2. In the Event of Persistent Arterial Hypotension Despite Volume Resuscitation (Septic Shock) or Initial Lactate $\geq 4$ 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 $\geq 4$ mmol/L (36 mg/dL) measure central venous oxygen saturation ($\text{ScvO}_2$). (The target is $\geq 70$ percent.*)

*Mixed venous oxygen saturation ($\text{SvO}_2$) $\geq 65$ 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 ($\text{ScvO}_2$).

Following the bundle, once lactate is $\geq 4$ 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 $\geq 8$ mm Hg and central venous oxygen saturation ($\text{ScvO}_2$) should be maintained at $\geq 70$ percent.

These recommendations are consistent with Rivers, et al., the only trial to demonstrate a mortality benefit in early goal-directed therapy using $\text{ScvO}_2$ 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 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 supranormal 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•min. 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

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 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 (ScvO₂, 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 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 $\geq 70$ percent or $\geq 65$ percent respectively is not achieved with fluid resuscitation to the CVP target, then transfusion of packed red blood cells to achieve a hematocrit of $\geq 30$ 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 ScvO2 to $\geq 70$ 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.