Management of Septic Shock

This interactive feature addresses the approach to a clinical issue. A case vignette is followed by specific options, neither of which can be considered either correct or incorrect. In short essays, experts in the field then argue for each of the options. Readers can participate in forming community opinion by choosing one of the options and, if they like, providing their reasons.

CASE VIGNETTE

A Woman with Septic Shock

Rebecca E. Berger, M.D.

Ms. Jones is a 65-year-old woman with a history of hypertension who presents to the emergency department with a 3-day history of chills and dysuria. The only medication she is taking is amlodipine, at a dose of 10 mg daily; she had had normal electrolyte levels and renal function at a routine visit 6 weeks earlier. On arrival at the emergency department, she reports feeling dizzy.

She is 165 cm (65 in.) tall and weighs 70 kg (154 lb). Her temperature is 38.6°C (101.5°F), heart rate 125 beats per minute, blood pressure 85/55 mm Hg (mean arterial pressure, 65 mm Hg), respiratory rate 28 breaths per minute, and oxygen saturation as measured by pulse oximetry 94% while she is breathing ambient air. A physical examination reveals dry mucous membranes; undetectable jugular venous pulsation; tachycardia without gallops, rubs, or murmurs; clear lungs; and warm extremities. She has tenderness on palpation of her suprapubic region. You begin intravenous administration of a bolus of crystalloid solution.

Laboratory testing shows a creatinine level of 1.8 mg per deciliter (159 μmol per liter) (normal range, 0.5 to 1.1 mg per deciliter [44 to 97 μmol per liter]), blood urea nitrogen 76 mg per deciliter (27 mmol per liter) (normal range, 7 to 20 mg per deciliter [2 to 7 mmol per liter]), lactate 5.0 mmol per liter (normal value, <2.0), anion gap 25 mmol per liter (normal range, 8 to 15), white-cell count 20,000 per cubic millimeter (normal range, 4500 to 11,000), and hemoglobin 9.0 g per deciliter (normal range, 12.0 to 15.5). Urinalysis shows 3+ leukocyte esterase, more than 100 white cells per high-power field, and abundant bacteria.

You make a presumptive diagnosis of sepsis from a urinary source and begin treatment with intravenous antibiotics to target likely urinary pathogens. Ultrasonography of the kidneys and bladder reveals no hydronephrosis or evidence of obstruction.

After administration of 2100 ml of crystalloid fluid (30 ml per kilogram of body weight), the patient's jugular venous pressure is 8 cm of water, but her systemic arterial pressure has decreased to 80/50 mm Hg (mean arterial pressure, 60 mm Hg). During the 3 hours that she has been in the emergency department, she has produced 20 ml of urine, as measured through a Foley catheter that was placed on her arrival.

You place a central venous catheter and initiate a norepinephrine infusion, which you adjust with a goal of raising her mean arterial pressure to 65 to 70 mm Hg. She is transferred to the intensive care unit (ICU); on arrival in the ICU, her mean arterial pressure is 65 mm Hg while she is receiving 40 μg of norepinephrine per minute, and her heart rate is 100 beats per minute. A chest radiograph shows early evidence of acute lung injury and good central catheter placement. Her arterial oxygen saturation is 100% while she is receiving 4 liters of oxygen through a nasal cannula.

You are aware that there are two main approaches to the management of septic shock in a patient such as Ms. Jones. One approach involves serial measurement of central venous pressure, central venous oxygen saturation ($Scvo_2$), and hemoglobin, and following the early, goal-directed therapy (EGDT) protocol, in which specified targets are used for the initiation of inotropic agents or transfusion of red cells.[1] For example, if the central venous pressure is less than 8 mm Hg, additional fluid resuscitation is administered; if the $Scvo_2$ is less than 70%, the

patient receives a transfusion of red cells until a hematocrit goal of at least 30% is reached, and if the Scvo$_2$ remains less than 70%, inotropic support is initiated.

The second approach involves continuing intravenous administration of antibiotics and vasopressors, guided by clinical signs including blood pressure and urine output, without serial central venous pressure monitoring, serial Scvo$_2$ monitoring, transfusion of red cells, or administration of inotropic agents. You are undecided about which of these approaches would maximize the chance of survival for your patient with septic shock.

TREATMENT OPTIONS

Which of the following treatment strategies should you pursue for this patient?

1. **Follow the EGDT protocol.**
2. **Monitor the patient and administer treatment on the basis of clinical signs.**

To aid in your decision making, each of these approaches is defended in a short essay by an expert in the field. Given your knowledge of the patient and the points made by the experts, which option would you choose? Make your choice, vote, and offer your comments at NEJM.org.

OPTION 1

Follow the EGDT Protocol

Emanuel Rivers, M.D.

Ms. Jones has been admitted to the ICU with septic shock and is receiving vasopressors to elevate her mean arterial pressure. Shortly after her arrival, her condition deteriorates, and intubation and mechanical ventilation are initiated because of acute lung injury. The increased lactate level and low Scvo$_2$ indicate inadequacy of systemic oxygen delivery (hypoxia, anemia, or decreased cardiac output) to meet demands (increased work of breathing).

The EGDT protocol expanded the landscape of sepsis management outside the ICU with a series of steps.[1] Step one is early detection of patients at high risk for infection according to the criteria for diagnosis of the systemic inflammatory response syndrome, followed by culturing of appropriate specimens and initiation of antibiotics. Step two is risk stratification on the basis of serum lactate levels, response to fluid challenge if the patient has hypotension, or both, for appropriate disposition. Patients who are stratified for risk on the basis of lactate level and a fluid challenge of 30 ml per kilogram have more than 19% lower mortality than patients who are not stratified in this way.[2] Early risk stratification also reduces mortality from acute cardiopulmonary deterioration, which may occur in up to 20% of patients in the early course of septic shock.[2] These initial steps alone or in combination significantly affect mortality.[2]

The remaining steps of the EGDT protocol include effective hemodynamic management of preload, afterload, and cardiac contractility and assessment of perfusion to balance systemic oxygen delivery with demands by measurement of Scvo$_2$ and central venous pressure. Early placement of a central venous catheter has been associated with improved outcomes.[2] A low Scvo$_2$ on admission to the ICU is associated with mortality that is at least 10% higher than that with a normal Scvo$_2$.[3] Normalization of Scvo$_2$ in acute lung injury is associated with decreased duration of mechanical ventilation and 15% lower mortality.[4] If the Scvo$_2$ is low and the partial pressure of arterial oxygen (Pao$_2$) is normal, effective hemodynamic support begins with transfusion of one unit of packed red cells to attain a hemoglobin level above 10 g per deciliter. Although the hemoglobin target in this hemodynamic phenotype (low Scvo$_2$ and increased lactate level) is not known, transfusion has not been associated with increased complications and may decrease the risk of death.[5,6] After correction of arterial oxygen content with transfusion, the remaining variable that has to be addressed to correct oxygen delivery is decreased cardiac output (myocardial suppression, which can occur in up to 15% of patients). Inotropic agents, such as dobutamine, are included in the EGDT algorithm to increase cardiac output.[2]

After the original EGDT trial was performed and the Surviving Sepsis Campaign was initiated, the standard of care changed, and mortality from sepsis has decreased over the past decade.[2] A recent meta-analysis of three trials (Protocolized

Resuscitation in Sepsis Meta-Analysis [PRISM]) concluded that there was no mortality benefit of protocolized care for sepsis.[7] However, the PRISM trials provided steps one and two of the EGDT protocol as usual care for all treatment groups before randomization, and the care was unblinded. As a result, many of the patients had reached normal $Scvo_2$ and central venous pressure values by the time of randomization and also had a lower baseline illness severity, as evidenced by the fact that mechanical ventilation rates were lower than those in the original EGDT trial. These patients had little or no chance to benefit from the later steps in the EGDT algorithm that targeted $Scvo_2$-guided effective hemodynamic management. In addition, ICU admission in these three trials occurred within 2 to 3 hours after presentation, as compared with 6 to 8 hours in the original EGDT study. Although early admission to the ICU is a worthwhile goal, it is not a universal reality; thus, the results are not generalizable.

The results of the PRISM trials confirm that early intervention strategies, including early detection of sepsis, risk stratification, early administration of antibiotics, and appropriate fluid resuscitation, improve the outcomes in patients with severe sepsis and septic shock. All these steps were components of the original EGDT protocol and led to historically low mortality rates in both the control groups and the intervention groups in the PRISM studies.[2] However, because of the limitations of the PRISM trials with respect to the patient populations and trial methods, the potential benefit of the EGDT steps that involved effective hemodynamic management was diminished, which increased the probability of equivalency among the treatment groups.[2]

In the case of Ms. Jones, I would continue monitoring her condition by serial measurements of central venous pressure, $Scvo_2$, and lactate levels and following the EGDT protocol. EGDT is more effective than usual care across a broader range of hemodynamic phenotypes, including in patients receiving mechanical ventilation. This strategy maximizes her chances of survival from septic shock.

Disclosure forms provided by the author are available at NEJM.org.

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OPTION 2

Monitor the Patient and Administer Treatment on the Basis of Clinical Signs

Mitchell M. Levy, M.D.

Ms. Jones has been admitted to the ICU with septic shock and is receiving vasopressors; she has received 30 ml per kilogram of fluid resuscitation but continues to have hypotension and oliguria. Her treatment should include continuation of intravenous antibiotics and vasopressors, together with further volume resuscitation guided by lactate levels and blood pressure, and should not include serial measurement of central venous pressure or $Scvo_2$. I would not administer blood transfusions or inotropic agents on the basis of prespecified target values.

Resuscitation targets and goals have been debated extensively among critical care specialists. In 2001, a trial performed by Rivers et al.[1] provided clinicians with practical, evidence-based targets for resuscitation with the EGDT algorithm, which was aimed at reducing mortality among patients as it had in the trial. Given the dearth of previously proven resuscitation targets, the field moved quickly to adopt EGDT, including its incorporation into international guidelines. For the next 13 years, the study by Rivers et al. redefined the resuscitation of critically ill patients and established the importance of early, aggressive fluid intervention for resuscitation of patients with septic shock.

However, the Protocolized Care for Early Septic Shock (ProCESS),[8] Protocolised Management in Sepsis (ProMISE),[9] and Australasian Resuscitation in Sepsis Evaluation (ARISE)[10] trials, as well as PRISM,[7] which was the patient-level meta-analysis of those three trials, failed to confirm the survival advantage of protocolized targets for central venous pressure, $Scvo_2$, and hemoglobin in sepsis resuscitation. It is important for clinicians to realize that even in the ARISE and ProCESS trials, after patients received 30 ml per kilogram of fluid resuscitation, the mean $Scvo_2$ before randomization was already more than 70%, which was the target in the intervention group in the study by Rivers et al. However, with the publication of the PRISM patient-level meta-analysis,

the evidence puts to rest the need for mandated placement of a central venous catheter in every patient with severe sepsis and septic shock for the purpose of serial monitoring of central venous pressure or Scvo$_2$ to guide resuscitation.

The challenge for practicing clinicians is how to understand "usual care" in the settings of these large randomized, controlled trials. The trial by Rivers et al. and subsequent studies heightened awareness of sepsis as an urgent medical condition, which over the ensuing years has led to an unmistakable change in the standard of care for critically ill patients with sepsis. Regardless of attitudes about the validity of the specific details of the EGDT protocol, clinicians have come to embrace the need for rapid identification of sepsis and early treatment with antibiotics and fluids.

So the question remains, what can clinicians use at the bedside to guide resuscitation? After administration of the minimal suggested fluid volume (30 ml per kilogram), the proper balance between the use of additional fluids and the use of vasopressors alone to maintain a mean arterial pressure of greater than 65 mm Hg remains uncertain. In the case of Ms. Jones, I would guide resuscitation by serial lactate measurement. Two separate randomized, controlled trials have shown the benefit of lactate-guided therapy in resuscitation.[11,12] Measurement of urine output may be helpful, but in a patient with preexisting hypertension who may have unrecognized kidney disease, restoration of adequate urine output may be delayed. Normalization of the lactate level may be the most practical target in deciding whether further fluid administration is needed. Several clinical trials are now under way that will evaluate restricted volume resuscitation in comparison with a more liberal approach. For now, the precise total amount of fluids administered to a patient with septic shock can be guided by targeting a mean arterial pressure of 65 mm Hg with fluids and vasopressors while normalizing the lactate level.

In conclusion, I would treat Ms. Jones according to updated guidelines[13] for patients with septic shock, which incorporate findings from the trials outlined above. Antibiotics, vasopressors, and fluids remain the cornerstones of therapy; serial measurement of central venous pressure and Scvo$_2$ along with blood transfusions and administration of inotropic agents is not likely to improve her outcome.

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