomization was better with vasopressin. It should be noted however that the pre-trial rationale for this stratification was based on exploring potential benefit in the 15 µg or greater norepinephrine requirement population. Higher doses of vasopressin have been associated with cardiac, digital, and splanchnic ischemia and should be reserved for situations where alternative vasopressors have failed. [40] Cardiac output measurement to allow maintenance of a normal or elevated flow is desirable when these pure vasopressors are instituted.

References


Content adapted extensively from:

Tips
1. Include the use of vaspressors on a standardized protocol for the treatment of hypotension not responding to fluid administration.
2. Be sure that emergency department and intensive care nurses and staff are familiar with the appropriate dosing of dopamine, dobutamine, and norepinephrine.
3. Do not wait to start vasopressors until a fluid challenge or bolus of intravenous fluid is completed before using vasopressor agents if severe hypotension is present.
4. If you are unable to wean vasopressors, consider other diagnoses such as depressed cardiac function, adrenal insufficiency, tension pneumothorax, or cardiac tamponade, etc.

6-Hour Septic Shock Bundle

2. In the Event of Persistent Arterial Hypotension Despite Volume Resuscitation (Septic Shock) or Initial Lactate ≥4 mmol/L (36 mg/dL):
   a. Maintain Adequate Central Venous Pressure

   In the event of persistent hypotension despite fluid resuscitation (septic shock) or lactate ≥4 mmol/L (36 mg/dL) measure central venous pressure (CVP). (The target for CVP is ≥8 mm Hg.)

Related Measures

Central Venous Pressure Goal
Background
Early goal-directed therapy represents an attempt to predefine resuscitation end points to help clinicians at the bedside to resuscitate patients in septic shock. The end points used vary according to the clinical study, but attempt to adjust cardiac preload, contractility, and afterload to balance systemic oxygen delivery with demand.

Two essential features of early goal-directed therapy include: 1) maintaining an adequate central venous pressure (CVP) to carry out other hemodynamic adjustments; and 2) maximizing mixed or central venous oxygen saturation (ScvO2) [see bundle element 2b, described below].

Following the bundle, once lactate is ≥4 mmol/L (36 mg/dL), or hypotension has been demonstrated to be refractive to an initial fluid challenge with 30 mL/kg of crystalloid, patients should then have their CVP maintained at >8 mm Hg.

Of note, in adhering to this strategy, patients receive the initial minimum 30 mL/kg fluid challenge prior to placement of a central venous catheter and attempts to maximize CVP. This recommendation is consistent with the methods used in Rivers et al. [1]

Maintaining CVP
Techniques to maintain an appropriate CVP include placing a central venous catheter and delivering repeated fluid challenges until the target value is achieved. Fluid challenges are distinct from an increase in the rate of maintenance fluid administration (see Severe Sepsis 3-Hour Resuscitation Bundle, element #4: Administer 30 mL/kg Crystalloid for Hypotension or Lactate ≥4 mmol/L).

Consider Blood Products
In carrying out early goal-directed therapy, one key aim is central venous pressure, but it is also imperative to maintain central or mixed venous oxygen saturation targets. If a patient is both hypovolemic and anemic with a hematocrit less than 30 percent of blood volume, it is appropriate to transfuse packed red blood cells. This may have the dual advantage of increasing oxygen delivery to ischemic tissue beds and keeping central venous pressure >8 mm Hg for longer periods than fluids alone.

Special Considerations
In mechanically ventilated patients, a higher target central venous pressure of 12–15 mm Hg is recommended to account for the presence of positive end expiratory pressure and increases in intrathoracic pressure.

Similar consideration to the above may be warranted in circumstances of increased abdominal pressure.
Although the cause of tachycardia in septic patients may be multifactorial, a decrease in elevated pulse with fluid resuscitation is often a useful marker of improving intravascular filling.

**Early Goal-Directed Therapy Study Protocol**

Rivers, et al. performed a randomized, controlled, predominantly blinded study in an 850-bed tertiary referral center over a three-year period. [1] This study was performed in the emergency department of the hospital and enrolled patients presenting with severe sepsis or septic shock who fulfilled two of the four systemic inflammatory response syndrome criteria in association with a systolic blood pressure of <90 mm Hg after a 20–30 mL/kg crystalloid challenge or a blood lactate concentration of ≥4 mmol/L (36 mg/dL).

The patients were randomized to receive six hours of standard therapy or six hours of early goal-directed therapy before admission to the intensive care unit. Clinicians who were subsequently involved in the care of these patients were blinded to the treatment arm of the study.

The control group’s care was directed according to a protocol for hemodynamic support. The aims of this protocol were to ensure that the patients had a central venous pressure of between 8 and 12 mm Hg, a mean arterial pressure of ≥65 mm Hg, and a urine output of ≥0.5 mL·kg\(^{-1}\)·hr\(^{-1}\). These goals were targeted with the use of 500 mL boluses of crystalloid or colloid and vasopressor agents as necessary. The patients assigned to the early goal-directed therapy group received a central venous catheter capable of measuring ScvO2. Their treatment aims were then the same as the control groups, except that they also had to achieve a ScvO2 of ≥70 percent.

The patients assigned to the early goal-directed therapy group received a central venous catheter capable of measuring ScvO2. Their treatment aims were then the same as the control groups, except that they also had to achieve a ScvO2 of ≥70 percent. This was achieved first by the administration of transfused red blood cells, then with positive inotropic therapy, and if this goal was then not achieved, by sedation and mechanical ventilation to reduce oxygen demand.

The study enrolled 263 patients equally between the two groups. There were no significant differences between the two groups at baseline. During the initial 6 hours of therapy, the early goal-directed therapy group received more intravenous fluid (5.0 vs. 3.5 L, p<0.001), red cell transfusions (p<0.001), and inotropic therapy (p<0.001). During the subsequent 66 hours, the control group received more red cell transfusions (p<0.001), more vasopressors (p=0.03), and had a greater requirement for mechanical ventilation (p<0.001) and pulmonary artery catheterization (p=0.04). This in part reflects the fact that the control group patients were relatively under-resuscitated initially, and this was noticed and thus acted on by clinicians later on in their treatment course. In-hospital mortality was significantly higher in the control group.
than in the early goal-directed therapy group (46.5 percent vs. 30.5 percent, p=0.009). These differences were maintained through to 28 (p=0.01) and 60 days (p=0.03).

**Grading the Evidence** [See Ranking the Evidence]
The Grade 1 recommendations below are based on strong evidence for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

- The **2012 Surviving Sepsis Campaign Guidelines** recommend the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission. During the first 6 hours of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol (Grade 1C):
  - Central venous pressure (CVP) 8–12 mm Hg
  - Mean arterial pressure (MAP) ≥65 mm Hg
  - Urine output ≥0.5 mL·kg⁻¹·hr⁻¹
  - Central venous (superior vena cava) or mixed venous oxygen saturation ≥70 percent or ≥65 percent, respectively

Early goal-directed resuscitation has been shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single-center study. [1] Resuscitation directed toward the previously mentioned goals for the initial 6-hour period of the resuscitation was able to reduce 28-day mortality rate. The consensus panel judged use of central venous and mixed venous oxygen saturation targets to be equivalent. Either intermittent or continuous measurements of oxygen saturation were judged to be acceptable. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation. In mechanically ventilated patients or patients with known pre-existing decreased ventricular compliance, a higher target CVP of 12–15 mm Hg is recommended to account for the impediment to filling. [2] Similar consideration may be warranted in circumstances of increased abdominal pressure or diastolic dysfunction. [3]

Elevated central venous pressures may also be seen with pre-existing clinically significant pulmonary artery hypertension. Although the cause of tachycardia in septic patients may be multifactorial, a decrease in elevated pulse rate with fluid resuscitation is often a useful marker of improving intravascular filling. Observational studies have demonstrated an association between good clinical outcome in septic shock and MAP
≥65 mm Hg as well as central venous oxygen saturation (ScvO2, measured in superior vena cava, either intermittently or continuously) of ≥70 percent. [4] Many studies support the value of early protocolized resuscitation in severe sepsis and sepsis-induced tissue hypoperfusion. [5-10] Studies of patients with shock indicate that SvO2 runs 5 percent to 7 percent lower than central venous oxygen saturation (ScvO2), [11] and that an early goal-directed resuscitation protocol can be established in a non-research general practice venue. [12]

There are recognized limitations to ventricular filling pressure estimates as surrogates for fluid resuscitation. [13,14] However, measurement of CVP is currently the most readily obtainable target for fluid resuscitation. There may be advantages to targeting fluid resuscitation to flow and perhaps to volumetric indices (and even to microcirculation changes). [15-18] Technologies currently exist that allow measurement of flow at the bedside. [19, 20]

The Grade 2 suggestion below is a weaker recommendation for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

- Following the Rivers protocol, [1] if during the first 6 hours of resuscitation of severe sepsis or septic shock, if ScvO2 or SvO2 of 70 percent or 65 percent respectively is not achieved with fluid resuscitation to the CVP target, then transfusion of packed red blood cells to achieve a hematocrit of ≥30 percent and/or administration of a dobutamine infusion (up to a maximum of 20 μg.kg⁻¹.min⁻¹) be utilized to achieve this goal.

The protocol used in the study targeted an increase in ScvO2 to ≥70 percent. [1] This was achieved by sequential institution of initial fluid resuscitation, then packed red blood cells, and then dobutamine. This protocol was associated with an improvement in survival. Based on bedside clinical assessment and personal preference, a clinician may deem either blood transfusion (if Hct is less than 30 percent) or dobutamine to be the best initial choice to increase oxygen delivery and thereby elevate ScvO2 when fluid resuscitation is believed to be already adequate. The design of the aforementioned trial did not allow assessment of the relative contribution of these two components (i.e., increasing O2 content or increasing cardiac output) of the protocol on achievement of improved outcome.

References

Content adapted extensively from:

Tips
1. Create a standardized protocol that includes a goal CVP ≥8 mm Hg for patients with lactate ≥4 mmol/L (36 mg/dL) or hypotension not responding to initial fluid resuscitation (septic shock).
2. Stress the importance of prioritization: initial fluid challenge as defined, followed by central line placement, followed by assessment of CVP; if CVP is low, the addition of PRBCs is appropriate if hematocrit is less than 30 percent and MAP remains <65 mm Hg, followed by further fluid challenges to keep CVP >8 mm Hg.
3. If your emergency department does not commonly perform these techniques, provide in-service training to emergency department personnel regarding CVP monitoring and the importance of leveling equipment relative to the patient’s heart.
4. Do not wait for transfer to the ICU to initiate CVP monitoring.

6-Hour Septic Shock Bundle

2. In the Event of Persistent Arterial Hypotension Despite Volume Resuscitation (Septic Shock) or Initial Lactate ≥4 mmol/L (36 mg/dL):
   b. Maintain Adequate Central Venous Oxygen Saturation

In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate ≥4 mmol/L (36 mg/dL) measure central venous oxygen saturation (ScvO2). (The target is ≥70 percent.*)

*Mixed venous oxygen saturation (SvO2) ≥65 percent is an acceptable alternative.

Related Measures
Central Venous Oxygen Saturation Goal

Background
Goal-directed therapy represents an attempt to predefine resuscitation end points to help clinicians at the bedside to resuscitate patients in septic shock. The end points used vary according to the clinical study but attempt to adjust cardiac preload, contractility, and afterload to balance systemic oxygen delivery with demand.

Two essential features of early goal-directed therapy include: 1) maintaining an adequate central venous pressure (CVP) to carry out other hemodynamic adjustments [see bundle
element 2a, described above]; and 2) maximizing mixed or central venous oxygen saturation (ScvO2).

Following the bundle, once lactate is ≥4 mmol/L (36 mg/dL), or hypotension has been demonstrated to be refractive to an initial fluid challenge with 20 mL/kg of crystalloid or colloid equivalent, patients should then have their central venous pressure (CVP) maintained at ≥8 mm Hg and central venous oxygen saturation (ScvO2) should be maintained at ≥70 percent.

These recommendations are consistent with Rivers, et al., the only trial to demonstrate a mortality benefit in early goal-directed therapy using ScvO2 as one of its major end points. [1]

**Importance of Early Therapies**
The resuscitation of severely septic individuals with lactate ≥4 mmol/L (36 mg/dL) or who are in septic shock must start early. The longer the resuscitation is delayed, the less likely a beneficial effect will occur. This makes sense, as the purpose of resuscitating a patient is to prevent further organ dysfunction and failure. If the resuscitation is delayed until after cellular dysfunction and cell death are present, then strategies designed to provide the cells with more oxygen are unlikely to be helpful. It is unclear, however, when the transition from reversible cellular dysfunction to irreversible cellular dysfunction occurs. At present, the only effective strategy is to provide the resuscitation at the earliest stage possible.

**Maintaining ScvO2**
Techniques to maintain ScvO2 include two principal strategies. In carrying out early goal-directed therapy, if a patient is both hypovolemic and the hematocrit is less than 30 percent, it is appropriate to transfuse packed red blood cells provided that the fluid resuscitation has achieved a CVP >8 mm Hg. If CVP >8 mm Hg has not been achieved, additional fluid challenges are needed. Once the decision to use blood products has been made, this may accomplish the dual purpose of 1) increasing ScvO2 due to increased oxygen delivery to ischemic tissue beds, and 2) keeping the central venous pressure >8 mm Hg for longer periods than fluids alone.

The second strategy involves attempting to improve the patient’s hemodynamic profile with inotropes. Provided that the patient has been adequately resuscitated and the CVP is >8 mm Hg, cardiac output may remain insufficient to meet metabolic needs of certain tissue beds despite an adequate circulating volume. In some cases, cardiac output itself may be diminished due to sepsis-induced cardiac dysfunction. In these cases, dobutamine infusion (up to a maximum of 20 μg·kg\(^{-1}\)·min\(^{-1}\)) should be given to increase oxygen delivery to the periphery and prevent further organ dysfunction due to hypoperfusion and ischemia. If dobutamine infusion results in hypotension, norepinephrine should be used to counteract the vasodilatory effects of dobutamine.
Special Considerations
Evidence is not conclusive on attempting to maximize a patient’s cardiac index to surpranormal levels to overcome increased oxygen demand, abnormalities in oxygen extraction, and myocardial depression associated with sepsis. [2, 3] Therefore, a strategy of increasing cardiac index to achieve an arbitrarily predefined elevated level is not recommended.

Before attempting to use inotropes to maximize central venous oxygen saturation in mechanically ventilated patients, a higher target central venous pressure of 12–15 mm Hg is recommended to account for the presence of positive end expiratory pressure and increases in intrathoracic pressure.

Similar consideration to the above may be warranted in circumstances of increased abdominal pressure.

Early Goal-Directed Therapy Study Protocol
It is impossible to determine from the study which particular facet of the protocol was beneficial for the patients, so the protocol as a whole must be recommended.

Rivers, et al. performed a randomized, controlled, predominantly blinded study in an 850-bed tertiary referral center over a three-year period. [1] This study was performed in the emergency department of the hospital and enrolled patients presenting with severe sepsis or septic shock who fulfilled two of the four systemic inflammatory response syndrome criteria in association with a systolic blood pressure of <90 mm Hg after a 20–30 mL/kg crystalloid challenge or a blood lactate concentration of ≥4 mmol/L (36 mg/dL).

The patients were randomized to receive six hours of standard therapy or six hours of early goal-directed therapy before admission to the intensive care unit. Clinicians who were subsequently involved in the care of these patients were blinded to the treatment arm of the study.

The control group’s care was directed according to a protocol for hemodynamic support. The aims of this protocol were to ensure that the patients had a central venous pressure of between 8 and 12 mm Hg, a mean arterial pressure of ≥65 mm Hg, and a urine output of ≥0.5 mL·kg⁻¹·hr⁻¹. These goals were targeted with the use of 500 mL boluses of crystalloid or colloid and vasopressor agents as necessary. The patients assigned to the early goal-directed therapy group received a central venous catheter capable of measuring ScvO2. Their treatment aims were then the same as the control groups, except that they also had to achieve a ScvO2 of ≥70 percent.

The patients assigned to the early goal-directed therapy group received a central venous catheter capable of measuring ScvO2. Their treatment aims were then the same as the control
groups, except that they also had to achieve a ScvO2 of ≥70 percent. This was achieved first by
the administration of transfused red blood cells, then with positive inotropic therapy, and if this
goal was then not achieved, by sedation and mechanical ventilation to reduce oxygen demand.

The study enrolled 263 patients equally between the two groups. There were no significant
differences between the two groups at baseline. During the initial 6 hours of therapy, the early
goal-directed therapy group received more intravenous fluid (5.0 vs. 3.5 L, p<0.001), red cell
transfusions (p<0.001), and inotropic therapy (p<0.001). During the subsequent 66 hours, the
control group received more red cell transfusions (p<0.001), more vasopressors (p=0.03), and
had a greater requirement for mechanical ventilation (p<0.001) and pulmonary artery
catheterization (p=0.04). This in part reflects the fact that the control group patients were
relatively under-resuscitated initially, and this was noticed and thus acted on by clinicians later
on in their treatment course. In-hospital mortality was significantly higher in the control group
than in the early goal-directed therapy group (46.5 percent vs. 30.5 percent, p=0.009). These
differences were maintained through to 28 (p=0.01) and 60 days (p=0.03).

Grading the Evidence [See Ranking the Evidence]
The Grade 1 recommendations below are based on strong evidence for care based on a
number of qualitative considerations. “B” level evidence generally derives from randomized
control trials with certain limitations or very well-done observational or cohort studies. “C” level
evidence reflects well-done observational or cohort studies with controls. “D” level evidence
generally reflects downgraded controlled studies or expert opinion based on other evidence.

- The 2012 Surviving Sepsis Campaign Guidelines recommend the protocolized
resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion
(hypotension persisting after initial fluid challenge or blood lactate concentration ≥4
mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and
should not be delayed pending ICU admission. During the first 6 hours of resuscitation,
the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the
following as one part of a treatment protocol (Grade 1C):
  - Central venous pressure (CVP) 8–12 mm Hg
  - Mean arterial pressure (MAP) ≥65 mm Hg
  - Urine output ≥0.5 mL.kg⁻¹.hr⁻¹
  - Central venous (superior vena cava) or mixed venous oxygen saturation ≥70
    percent or ≥65 percent, respectively

Early goal-directed resuscitation has been shown to improve survival for emergency
department patients presenting with septic shock in a randomized, controlled, single-
center study. [1] Resuscitation directed toward the previously mentioned goals for the
initial 6-hour period of the resuscitation was able to reduce 28-day mortality rate. The
consensus panel judged use of central venous and mixed venous oxygen saturation

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targets to be equivalent. Either intermittent or continuous measurements of oxygen saturation was judged to be acceptable. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation. In mechanically ventilated patients or patients with known pre-existing decreased ventricular compliance, a higher target CVP of 12–15 mm Hg is recommended to account for the impediment to filling. [4] Similar consideration may be warranted in circumstances of increased abdominal pressure or diastolic dysfunction. [5]

Elevated central venous pressures may also be seen with pre-existing clinically significant pulmonary artery hypertension. Although the cause of tachycardia in septic patients may be multifactorial, a decrease in elevated pulse rate with fluid resuscitation is often a useful marker of improving intravascular filling. Observational studies have demonstrated an association between good clinical outcome in septic shock and MAP $\geq 65$ mm Hg as well as central venous oxygen saturation (ScvO2, measured in superior vena cava, either intermittently or continuously) of $\geq 70$ percent. [6] Many studies support the value of early protocolized resuscitation in severe sepsis and sepsis-induced tissue hypoperfusion. [7-12] Studies of patients with shock indicate that SvO2 runs 5 percent to 7 percent lower than central venous oxygen saturation (ScvO2), [13] and that an early goal-directed resuscitation protocol can be established in a non-research general practice venue. [14]

There are recognized limitations to ventricular filling pressure estimates as surrogates for fluid resuscitation. [15,16] However, measurement of CVP is currently the most readily obtainable target for fluid resuscitation. There may be advantages to targeting fluid resuscitation to flow and perhaps to volumetric indices (and even to microcirculation changes). [17-20] Technologies currently exist that allow measurement of flow at the bedside. [21, 22]

The Surviving Sepsis Campaign suggests targeting resuscitation to normalize lactate in patients with elevated lactate levels as a marker of tissue hypoperfusion (Grade 2C). If ScvO2 is not available, lactate normalization may be a feasible option in the patient with severe sepsis-induced tissue hypoperfusion. ScvO2 and lactate normalization may also be used as a combined end point when both are available. Two multicenter randomized trials evaluated a resuscitation strategy that included lactate reduction as a single target or a target combined with ScvO2 normalization. [23, 24] The first trial reported that early quantitative resuscitation based on lactate clearance (decrease by at least 10 percent) was noninferior to early quantitative resuscitation based on achieving ScvO2 of 70 percent or more. [23]

The Grade 2 suggestion below is a weaker recommendation for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials
with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

- The 2012 Surviving Sepsis Campaign Guidelines suggest that during the first 6 hours of resuscitation of severe sepsis or septic shock, if ScvO2 or SvO2 of ≥70 percent or ≥65 percent respectively is not achieved with fluid resuscitation to the CVP target, then transfusion of packed red blood cells to achieve a hematocrit of ≥30 percent and/or administration of a dobutamine infusion (up to a maximum of 20 μg.kg\(^{-1}\).min\(^{-1}\)) be utilized to achieve this goal (Grade 2C).

The protocol used in the study cited previously targeted an increase in ScvO2 to ≥70 percent. [1] This was achieved by sequential institution of initial fluid resuscitation, then packed red blood cells, and then dobutamine. This protocol was associated with an improvement in survival. Based on bedside clinical assessment and personal preference, a clinician may deem either blood transfusion (if Hct is less than 30 percent) or dobutamine to be the best initial choice to increase oxygen delivery and thereby elevate ScvO2 when fluid resuscitation is believed to be already adequate. The design of the aforementioned trial did not allow assessment of the relative contribution of these two components (i.e., increasing O2 content or increasing cardiac output) of the protocol on achievement of improved outcome.

References

Content adapted extensively from:
Tips

1. Create a standardized protocol that includes a goal CVP $\geq 8$ mm Hg for patients with lactate $\geq 4$ mmol/L (36 mg/dL) or hypotension not responding to initial fluid resuscitation (septic shock).

2. Stress the importance of prioritization: initial fluid challenge as defined, followed by central line placement, followed by assessment of CVP; if CVP is low, the addition of PRBCs is appropriate if hematocrit is less than 30 percent and MAP remains $< 65$ mm Hg, followed by further fluid challenges to keep CVP $\geq 8$ mm Hg.

3. If your emergency department does not commonly perform these techniques, provide in-service training to emergency department personnel regarding CVP monitoring and the importance of leveling equipment relative to the patient’s heart.

4. Do not wait for transfer to the ICU to initiate CVP monitoring.

6-Hour Septic Shock Bundle

3. Remeasure Lactate If Initial Lactate Was Elevated

Related Measure
Remeasure Lactate If Initial Lactate was Elevated Goal

Background

Hyperlactatemia is typically present in patients with severe sepsis or septic shock and may be secondary to anaerobic metabolism due to hypoperfusion. The prognostic value of raised blood lactate levels has been well established in septic shock patients, [1] particularly if the high levels persist. [2,3] In addition, blood lactate levels have been shown to have greater prognostic value than oxygen-derived variables. [4] Obtaining a lactate level is essential to identifying tissue hypoperfusion in patients who are not yet hypotensive but who are at risk for septic shock.

Limitations

The interpretation of blood lactate levels in septic patients is not always straightforward. A number of studies have suggested that elevated lactate levels may result from cellular metabolic failure in sepsis rather than from global hypoperfusion. Elevated lactate levels can also result from decreased clearance by the liver. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation.

Implications

Mortality rate is high in septic patients with both hypotension and lactate $\geq 4$ mmol/L, and is also increased in severely septic patients with hypotension alone and lactate $\geq 4$ mmol/L. [5] If ScvO2 is not available, lactate normalization may be a feasible option in the patient with severe sepsis.
induced tissue hypoperfusion. ScvO2 and lactate normalization may also be used as a combined end point when both are available. [6, 7]

**Turnaround Time**

Serum lactate must be available in your institution with rapid turnaround time (within minutes) to treat severely septic patients effectively. An arterial blood gas analyzer located in the clinical laboratories usually accomplishes this. However, any means of rapid turnaround time will be acceptable. It is essential for hospitals to invest in adequate equipment in order to meet present standards of care for septic patients.

The technique of obtaining serum lactate by venipuncture typically carries a 24- to 48-hour turnaround time and will not be suitable to care for septic patients. This technique also requires special collection conditions, such as without the use of tourniquet, hindering clinical care.

**Arterial vs. Venous Lactate**

In the course of the Surviving Sepsis Campaign the question has been raised many times as to whether an arterial or venous lactate sample is appropriate. While there is no published consensus on this question, an elevated lactate of any variety is typically abnormal, although this may be influenced by other conditions such as a variety of medications, hepatic insufficiency, or hyperlactatemia due to primarily cardiac causes of hypoperfusion.

**Grading the Evidence** [See *Ranking the Evidence*]

The Grade 2 suggestion below is a weaker recommendation for care based on a number of qualitative considerations. “C” level evidence reflects well-done observational or cohort studies with controls.

- The use of lactate as a method to detect severe sepsis and septic shock and as a rationale for further therapies was evaluated as part of the larger recommendation on initial resuscitation in the 2008 *Surviving Sepsis Campaign Guidelines*. There, the guidelines committee recommended the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L) (Grade 2C).

**References**


Severe Sepsis Bundles: Other Supportive Therapies

Reducing mortality due to severe sepsis requires an organized process that guarantees early recognition and consistent application of the evidence-based practices in the 2012 Surviving Sepsis Campaign guidelines.

The Severe Sepsis Bundles are a distillation of the concepts and recommendations found in the 2012 Surviving Sepsis Campaign guidelines. The bundles are designed to allow teams to follow the timing, sequence, and goals of the individual elements of care and collect the data to measure their improvement.

Individual hospitals should use the bundles to create customized protocols and pathways specific to their institutions. However, all of the elements in the bundles must be incorporated in those protocols. The addition of other strategies not found in the bundles is not recommended. The bundles will form the basis for the measurements that improvement teams will conduct to follow their progress as they make changes.

The Severe Sepsis Bundles are a series of evidence-based therapies that, when implemented together, will achieve better outcomes than if implemented individually.

Other selected therapies recommended by the 2012 Surviving Sepsis Campaign:

1. Blood Product Administration
2. Maintain Adequate Glycemic Control
3. Mechanical Ventilation of Sepsis-Induced Acute Respiratory Distress Syndrome (ARDS)
4. Sedation, Analgesia, and Neuromuscular Blockade
5. Deep Vein Thrombosis (DVT) and Peptic Ulcer Disease (PUD) Prophylaxis
6. Nutrition
7. Setting Goals of Care

The intention in applying the other selected therapies is to perform evidence-based treatments that will contribute to improving care of patients with severe sepsis and septic shock.

**Severe Sepsis Bundles: Other Supportive Therapies**

1. Blood Products Administration

**Background**

Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic coronary artery disease, the 2012 Surviving Sepsis Campaign guidelines recommend that red blood cell transfusion occur when the hemoglobin concentration decreases to <7.0 g/dL to target a hemoglobin concentration of 7.0 to 9.0 g/dL in adults (Grade 1B).

**Grading the Evidence** [See Ranking the Evidence]

The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. The Grade 2 suggestion is a weaker recommendation for care based on a number of qualitative considerations. “D” level evidence generally reflects case series data or expert opinion.

The 2012 Surviving Sepsis Campaign guidelines suggest *not* using:

- Erythropoietin as a specific treatment of anemia associated with severe sepsis (Grade 1B)
- Fresh frozen plasma to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (Grade 2D)
- Antithrombin for the treatment of severe sepsis and septic shock (Grade 1B)

Although the optimum hemoglobin concentration for patients with severe sepsis has not been specifically investigated, the Transfusion Requirements in Critical Care trial suggested that a hemoglobin level of 7 to 9 g/dL, compared with 10 to 12 g/dL, was not associated with increased mortality in critically ill adults. [1] No significant differences in 30-day mortality rates were observed between treatment groups in the subgroup of patients with severe infections and septic shock (22.8 percent and 29.7 percent, respectively; p=0.36).

Although less applicable to septic patients, results of a randomized trial in patients undergoing cardiac surgery with cardiopulmonary bypass support a restrictive transfusion strategy using a threshold hematocrit of <24 percent (hemoglobin ≈8 g/dL) as equivalent to a transfusion
threshold of hematocrit of <30 percent (hemoglobin ≈10 g/dL). [2] Red blood cell transfusion in septic patients increases oxygen delivery but does not usually increase oxygen consumption. [3-5] The transfusion threshold of 7 g/dL contrasts with early goal-directed resuscitation protocols that use a target hematocrit of 30 percent in patients with low ScvO2 during the first 6 hours of resuscitation of septic shock. [6]

Administer Platelets Prophylactically
In patients with severe sepsis, administer platelets prophylactically when counts are <10,000/mm3 (10 x 109/L) in the absence of apparent bleeding. The 2012 Surviving Sepsis Campaign guidelines suggest prophylactic platelet transfusion when counts are <20,000/mm3 (20 x 109/L) if the patient has a significant risk of bleeding. Higher platelet counts of ≥50,000/mm3 (50 x 109/L) are advised for active bleeding, surgery, or invasive procedures (Grade 2D).

References

Content adapted extensively from:

Severe Sepsis Bundles: Other Supportive Therapies

2. Maintain Adequate Glycemic Control

Related Measure
Glycemic Control Goal
Background
Effective glucose control in the intensive care unit (ICU) has been shown to decrease morbidity across a large range of conditions and also to decrease mortality.

Hyperglycemia, caused by insulin resistance in the liver and muscle, is a common finding in ICU patients. Some have considered it to be an adaptive response, providing glucose for the brain, red blood cells, and wound healing. Traditionally, hyperglycemia has only been treated when blood glucose increases to >215 mg/dL (>12 mmol/L). Conventional wisdom in the ICU has been that some degree of hyperglycemia is beneficial and that hypoglycemia is dangerous and should be avoided. The extent of appropriate glucose control has been evaluated in recent years.

Initial Investigations: Intensive Insulin Therapy
An initial investigation by Van den Berghe and colleagues suggested that controlling blood glucose levels by intensive insulin therapy decreased mortality and morbidity in surgical critically ill patients. [2] The trial was a large single-center study of postoperative surgical patients. The design employed a continuous infusion of insulin to maintain glucose between 80 and 110 mg/dL (4.4–6.1 mmol/L). Exogenous glucose was begun simultaneously with insulin, with frequent monitoring of glucose (every 1 hour) and intensity of monitoring was greatest at the time of initiation of insulin. This protocol called for implementing a strategy to maintain normoglycemia with an insulin infusion while providing for normal intake of glucose (9 g/hour) and calories (19 kcal·kg⁻¹·day⁻¹).

A total of 35 of 765 patients (4.6 percent) in the intensive insulin group died in the ICU in Van den Berghe et al. study, compared with 63 patients (8.0 percent) in the conventional therapy group.

Intensive insulin therapy halved the prevalence of:
- Bloodstream infections
- Prolonged inflammation
- Acute renal failure (ARF) requiring dialysis or hemofiltration
- Critical illness polyneuropathy
- Transfusion requirements

Patients receiving intensive insulin therapy were also less likely to require prolonged mechanical ventilation and intensive care.

Rigorous insulin treatment reduced the number of deaths from multi-organ failure with sepsis, regardless of whether there was a history of diabetes or hyperglycemia.
Surgical vs. Medical Patients
The same protocol used in the first Van den Berghe et al. trial for surgical patients was subsequently tested in medical patients. [3]

Patients who were considered to need intensive care for at least three days were enrolled in a prospective, randomized, single-center, controlled study. On admission, patients were randomly assigned to strict normalization of blood glucose levels (80 to 110 mg/dL [4.4 to 6.1 mmol/L]) with the use of insulin infusion or conventional therapy (i.e., insulin administered when the blood glucose level exceeded 215 mg/dL [12 mmol/L], with the infusion tapered when the level fell below 180 mg/dL [10 mmol/L]).

Intensive insulin therapy reduced blood glucose levels but did not significantly reduce in-hospital mortality (40.0 percent in the conventional treatment group vs. 37.3 percent in the intensive treatment group, p=0.33). However, morbidity was significantly reduced by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation, and accelerated discharge from the ICU and the hospital.

Although length of stay in the ICU could not be predicted on admission, among 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapy. In contrast, among 767 patients who stayed in the ICU for three or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5 to 43.0 percent (p=0.009) and morbidity was also reduced.

The authors concluded that intensive insulin therapy significantly reduced morbidity but not mortality among all patients in the medical ICU. Although the risk of subsequent death and disease was reduced in patients treated for three or more days, these patients could not be identified before therapy.

Meta-Analyses and Severe Sepsis Specific Inquiries
A meta-analysis of 35 trials on insulin therapy in critically ill patients, including 12 randomized trials, demonstrated a 15 percent reduction in short-term mortality (relative risk 0.85, 95 percent confidence interval 0.75-0.97) but did not include any studies of insulin therapy in medical ICUs. [4]

A multi-center randomized control trial (VISEP) focusing on patients with severe sepsis failed to demonstrate improvement in mortality. [5] In VISEP, the investigators randomly assigned patients with severe sepsis to receive either intensive insulin therapy to maintain euglycemia or conventional insulin therapy. Of the 537 patients who could be evaluated, the mean morning blood glucose level was lower in the intensive therapy group (112 mg/dL [6.2 mmol/L]) than in
the conventional therapy group (151 mg/dL [8.4 mmol/L], p<0.001). However, at 28 days, there was no significant difference between the two groups in the rate of death or the mean score for organ failure.

Further, the VISEP investigators found that the rate of severe hypoglycemia (glucose level ≤40 mg/dL [2.2 mmol/L]) was higher in the intensive therapy group than in the conventional therapy group (17.0 percent vs. 4.1 percent, p<0.001), as was the rate of serious adverse events (10.9 percent vs. 5.2 percent, p=0.01). The trial was stopped earlier than planned for these reasons.

**NICE-SUGAR Study**

Based on the foregoing studies, most clinicians believed that there was a benefit to glucose control in terms of mortality and morbidity. However, the optimal target range for blood glucose in critically ill patients remained unclear.

The NICE-SUGAR study investigators [1] chose to evaluate whether there was a difference in mortality between subjects randomly assigned to either intensive glucose control, with a target blood glucose range of 81 to 108 mg/dL (4.5 to 6.0 mmol/L), or conventional glucose control, with a target of 180 mg or less per deciliter (10.0 mmol or less per liter). To be considered, patients were expected to require treatment in the ICU on 3 or more consecutive days.

Of the 6,104 patients who underwent randomization, 3,054 were assigned to undergo intensive control and 3,050 to undergo conventional control. A total of 829 patients (27.5 percent) in the intensive-control group and 751 (24.9 percent) in the conventional-control group died. Thus, the odds of dying with intensive control were 1.14 times greater than with conventional control (p=0.02). In addition, severe hypoglycemia (blood glucose level of 40 mg/dL [2.2 mmol/L]) was reported in 206 of 3,016 patients (6.8 percent) in the intensive-control group and in 15 of 3,014 patients (0.5 percent) in the conventional-control group (p<0.001). Thus, the incidence of hypoglycemia was lower in the conventional group.

With regard to morbidity and length of stay, NICE-SUGAR demonstrated that there was no significant difference between the two treatment groups in the median number of days in the ICU or hospital, or the median number of days of mechanical ventilation or renal-replacement therapy.

The NICE-SUGAR investigators concluded that intensive glucose control increased mortality among adults in the ICU and that a blood glucose target of 180 mg or less per deciliter resulted in lower mortality than did a target of 81 to 108 mg per deciliter.

**Grading the Evidence** [See Ranking the Evidence]

The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. “B” quality evidence generally derives from randomized control trials.
with certain limitations or very well-done observational or cohort studies. “C” quality evidence reflects well-done observational or cohort studies with controls. “D” quality evidence generally reflects downgraded controlled trials or expert opinion based on other experience.

The Surviving Sepsis Campaign formerly recommended in the 2008 Surviving Sepsis Campaign Guidelines that, following initial stabilization, patients with severe sepsis and hyperglycemia who are admitted to the ICU receive IV insulin therapy to reduce blood glucose levels (Grade 1B).

The Surviving Sepsis Campaign reviewed its specific recommendations and ranges for glucose control after publication of NICE-SUGAR and issued a statement on glucose control ranges for severely septic patients in June 2009:

“There is insufficient information from randomized controlled trials to determine the optimal target range of blood glucose in the severely septic patient. [6] The NICE-SUGAR trial is the largest most compelling study to date on glucose control in ICU patients given its inclusion of multiple ICUs and hospitals, and a more general patient population. [1] Based on the results of this trial, we recommend against intravenous insulin therapy titrated to keep blood glucose in the normal range (80–110 mg/dL) in patients with severe sepsis. It is clear that attempts to normalize blood glucose with IV insulin during critical illness results in higher rates of hypoglycemia. [6, 7, 8] Until additional information is available, teams seeking to implement glucose control should consider initiating insulin therapy when blood glucose levels exceed 180 mg/dL with a goal blood glucose approximating 150 mg/dL as was observed in the beneficial arm of the NICE-SUGAR trial.”

Similarly, IHI advocates for a target threshold less than <180 for critically ill patients based on the NICE-SUGAR trial data.

References


Content adapted extensively from:

**Tips**
1. Create a standardized protocol that provides for continuous intravenous insulin infusion and nutritional support for cases of severe sepsis and septic shock.
2. Allow the protocol to be adjusted automatically by the nursing staff to accomplish tight glucose control safely with a reliable bedside presence.
3. Administer glucose or enteral feedings while the insulin infusion is active, with frequent glucose monitoring by finger stick.
4. Adopt a specific treatment plan for hypoglycemia.
5. Educate the nursing staff about the benefits of tight glucose control and relieve the fear of increasing the incidence of hypoglycemia. Tight glycemic control in patients can be so foreign to routine clinical practice that fear can defeat the success of the project.
6. Work closely with nursing in creating the protocols to make sure the increased burden of frequent glucose checks can be integrated into their workflow.

**Severe Sepsis Bundles: Other Supportive Therapies**

**3. Mechanical Ventilation of Sepsis-Induced Acute Respiratory Distress Syndrome**

The 2012 Surviving Sepsis Campaign guidelines recommend:
- Target a tidal volume of 6 mL/kg predicted body weight in patients with sepsis-induced acute respiratory distress syndrome (ARDS) (Grade 1A, vs 12 mL/kg).
- Measure plateau pressures in patients with ARDS and that the initial upper limit goal for plateau pressures in a passively inflated lung be ≤30 cm H2O (Grade 1B).
- Apply positive end-expiratory pressure (PEEP) to avoid alveolar collapse at end expiration (atelectotrauma) (Grade 1B). Apply strategies based on higher rather than
lower levels of PEEP for patients with sepsis-induced moderate to severe ARDS (Grade 2C).

- Apply recruitment maneuvers in sepsis patients with severe refractory hypoxemia due to ARDS (Grade 2C).
- Maintain prone positioning in sepsis-induced ARDS patients with a PaO2/FIO2 ratio ≤100 mm Hg in facilities that have experience with such practices (Grade 2B).
- Elevate head of the bed between 30 and 45 degrees to limit aspiration risk and to prevent the development of ventilator-associated pneumonia (VAP) (Grade 1B).
- Use noninvasive mask ventilation (NIV) in that minority of sepsis-induced ARDS patients in whom the benefits of NIV have been carefully considered and are thought to outweigh the risks (Grade 2B).
- Mechanically ventilated patients with severe sepsis undergo spontaneous breathing trials regularly to evaluate the ability to discontinue mechanical ventilation when they satisfy the following criteria: a) arousable; b) hemodynamically stable (without vasopressor agents); c) no new potentially serious conditions; d) low ventilatory and end-expiratory pressure requirements; and e) low FIO2 requirements which can be safely delivered with a face mask or nasal cannula. If the spontaneous breathing trial is successful, extubation should be considered (Grade 1A).
- Use conservative fluid strategy for patients with established sepsis-induced ARDS who do not have evidence of tissue hypoperfusion (Grade 1C).

Background
Patients with sepsis are at increased risk for developing acute respiratory failure, and most patients with severe sepsis and septic shock will require endotracheal intubation and mechanical ventilation. Nearly 50 percent of patients with severe sepsis will develop acute respiratory distress syndrome (ARDS). Patients with lung injury will have bilateral patchy infiltrates on chest x-ray, low PaO2:FIO2 ratios (less than 300 for mild or less than 200 for moderate ARDS), and pulmonary capillary wedge pressure less than 18 cm H2O, although this last measure is often clinically not available.

High tidal volumes that are coupled with high plateau pressures should be avoided in ARDS. Clinicians should use as a starting point a reduction in tidal volumes over 1 to 2 hours to a “low” tidal volume (6 mL·kg⁻¹·lean body weight⁻¹) as a goal in conjunction with the goal of maintaining end-inspiratory plateau pressures of <30 cm H2O.

Mortality Reduction
The largest trial of a volume- and pressure-limited strategy showed a 9 percent decrease of all-cause mortality in patients ventilated with tidal volumes of 6 mL/kg of estimated lean body weight (as opposed to 12 mL/kg) while aiming for a plateau pressure of <30 cm H2O. [1]

The formal ARDSnet protocol for mechanical ventilation is encouraged for use in septic patients.
Permissive Hypercapnia
Hypercapnia (allowing PaCO2 to increase above normal, so-called permissive hypercapnia) can be tolerated in patients with ARDS if required to minimize plateau pressures and tidal volumes.

Although an acutely elevated PCO2 may have physiologic consequences that include vasodilatation and increased heart rate, blood pressure, and cardiac output, allowing modest hypercapnia in conjunction with limiting tidal volume and minute ventilation has been demonstrated to be safe in small, nonrandomized series. [2, 3] No upper limit for PCO2 has been established. Some authorities recommend maintaining pH at >7.20–7.25, but this has not been prospectively established. The use of hypercarbia is limited in patients with pre-existing metabolic acidosis and is contraindicated in patients with increased intracranial pressure. [4] Sodium bicarbonate infusion may be considered in select patients to facilitate use of permissive hypercarbia. [1] Experimental models suggest that respiratory acidosis may confer protection against various forms of inflammatory injury. [6]

Positive End-Expiratory Pressure (PEEP)
Provide adequate supplemental oxygen to maintain a pulse oximetric saturation of >90 percent. A minimum amount of PEEP should be set to prevent lung collapse at end expiration. Setting PEEP based on severity of oxygenation deficit and guided by the FIO2 required to maintain adequate oxygenation is one acceptable approach.

For patients supported by mechanical ventilation or who are appropriate candidates for a pressurized face mask, PEEP or continuous positive airway pressure may be used to increase mean and end-expiratory airway pressures, allowing the reduction of the oxygen concentrations below potentially toxic levels (FIO2 <0.60).

Grading the Evidence [See Ranking the Evidence]
The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. The Grade 2 suggestions are weaker recommendations for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled trials or expert opinion based on other evidence.

- The 2012 Surviving Sepsis Campaign Guidelines recommend that clinicians target a tidal volume of 6 ml/kg (predicted) body weight in patients with ARDS (Grade 1A, vs 12 ml/kg). The Campaign also recommends that plateau pressures be measured in patients
with ARDS and that the initial upper limit goal for plateau pressures in a passively inflated patient be ≤30 cm H2O (Grade 1B).

Over the past 10 years, several multi-center randomized trials have been performed to evaluate the effects of limiting inspiratory pressure through moderation of tidal volume. [1, 6-9] These studies showed differing results that may have been caused by differences between airway pressures in the treatment and control groups. [1, 10] The largest trial of a volume- and pressure-limited strategy showed a 9 percent decrease of all-cause mortality in patients with ARDS ventilated with tidal volumes of 6 mL/kg of predicted body weight (PBW), as opposed to 12 mL/kg, and aiming for a plateau pressure ≤30 cm H2O. [1] The use of lung protective strategies for patients with ARDS is supported by clinical trials and has been widely accepted, but the precise choice of tidal volume for an individual patient with ARDS may require adjustment for such factors as the plateau pressure achieved, the level of positive end-expiratory pressure (PEEP) chosen, the compliance of the thoracoabdominal compartment and the vigor of the patient’s breathing effort. Some clinicians believe it may be safe to ventilate with tidal volumes higher than 6 ml/kg PBW as long as the plateau pressure can be maintained ≤30cm H2O. [11, 12]

The validity of this ceiling value will depend on breathing effort, as those who are actively inspiring generate higher trans-alveolar pressures for a given plateau pressure than those who are passively inflated. Conversely, patients with very stiff chest walls may require plateau pressures >30 cm H2O to meet vital clinical objectives. One retrospective study suggested that tidal volumes should be lowered even with plateau pressures ≤30 cm H2O. [13] An additional observational study suggested that knowledge of the plateau pressures was associated with lower plateau pressures; however, in this trial, plateau pressure was not independently associated with mortality rates across a wide range of plateau pressures that bracketed 30 cm H2O. [14] The largest clinical trial employing a lung protective strategy coupled limited pressure with limited tidal volumes to demonstrate a mortality benefit. [1]

High tidal volumes that are coupled with high plateau pressures should be avoided in ARDS. Clinicians should use as a starting point the objective of reducing tidal volumes over 1 to 2 hours from its initial value toward the goal of a “low” tidal volume (=6 mL per kilogram of predicted body weight) achieved in conjunction with an end-inspiratory plateau pressure less than or equal to 30 cm H2O. If plateau pressure remains >30 after reduction of tidal volume to 6 ml/kg/PBW, tidal volume should be reduced further to as low as 4 ml/kg/PBW.
No single mode of ventilation (pressure control, volume control, airway pressure release ventilation, high frequency ventilation, etc.) has been consistently shown advantageous when compared with any other that respects the same principles of lung protection.

Allowing PaCO2 to increase above its pre-morbid baseline, so-called permissive hypercapnia, may be allowed in patients with ARDS if needed to minimize plateau pressures and tidal volumes.

An acutely elevated PaCO2 may have physiologic consequences that include vasodilation as well as an increased heart rate, blood pressure, and cardiac output. Allowing modest hypercapnia in conjunction with limiting tidal volume and minute ventilation has been demonstrated to be safe in small, nonrandomized series. [2, 3] Patients treated in larger trials that have the goal of limiting tidal volumes and airway pressures have demonstrated improved outcomes, but permissive hypercapnia was not a primary treatment goal in these studies. [1] The use of hypercapnia is limited in patients with preexisting metabolic acidosis and is contraindicated in patients with increased intracranial pressure. Sodium bicarbonate or tromethamine infusion may be considered in selected patients to facilitate use of permissive hypercarbia. [15, 16]

- The Surviving Sepsis Campaign recommends that positive end-expiratory pressure (PEEP) be set so as to avoid extensive lung collapse at end-expiration (Grade 1B).

Raising PEEP in ARDS keeps lung units open to participate in gas exchange. This will increase PaO2 when PEEP is applied through either an endotracheal tube or a face mask. [17-19] In animal experiments, avoidance of end-expiratory alveolar collapse helps minimize ventilator-induced lung injury (VILI) when relatively high plateau pressures are in use. One large multi-center trial of the protocol-driven use of higher PEEP in conjunction with low tidal volumes did not show benefit or harm when compared to lower PEEP levels. [20] Neither the control nor experimental group in that study, however, was clearly exposed to hazardous plateau pressures. A recent multi-center Spanish trial compared a high PEEP, low-moderate tidal volume approach to one that used conventional tidal volumes and the least PEEP achieving adequate oxygenation. A marked survival advantage favored the former approach in high acuity patients with ARDS. [21] Two options are recommended for PEEP titration. One option is to titrate PEEP (and tidal volume) according to bedside measurements of thoracopulmonary compliance with the objective of obtaining the best compliance, reflecting a favorable balance of lung recruitment and overdistention. [22] The second option is to titrate PEEP based on severity of oxygenation deficit and guided by the FIO2 required to maintain adequate oxygenation. [1] Whichever the indicator — compliance or oxygenation — recruiting maneuvers are reasonable to employ in the process of PEEP selection. Blood pressure and oxygenation should be monitored and recruitment
discontinued if deterioration in these parameters is observed. A PEEP >5 cm H2O is usually required to avoid lung collapse. [23]

References


Content adapted extensively from:

Tips
1. Create a standardized protocol that prompts users to use tidal volumes <6 ml/kg IBW and to maintain plateau pressures <30 cm H20.
2. Make execution of an ARDSnet-like protocol the primary responsibility of the respiratory therapists, if possible.
3. Have stakeholders work in concert with the respiratory therapy department to create and deploy a clinical protocol for ARDS ventilation.
4. Avoid synchronized intermittent mandatory ventilation (SIMV) during the acute phase of illness. Instead, use mandatory modes of ventilation such as assist control (ACV) or pressure control (PCV) to prevent spontaneously large tidal volumes.
5. Do not allow peak pressures to govern ventilator management. The key value is the plateau pressure.
6. The weight for determining the Vt should be the ideal body weight. The ideal body weight is calculated from the patient’s height.

7. Do not worry about the pCO2 unless the pH is less than a threshold the clinical team cannot accept. Some intensivists are comfortable with pH as low as 7.10. Most clinicians like to see pH greater than 7.21. Some more conservative clinicians use pH in the range of 7.25 or 7.30. Where renal dysfunction prevents compensation, bicarbonate or tromethamine can be used to help maintain the pH. However, constant bicarbonate infusions can also contribute to CO2 production. Tromethamine does not have this side effect.

**Severe Sepsis Bundles: Other Supportive Therapies**

4. Sedation, Analgesia, and Neuromuscular Blockade
   - Minimize continuous or intermittent sedation in mechanically ventilated sepsis patients, targeting specific titration endpoints (Grade 1B).
   - When using neuromuscular blocking agents (NMBAs):
     - Avoid NMBAs if possible in the septic patient *without ARDS* due to the risk of prolonged neuromuscular blockade following discontinuation. If NMBAs must be maintained, either intermittent bolus as required or continuous infusion with train-of-four monitoring of the depth of blockade should be used (Grade 1C).
     - Apply a short course of a NMBA (≤48 hours) for patients *with* early, severe sepsis-induced ARDS (Grade 2C).

A growing body of evidence indicates that limiting the use of sedation in critically ill ventilated patients can reduce the duration of mechanical ventilation and ICU and hospital lengths of stay. [1-3] While studies limiting sedation have been performed in a wide range of critically ill patients, there is little reason to assume that septic patients will not derive benefit from this approach. [3] The use of protocols for sedation is one method to limit sedation use, and a randomized, controlled clinical trial found that protocolized sedation compared with usual care reduced duration of mechanical ventilation, lengths of stay, and tracheostomy rates. [3] Avoidance of sedation is another strategy.

**Grading the Evidence** [See Ranking the Evidence]

The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. The Grade 2 suggestions are weaker recommendations for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.
Decreasing Length of Stay on Ventilation

A recent observational study of 250 critically ill patients suggests that deep sedation is common in mechanically ventilated patients. [4] A randomized, controlled clinical trial found that patients treated with intravenous morphine boluses preferentially, with short-term propofol infusions for rescue therapy only, had significantly more days without ventilation, with shorter stays in the ICU and hospital, than patients who received propofol infusions in addition to bolus morphine. [5] However, agitated delirium was more frequently detected in the intervention group.

Intermittent vs. Continuous Sedation

Although not specifically studied in patients with sepsis, the administration of intermittent sedation, daily sedative interruption, and systematic titration to a predefined endpoint have been demonstrated to decrease the duration of mechanical ventilation. [3, 6-8] Patients receiving neuromuscular blocking agents (NMBAs) must be individually assessed regarding discontinuation of sedative drugs because the neuromuscular blockade must first be reversed. The use of intermittent vs. continuous methods for the delivery of sedation in critically ill patients has been examined in an observational study of mechanically ventilated patients that showed that patients receiving continuous sedation had significantly longer durations of mechanical ventilation and ICU and hospital lengths of stay. [8]

References


Content adapted extensively from:

Severe Sepsis Bundles: Other Supportive Therapies

5. Deep Vein Thrombosis (DVT) and Peptic Ulcer Disease (PUD) Prophylaxis

Deep Vein Thrombosis Prophylaxis

- It is recommended that patients with severe sepsis receive daily pharmacoprophylaxis against venous thromboembolism (VTE) (Grade 1B). This is accomplished with daily subcutaneous low-molecular weight heparin (LMWH) (Grade 1B, versus twice daily unfractionated heparin (UFH) (Grade 2C), versus three times daily UFH). If creatinine clearance is <30 mL/min and LMWH is used, the recommendation is use of dalteparin (Grade 1A) or another form of LMWH that has a low degree of renal metabolism (Grade 2C) or UFH (Grade 1A).
- It is recommended that patients with severe sepsis be treated with a combination of pharmacologic therapy and intermittent pneumatic compression devices whenever possible (Grade 2C).
- Septic patients who have a contraindication to heparin use (e.g., thrombocytopenia, severe coagulopathy, active bleeding, recent intracerebral hemorrhage) should not receive pharmacoprophylaxis (Grade 1B). Rather it is recommended they receive mechanical prophylactic treatment, such as graduated compression stockings or intermittent compression devices (Grade 2C), unless contraindicated. When the risk decreases, starting pharmacoprophylaxis is recommended (Grade 2C).

ICU patients are at risk for deep vein thrombosis (DVT). [1] It is logical that patients with severe sepsis would be at a similar or higher risk than the general ICU population. The consequences of VTE in the setting of sepsis (increased risk of potentially fatal pulmonary emboli in an already hemodynamically compromised patient) are dire. Therefore, prevention of VTE is highly desirable, especially if it can be done safely and effectively.

Prophylaxis is generally effective. In particular, nine placebo-controlled RCTs of VTE prophylaxis have been conducted in general populations of acutely ill patients. [2-10] All trials showed reduction in DVT or pulmonary embolism, a benefit that is also supported by meta-
analyses. [11, 12] Thus, the evidence strongly supports the value of VTE prophylaxis (Grade 1A). The prevalence of infection/sepsis was 17 percent in those studies in which this could be ascertained. One study investigated only ICU patients only, and 52 percent of those enrolled had infection/sepsis. The need to extrapolate from general, acutely ill patients to critically ill patients to septic patients downgrades the evidence. That the effect is pronounced and the data are robust somewhat mitigate against the extrapolation, leading to a Grade B determination. Because the patient’s risk of administration is small, the gravity of not administering may be great, and the cost is low, the strength of the recommendation is strong. [1]

**Peptic Ulcer Disease Prophylaxis**
Provide stress ulcer prophylaxis using H2 blocker or proton pump inhibitor to patients with severe sepsis/septic shock who have bleeding risk factors (Grade 1B). When stress ulcer prophylaxis is used, use of proton pump inhibitors rather than H2 receptor antagonists (H2RA) are recommended (Grade 2C).

Although no study has been performed specifically in patients with severe sepsis, trials confirming the benefit of stress ulcer prophylaxis in reducing upper gastrointestinal (GI) bleeding in general ICU populations included 20 percent to 25 percent of patients with sepsis. [13-15] This benefit should be applicable to patients with severe sepsis and septic shock. In addition, the risk factors for GI bleeding (e.g., coagulopathy, mechanical ventilation for at least 48 hours, possibly hypotension) are frequently present in patients with severe sepsis and septic shock. [16, 17] Patients without these risk factors are unlikely (0.2 percent; 95 percent CI, 0.02−0.5) to have clinically important bleeding. [16]

**Grading the Evidence** [See [Ranking the Evidence]](#)
The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. The Grade 2 suggestions are weaker recommendations for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

**References**


Content adapted extensively from:


**Severe Sepsis Bundles: Other Supportive Therapies**

### 6. Nutrition

- Administer oral or enteral (if necessary) feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hours after a diagnosis of severe sepsis/septic shock (Grade 2C).
- Avoid mandatory full caloric feeding in the first week, but rather provide low-dose feeding (e.g., up to 500 kcal per day), advancing only as tolerated (Grade 2B).
- Use intravenous glucose and enteral nutrition rather than total parenteral nutrition (TPN) alone or parenteral nutrition in conjunction with enteral feeding in the first 7 days after a diagnosis of severe sepsis/septic shock (Grade 2B).
- Use nutrition with no specific immunomodulating supplementation in patients with severe sepsis (Grade 2C).

Early enteral nutrition has theoretical advantages in the integrity of gut mucosa and prevention of bacterial translocation and organ dysfunction, but the risk of ischemia, mainly in hemodynamically unstable patients, is also a concern.

Unfortunately, no clinical trial has specifically addressed early feeding in septic patients. Studies on different subpopulations of critically ill patients, mostly surgical patients, are not consistent, with great variability in the intervention and control groups; all are of low methodological quality [1-10] and none was individually powered for mortality, with very low mortality rates [1-3, 6, 9]. Authors of previously published meta-analyses of optimal nutrition strategies for the critically ill all reported that the studies they included had high heterogeneity and low quality [1-13]. Although no consistent effect on mortality was observed, there was evidence of benefit from some early enteral feeding on secondary outcomes, such as reduced incidence of infectious complications, [1, 5, 9-13] reduced length of mechanical ventilation, [4, 10] and reduced ICU [4, 10] and hospital stays [11]. No evidence of harm was demonstrated in any of those studies. Therefore, there is insufficient evidence to issue a strong recommendation, but the suggestion of benefit and absence of harm supports a suggestion that some enteral feeding is warranted.

**Grading the Evidence** [See Ranking the Evidence]

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**References**


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**Severe Sepsis Bundles: Other Supportive Therapies**

**7. Setting Goals of Care**
- Discuss goals of care and prognosis with patients and families (Grade 1B).
- Incorporate goals into treatment and end-of-life care planning, utilizing palliative care principles where appropriate (Grade 1B).
- Address goals of care as early as feasible, but no later than within 72 hours of ICU admission (Grade 2C).

The majority of ICU patients receive full support with aggressive, life-sustaining treatments. Many patients with multiple organ system failure or severe neurologic injuries will not survive or will have a poor quality of life. Decisions to provide less-aggressive life-sustaining treatments or to withdraw life-sustaining treatments in these patients may be in the patient’s best interest and
may be what patients and their families desire. [1] Physicians have different end-of-life practices based on their region of practice, culture, and religion. [1]

Although the outcome of intensive care treatment in critically ill patients may be difficult to prognosticate accurately, establishing realistic treatment goals is important in promoting patient-centered care in the ICU. [2] Models for structuring initiatives to enhance care in the ICU highlight the importance of incorporating goals of care along with the prognosis into treatment plans. [3] Additionally, discussing the prognosis for achieving the goals of care and level of certainty of prognosis has been identified as an important component of surrogate decision making in the ICU. [4, 5] However, variations exist in the use of advanced care planning and integration of palliative and end-of-life care in the ICU, which can lead to conflicts that may threaten overall quality of care. [6, 7]

The use of proactive family care conferences to identify advanced directives and treatment goals within 72 hours of ICU admission promotes communication and understanding between the patient’s family and the care team; improves family satisfaction; decreases stress, anxiety, and depression in surviving relatives; facilitates end-of-life decision making; and shortens length of stay for patients who die in the ICU. [8–12] Clinical practice guidelines for support of the ICU patient and family promote: early and repeated care conferencing to reduce family stress and improve consistency in communication; open flexible visitation; family presence during clinical rounds and resuscitation; and attention to cultural and spiritual support. [13] Additionally, the integration of advanced care planning and palliative care focused on pain management, symptom control, and family support has been shown to improve symptom management and patient comfort, and to improve family communication. [3, 9, 14, 15]

Grading the Evidence [See Ranking the Evidence]
The Grade 1 recommendations are based on strong evidence for care based on a number of qualitative considerations. The Grade 2 suggestions are weaker recommendations for care based on a number of qualitative considerations. “B” level evidence generally derives from randomized control trials with certain limitations or very well-done observational or cohort studies. “C” level evidence reflects well-done observational or cohort studies with controls. “D” level evidence generally reflects downgraded controlled studies or expert opinion based on other evidence.

References


Content adapted extensively from: