Severe Sepsis/Septic Shock: Review Questions

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QUESTIONS

Choose the single best answer for each question.

Questions 1 and 2 refer to the following case.

A 65-year-old man with a history of chronic obstructive pulmonary disease, hypertension, and left-sided hemiparesis secondary to a hemorrhagic cerebrovascular accident (CVA) 2 months ago presents to the emergency department (ED) complaining of 3 days of fevers to 102°F, cough producing green sputum with some blood streaks, and pleuritic chest pain. The morning of admission, he became lightheaded and dizzy and had a presyncopal episode. The patient's temperature is 101.3°F, heart rate is 125 bpm, blood pressure is 80/30 mm Hg, and respiratory rate is 32 breaths/min. He is slightly lethargic but oriented to person, place, and time. Pupils are equal, round, and reactive to light and extraocular movements are intact. There is no jugular venous distention, with 2+ carotid pulses without bruits bilaterally. Lung examination is remarkable for diffuse crackles in all lung fields with some expiratory wheezing. Cardiac examination reveals a regular rate and rhythm, normal S_1 and S_2, 2/6 systolic ejection murmur at the right upper sternal border radiating into his carotids, and an S_4 gallop. No pericardial rubs are appreciated. The abdomen is soft, nontender, and nondistended with normoactive bowel sounds and no hepatosplenomegaly. Extremities are warm without cyanosis or edema. The patient has 1+ femoral pulses and weak posterior tibial pulses bilaterally. He has 3/5 strength in his left upper and lower extremities and 5/5 strength in his right upper and lower extremities, which is his reported baseline. Results of laboratory testing are shown in the **Table**. On 100% nonrebreather mask, blood gas analysis reveals an arterial pH of 7.20, $PaCo_2$ of 40 mm Hg, and Pao_2 of 53 mm Hg. Chest radiograph demonstrates diffuse bilateral infiltrates and normal heart size consistent with acute lung injury. The patient is intubated and a right internal jugular central venous line is placed. His central venous pressure (CVP) is 6 cm H_2O, prompting volume resuscitation with 3000 mL of 0.9% NaCl and 2000 mL lactated Ringer's solution, which increases his CVP to 12 cm H_2O. The patient's blood pressure remains low and he is started on a norepinephrine infusion, which is titrated to 12 µg/min to maintain a mean arterial pressure (MAP) greater than 65 mm Hg. A lumbar puncture is performed and evaluation of cerebrospinal fluid reveals 0 white blood cells, 2 red blood cells (RBCs), a protein level of 55 mg/dL, and a glucose level of 117 mg/dL. Urine output has totaled 20 mL over the last 2 hours. Gram stain of his sputum demonstrates gram-positive cocci in pairs and chains. The patient is admitted to the medical intensive care unit with the diagnosis of septic shock from pneumococcal pneumonia.

Table. Notable Results of Laboratory Testing in the Patient Described in Questions 1 and 2

Variable	Result
White blood cell count, cells/µL	23,500
Hematocrit, %	40
Platelet count, cells/µL	75,000
Sodium, mEq/L	142
Potassium, mEq/L	4.2
Chloride, mEq/L	106
Bicarbonate, mEq/L	16
Blood urea nitrogen, mg/dL	45
Serum creatinine, mg/dL	2.1
Serum glucose, mg/dL	180
Total serum bilirubin, mg/dL	2.5
Aspartate aminotransferase, U/L	75
Alanine aminotransferase, U/L	89
Alkaline phosphatase, U/L	82
Serum lactate, mEq/L	6.4
Prothrombin time, sec	22.1
International normalized ratio	1.9
Partial thromboplastin time, sec	37 (control, 27)

1. **Which of the following treatments has been shown in a large randomized, multicenter trial to reduce mortality in patients with septic shock?**
   (A) Drotrecogin alfa (activated)
   (B) High-intensity renal replacement therapy (RRT)
   (C) Intravenous (IV) hydrocortisone
   (D) IV immunoglobulin (IVIG)
   (E) IV pentastarch

2. **Which of the following represents an absolute contraindication to the use of the aforementioned treatment in this patient?**
   (A) International normalized ratio (INR) of 1.9
   (B) Platelet count of 75,000 cells/µL

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(C) Previous hemorrhagic CVA
(D) Recent lumbar puncture

Questions 3 and 4 refer to the following case.

A 51-year-old woman with a history of IV heroin use presents to the ED complaining of shortness of breath, chest pain, and lightheadedness on standing. Her temperature is 101.7°F, blood pressure is 75/30 mm Hg, heart rate is 115 bpm, and respiratory rate is 24 breaths/min. She is placed on 4 L of oxygen via nasal cannula with a saturation of 97% and is given 4500 mL of 0.9% NaCl IV fluids, which increases her CVP from 5 to 10 cm H_2O. She is started on a continuous infusion of norepinephrine, which is increased to 9 µg/min to maintain MAP above 65 mm Hg. A continuous infusion of vasopressin is initiated at 0.03 U/min to improve her blood pressure. Blood cultures show gram-positive cocci in clusters. She is started on vancomycin, levofloxacin, and piperacillin/tazobactam and admitted to the medical intensive care unit for further management of septic shock.

3. All of the following are components of early goal-directed therapy (EGDT) in the resuscitation of this patient with severe sepsis/septic shock EXCEPT
(A) IV fluid resuscitation targeting CVP 8 to 12 cm H_2O
(B) IV vasodilator infusion to maintain MAP < 90 mm Hg
(C) IV vasopressor infusion to maintain MAP > 65 mm Hg
(D) Transfusion of packed RBCs to achieve hematocrit > 35% if venous oxygen saturation (Svo_2) < 70%

4. Which of the following is true of vasopressin in septic shock?
(A) Continuous infusion at low doses improves 28-day overall mortality
(B) Continuous infusion at low doses improves mortality in patients with severe septic shock
(C) Continuous infusion at low doses increases cardiac output
(D) Continuous infusion at low doses reduces the catecholamine infusion requirement

ANSWERS AND EXPLANATIONS

1. (A) Drotrecogin alfa (activated). The patient clearly has sepsis as evidenced by the presence of all 4 criteria of the systemic inflammatory response syndrome: hyperthermia, leukocytosis, tachycardia, and tachypnea due to a presumed pneumococcal infection. The presence of organ dysfunction due to sepsis (renal, hepatic, respiratory, and central nervous system) as well as lactic acidosis constitute the diagnosis of severe sepsis. Furthermore, cardiovascular failure in the form of systemic hypotension further supports a diagnosis of septic shock. Recombinant human activated protein C (rhAPC), or drotrecogin alfa (activated), is the only treatment approved for reducing mortality in patients with severe sepsis and a high risk of death. Although the definition of "high risk" may vary, the case patient is clearly at a high risk of death as evidenced by his multisystem organ dysfunction, shock, and respiratory failure (APACHE II score, 30). In a large randomized, placebo-controlled trial of patients with severe sepsis (PROWESS trial),[1] drotrecogin alfa (activated) administered as a continuous IV infusion at 24 µg/kg/hr for 96 hours resulted in a 19.4% relative risk reduction in 28-day mortality and a 6.1% absolute reduction in the risk of death. This survival benefit was even more pronounced in patients with more than 1 organ dysfunction or APACHE II score of 24 or greater.

A small multicenter study suggested that low-dose IV hydrocortisone and oral fludrocortisone reduced mortality in septic shock patients with relative adrenal insufficiency, defined as a failure to increase serum cortisol levels by 9 mg/dL or more in response to adrenocorticotropin hormone (ACTH) stimulation.[2] However, the case patient's response to ACTH stimulation is unknown, and the study found no benefit in patients who responded appropriately to stimulation. A large multicenter study of a similar strategy demonstrated no survival benefit of hydrocortisone (overall or in nonresponders to ACTH stimulation) in patients with septic shock.[3] The effect of IVIG in patients with severe sepsis has had varying results. A recent multicenter study found no 7-day or 28-day survival benefit with IVIG in patients with severe sepsis.[4] A randomized, placebo-controlled, multicenter trial of 10% pentastarch showed no reduction in 28-day or 90-day mortality and an increased incidence of acute kidney injury (AKI) as compared with resuscitation with modified lactated Ringer's solution.[5] A large study of higher-intensity RRT in patients with AKI failed to demonstrate an improvement in any clinical outcome, including 28-day mortality, over standard RRT.[6] There are no data to suggest that RRT would benefit this patient at his current stage of AKI.

2. (C) Previous hemorrhagic CVA. In addition to anti-inflammatory properties, activated protein C also possesses anticoagulant and profibrinolytic properties, and, not unexpectedly, these properties increase the risk of bleeding in patients receiving drotrecogin alfa (activated). In the PROWESS trial, bleeding was the only adverse effect of administration of drotrecogin

alfa (activated).[1] Serious bleeding, defined as intracranial hemorrhage, life-threatening bleed, or bleeding that required administration of 3 U of packed RBCs on 2 consecutive days, occurred in 3.5% of patients receiving drotrecogin alfa (activated) as compared with 2% of those receiving placebo. This increased risk occurred primarily during the peri-infusion period. Any bleeding event during the 28-day study period also occurred more frequently in patients receiving drotrecogin alfa (activated) (24.9% versus 17.7% with placebo). rhAPC should not be given to any patient with a recent history (within 3 months) of hemorrhagic stroke due to the risk of intracranial hemorrhage. Post hoc analysis of PROWESS trial data found that increased bleeding was associated with a platelet count that fell below 30,000 cells/μL and/or INR that rose above 3.0.[1] As such, both represent relative contraindications to administration of rhAPC; the case patient has adequate platelets and an acceptable INR for rhAPC. Uncomplicated bedside procedures (eg, lumbar puncture) are not contraindications to rhAPC therapy; rhAPC should be discontinued for 2 hours prior to the procedure and restarted once hemostasis is acheived.

3. **(D) Transfusion of packed RBCs to achieve hematocrit > 35% if Svo_2 < 70%.** Therapy targeting a specific blood pressure and oxygen delivery has been tried unsuccessfully in many critical care diseases. However, goal-directed therapy, directed by continuous measurement of central Svo_2, has been shown to reduce mortality of patients with severe sepsis when initiated early in their hospital course.[7] The initiation and continuation of EGDT in the ED for 6 hours resulted in a 16% absolute and 34% relative reduction in hospital mortality (46.5% versus 30.5%) as compared with standard care. EGDT patients received protocolized care consisting of the following (in sequence): (1) placement of a central venous line able to continuously monitor Svo_2; (2) IV volume resuscitation using crystalloids or colloids to achieve a CVP of 8 to 12 cm H_2O; and (3) initiation of vasopressor agents to maintain MAP greater than 65 mm Hg or vasodilator agents to maintain MAP less than 90 mm Hg. Once the patient reached a CVP of 8 to 12 cm H_2O and MAP of 65 to 90 mm Hg, care was directed using Svo_2. Patients with Svo_2 less than 70% were transfused with packed RBCs to achieve hematocrit values above 30%. If the hematocrit was above 30% but the Svo_2 remained below 70%, dobutamine infusion was initiated.

4. **(D) Continuous infusion at low doses reduces the catecholamine infusion requirement.** Vasopressin is a peptide synthesi zed in the hypothalamus and released from the posterior pituitary. Vasopressin produces a wide range of physiologic effects, including blood pressure maintenance. Acting through vascular V_1-receptors, the endogenous hormone directly induces vasoconstriction in hypotensive patients but does not significantly alter vascular smooth muscle constriction in humans with normal blood pressure. Landry and colleagues[8] demonstrated that patients with septic shock had inappropriately low levels of serum vasopressin compared with patients with cardiogenic shock, who had normal or elevated levels. In addition, they demonstrated that supplementing a low-dose infusion of vasopressin in septic shock patients allowed for the reduction or removal of the other catecholamine vasopressors. This was seen despite a reduction in cardiac output. Although these results were duplicated in subsequent studies, none evaluated outcomes such as length of stay or mortality until recently. A randomized double-blind study comparing vasopressin versus norepinephrine for the treatment of septic shock demonstrated no difference in 28-day mortality between the 2 treatment groups.[9] Subgroup analysis of patients with severe septic shock, defined as requiring 15 μg/min of norepinephrine or its equivalent, also did not demonstrate a mortality benefit. However, patients with less severe septic shock (ie, requiring 5–15 μg/min of norepinephrine) experienced a trend toward lower mortality when treated with low-dose (0.01–0.03 U/min) vasopressin.

REFERENCES

1. Bernard GR, Vincent JL, Laterre PF, et al; Recombinant human protein C Worldwide Evaluation in Severe Sepsis (PROWESS) Study Group. Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 2001;344:699–709.
2. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 2002;288:862–71.
3. Sprung CL, Annane D, Keh D, et al; the Corticosteroid Therapy of Septic Shock (CORTICUS) Study Group. Hydrocortisone therapy for patients with septic shock. N Engl J Med 2008;358:111–24.
4. Werdan K, Pilz G, Bujdoso O, et al; Score-Based Immunoglobulin Therapy of Sepsis (SBITS) Study Group. Score-based immunoglobulin G therapy for patients with sepsis: the SBITS study. Crit Care Med 2007;35:2693–701.
5. Brunkhorst FM, Engel C, Bloos F, et al; German Competence Network Sepsis (SepNet). Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125–39.
6. Palevsky PM, Zhang JH, O'Connor TZ, et al; VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 2008;359:7–20.
7. Rivers E, Nguyen B, Havstad S, et al; Early Goal-Directed Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–77.
8. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. Circulation 1997;95:1122–5.
9. Russell JA, Walley KR, Singer J, et al; VASST Investigators. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008; 358:877–87.