3-Hour 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

- 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].

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- Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine*. 2013 Feb;41(2):580-637.

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.

3-Hour Bundle

2. Obtain Blood Cultures Prior to Administration of Antibiotics

Related Measures

Timing 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

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.

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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.

3-Hour 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.

Surviving Sepsis Campaign

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

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).

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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.

3-Hour 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 ($ScvO_2$)*

**Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, $ScvO_2$ 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, $ScvO_2$ 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 SvO_2 saturation as similar to a 70 percent $ScvO_2$.[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

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).

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