6-Hour Bundle

Revised November 22, 2013

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 a central venous 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

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.

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Content adapted extensively from:

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TIPS

1. Include the use of vasopressors 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 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 ($ScvO_2$) [see bundle element 2b].

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.

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 $mL \cdot kg^{-1} \cdot hr^{-1}$. 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 $ScvO_2$. Their treatment aims were then the same as the control groups, except that they also had to achieve a $ScvO_2$ of ≥70 percent.

The patients assigned to the early goal-directed therapy group received a central venous catheter capable of measuring $ScvO_2$. Their treatment aims were then the same as the control groups, except that they also had to achieve a $ScvO_2$ 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 ($ScvO_2$, 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 SvO_2 runs 5 percent to 7 percent lower than central venous oxygen saturation ($ScvO_2$)[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, $ScvO_2$ or SvO_2 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 $\mu g \bullet kg^{-1} \bullet min^{-1}$) be utilized to achieve this goal.

  The protocol used in the study targeted an increase in $ScvO_2$ 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 $ScvO_2$ 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 O_2 content or increasing cardiac output) of the protocol on achievement of improved outcome.

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- Rhodes A, Bennett ED. Early goal-directed therapy: An evidence-based review. *Critical Care Medicine*. 2004;32(Suppl):S448-S450.

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 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 ($ScvO_2$). (The target is ≥70 percent.*)

**Mixed venous oxygen saturation (SvO_2) ≥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]; and 2) maximizing mixed or central venous oxygen saturation ($ScvO_2$).

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 ($ScvO_2$) 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 $ScvO_2$ 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 $ScvO_2$

Techniques to maintain $ScvO_2$ 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 $ScvO_2$ 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 $\mu g \cdot kg^{-1} \cdot min^{-1}$) 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 $mL \bullet kg^{-1} \bullet min^{-1}$. 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 $ScvO_2$. Their treatment aims were then the same as the control groups, except that they also had to achieve a $ScvO_2$ of ≥70 percent.

The patients assigned to the early goal-directed therapy group received a central venous catheter capable of measuring $ScvO_2$. Their treatment aims were then the same as the control groups, except that they also had to achieve a $ScvO_2$ 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

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 $mL \bullet kg^{-1} \bullet hr^{-1}$
  - 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 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 ≥65 mm Hg as well as central venous oxygen saturation ($ScvO_2$, measured in superior vena cava, either intermittently or continuously) of ≥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 SvO_2 runs 5 percent to 7 percent lower than central venous oxygen saturation ($ScvO_2$),[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 $ScvO_2$ is not available, lactate normalization may be a feasible option in the patient with severe sepsis-induced tissue hypoperfusion. $ScvO_2$ 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 $ScvO_2$ 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 $ScvO_2$ 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 $ScvO_2$ or SvO_2 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 $\mu g.kg^{-1}.min^{-1}$) be utilized to achieve this goal (Grade 2C).

  The protocol used in the study cited previously targeted an increase in $ScvO_2$ 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 $ScvO_2$ 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 O_2 content or increasing cardiac output) of the protocol on achievement of improved outcome.

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Content adapted extensively from:

- 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;41(2):580-637.
- Rhodes A, Bennett ED. Early goal-directed therapy: An evidence-based review. *Critical Care Medicine*. 2004;32(Suppl):S448-S450.

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 Bundle

3. Remeasure Lactate If Initial Lactate Was Elevated

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 ≥4 mmol/L, and is also increased in severely septic patients with hypotension alone and lactate ≥4 mmol/L.[5] If $ScvO_2$ is not available, lactate normalization may be a feasible option in the patient with severe sepsis-induced tissue hypoperfusion. $ScvO_2$ 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

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).

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