# 63-Year-Old Woman With Generalized Fatigue and Left Flank Pain

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A 63-year-old woman presented to the emergency department with a 5-day history of progressive generalized fatigue, left flank pain, and fevers. The flank pain was dull and achy with occasional sharp stabbing pains that radiated from her left flank to her left costovertebral angle. One day prior, she had a temperature of 39.5°C. Additional symptoms included headache and loss of appetite. She did not endorse nausea, vomiting, diarrhea, constipation, dysuria, urinary frequency, rashes, or cough. She had no personal history of kidney stones.

Her medical history was notable for relapsing multiple sclerosis complicated by a neurogenic bladder, which required approximately 5 in-and-out self-catheterizations a day. Her surgical history was notable for a hysterectomy. Her medications included gabapentin and interferon for management of her multiple sclerosis. She was a nonsmoker and did not consume alcohol.

On initial examination, her vital signs were as follows: blood pressure, 76/48 mm Hg; heart rate, 118 beats/min; respiratory rate, 22 breaths/min; and temperature, 37.3°C. She was awake, alert, oriented, and able to provide an adequate history. Her physical examination revealed diaphoresis, tachycardia, suprapubic tenderness, and left-sided costovertebral angle tenderness. No abdominal guarding or rebound tenderness was appreciated. Digital rectal examination revealed no abnormalities. She had no vertebral tenderness. Left leg raise did not elicit pain, and there was no lower extremity swelling.

A complete blood cell count and renal profile revealed the following (reference ranges provided parenthetically): leukocytes, 152 × $10^9$/L (3.5-10.5 × $10^9$/L); hemoglobin, 10.3 g/dL (12.0-15.5 g/dL); platelet count, 188 × $10^9$/L (150-450 × $10^9$/L); sodium, 135 mmol/L (135-145 mmol/L); potassium, 3.3 mmol/L (3.6-5.2 mmol/L); chloride, 103 mmol/L (98-107 mmol/L); bicarbonate, 21 mmol/L (22-29 mmol/L); serum urea nitrogen, 21 mg/dL (6-21 mg/dL); creatinine, 1.7 mg/dL (0.6-1.1 mg/dL); prothrombin time, 15.1 seconds; internal normalized ratio, 1.1; and lactate, 2.0 mmol/L (0.6-2.3 mmol/L). The patient's baseline creatinine level was 0.8 mmol/L. Urinalysis was positive for leukocyte esterase, white blood cells in clumps, and the presence of bacteria. Urine cultures were obtained.

**1. Which *one* of the following would *best* classify the patient's current condition?**

a. Systemic inflammatory response syndrome (SIRS)
b. Sepsis
c. Severe sepsis
d. Septic shock
e. None of the above

It is important to identify and differentiate these clinical syndromes during the initial evaluation of the patient to help characterize the severity of the patient's condition. SIRS is a dysregulation of the inflammatory response with an infectious or noninfectious etiology (pancreatitis, burns, lung contusion, or postoperative state). It is defined as the presence of 2 or more of the following criteria: temperature greater than 38.0°C or less than 36°C, heart rate greater than 90 beats/min, respiratory rate greater than 20 breaths/min, $Paco_2$ less than 32 mm Hg, and white blood cell count greater than 12 × $10^9$/L or less than 4 × $10^9$/L in the absence of infection. If SIRS criteria are present in a patient with suspected infection, the condition is classified as sepsis. Sepsis is defined as documented or suspected infection plus systemic manifestations of infection (any of the SIRS criteria, elevations of procalcitonin and C-reactive protein levels, hyperglycemia in those without diabetes, altered mental status).[1] Severe sepsis

**See end of article for correct answers to questions.**

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is defined as sepsis with evidence of organ dysfunction.[1,2] This patient met 3 SIRS criteria (tachycardia, tachypnea, and leukocytosis) in the presence of a suspected urologic infection and an acute kidney injury. Therefore, the most likely diagnosis is severe sepsis. Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation. In this patient, adequate fluid resuscitation had not yet been administered.

Two large-bore peripheral venous catheters were placed.

**2. At this time, which *one* of the following is the *best* initial option?**

a. Crystalloid fluid replacement
b. Antibiotics directed toward a urogenital source
c. Blood cultures
d. Colloid fluid replacement
e. Appropriate imaging to confirm the source of infection

Establishing vascular access and initiating aggressive fluid resuscitation are the first priorities when managing patients with severe sepsis.[2] The initial fluid challenge should be the administration of 30 mL/kg of a crystalloid fluid. According to the most recent Surviving Sepsis Guidelines,[2] the goals in the first 3 hours of resuscitation are (1) administration of at least 30 mL/kg of crystalloid, (2) administration of broad-spectrum antibiotics, (3) performance of blood cultures before antibiotic administration, and (4) measurement of the serum lactate level. According to these guidelines, the goals at 6 hours of resuscitation should include a central venous pressure (CVP) of 8 to 12 mm Hg, a mean arterial pressure (MAP) of 65 mm Hg or higher, urinary output of 0.5 mL/kg or more per hour, and superior vena cava oxygen saturation greater than 70% or mixed venous oxygen saturation greater than 65%. Colloids can be administered if large amounts of volume are needed but should not be used for initial fluid resuscitation. Identifying the source of infection is important to implement directed therapy and should be completed within 12 hours of admission.[2]

Initial fluid resuscitation with normal saline was begun, and the patient's blood pressure increased to 85/55 mm Hg with a MAP of 65 mm Hg. Abdominal computed tomography was performed and confirmed the suspicion of acute pyelonephritis. The patient continued to be alert and oriented with no signs of respiratory distress or symptoms of hypotension. One hour after the initial evaluation, blood cultures had not been obtained and antibiotics had not yet been administered because of a communication error.

**3. Which *one* of the following is the *most important* next step in the management of this patient's condition?**

a. Administer vasopressor medications
b. Administer broad-spectrum antibiotics directed toward treating pyelonephritis
c. Obtain blood cultures
d. Place a central venous catheter to monitor central venous pressures and oxygen saturations
e. Transfer the patient to the intensive care unit

Vasopressor medications should not be administered in a hemodynamically stable patient. The intravenous administration of effective antimicrobials within the first 45 minutes of recognition of septic shock and severe sepsis is of critical importance. The antibiotics used should include one or more drugs that have activity against all likely pathogens and that penetrate in adequate concentration into the tissues presumed to be the source of sepsis.[2] Blood cultures should be obtained as soon as possible, but their collection should not delay the administration of antibiotics. Although a central venous catheter and transfer to the intensive care unit may be required if the patient's status declines, she is now hemodynamically stable and does not require such an advanced level of care.

Levofloxacin and piperacillin-tazobactam were administered to provide broad coverage for gram-negative and gram-positive bacteria that cause pyelonephritis, including double coverage for *Pseudomonas aeruginosa*, and blood cultures were obtained. However, despite the administration of 30 mL/kg of normal saline, the patient once again became hypotensive (blood pressure, 78/45 mm Hg) with a MAP of 56 mm Hg. At that time, the physical examination findings were unchanged.


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**4. Which *one* of the following is the *most appropriate* management option at this time?**

a. Change to hydroxyethyl starch (HES) for fluid resuscitation
b. Administer IV hydrocortisone
c. Place a central line to measure central venous pressures
d. Administer vasopressors
e. Continue with empirical resuscitation with crystalloid solutions and albumin

Persistent hypotension despite aggressive fluid replacement now places the patient's condition in the category of septic shock. She has been receiving aggressive fluid resuscitation with crystalloid solution, and the addition of HES will be of no further benefit at this point, with more recent studies reporting potential harm.[3] The administration of IV hydrocortisone at a dosage of 200 mg/d should be reserved for patients who are hemodynamically unstable despite adequate resuscitation with fluid and vasopressors.[2] At this point, it was difficult to assess by physical examination alone whether sufficient amounts of fluid had been administered. Thus, placement of a central venous line and measurement of CVP, for a more accurate determination of intravascular volume, is the best option. According to the Surviving Sepsis Campaign, the choice to begin vasopressors or continue with fluid resuscitation should be made once the CVP has been measured.

A central venous line was placed. The patient's measured CVP was 6 mm Hg. Over the next 24 hours, the patient became hemodynamically stable with continued aggressive fluid replacement. Her blood pressure was 134/88 mm Hg with a MAP of 103 mm Hg. Blood and urine cultures grew pansensitive *Escherichia coli*. Repeated laboratory studies revealed a white blood cell count of 7.8 × $10^9$/L and a serum lactate level of 1.0 mmol/L.

**5. Considering the patient's improved hemodynamic status and blood culture results, which *one* of the following is the *most appropriate* modification to her antibiotic therapy?**

a. No adjustment should be made until repeated blood cultures yield negative results
b. Discharge home at this time with oral antibiotics
c. De-escalate broad-spectrum coverage to a single antimicrobial agent
d. Continue with at least 2 antimicrobial agents known to be effective against *E coli*
e. Broaden antibiotic coverage further

Antibiotics can be adjusted before blood culture results are negative once the antibiotic sensitivities of the organism are known. Blood cultures should be monitored to ensure negativity for 48 to 72 hours, so discharging the patient home with oral antibiotics is not appropriate at this time. Antibiotics can be safely de-escalated to one antibiotic to which the organism is sensitive once the causative pathogen has been identified.[2] Because the laboratory studies identified pansensitive *E coli*, 2 antimicrobials are not required, and broadening antibiotic coverage would be unnecessary.

We initiated a treatment regimen of 750 mg/d of oral levofloxacin for 10 days, and the patient fully recovered.

## DISCUSSION

Timely recognition and aggressive, efficient management of severe sepsis/septic shock is of paramount importance, particularly with the increasing incidence, costs, and burden of morbidity and mortality associated with the mismanagement of these conditions.[4] Severe sepsis is defined as sepsis with evidence of organ dysfunction resulting in any of the following that are thought to be due to infection: arterial hypoxemia, acute oliguria, increase of creatinine level (>0.5 mg/dL), coagulation abnormalities, paralytic ileus, thrombocytopenia, or hyperbilirubinemia. Septic shock is defined as sepsis plus hypotension refractory to fluids or hyperlactemia.[1]

The Surviving Sepsis Campaign has developed early goal-directed therapy (EGDT) bundles for the management of patients with severe sepsis or septic shock. The application of the sepsis bundles has led to sustained, continuous quality improvement in sepsis care and is associated with reduced mortality.[1,5] Goals within the first 3 hours of admission include measurement of serum lactate level, acquisition of blood cultures (before the administration of antibiotics), administration of broad-spectrum antibiotics, and fluid replacement with crystalloids for hypotension

or a serum lactate concentration of 4 mmol/L or greater.[2] Goals during the first 6 hours of resuscitation should include attainment of a CVP of 8 to 12 mm Hg, a MAP of 65 mm Hg or greater, urinary output of 0.5 mL/kg per hour, superior vena cava oxygen saturation and mixed venous oxygen saturation of 70% and 65%, respectively, and in patients with elevated lactate levels, resuscitation targeted toward normalization.[2]

In hypotensive patients, initial fluid resuscitation should performed with 30 mL/kg of crystalloid fluids.[2] If large amounts of fluid are required, supplementation with colloid is appropriate. Hydroxyethyl starch should be avoided for fluid replacement in patients with severe sepsis and septic shock because the use of HES for fluid replacement has been reported to be associated with an increased need for renal replacement therapy and increased mortality when compared with crystalloid solutions.[1,3]

Initial empirical anti-infective therapy should include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentration into the tissues presumed to be the source of sepsis.[2] Blood cultures should be obtained before the administration of antibiotics. However, antibiotic administration should take precedence in the event that there is more than a 45-minute delay in obtaining blood cultures.[2] In the presence of septic shock, each hour delay in administration of effective antibiotics is associated with a measurable increase in mortality.[1,5] The antimicrobial regimen should be readdressed daily for potential de-escalation to prevent the development of resistance, reduce toxicity, and decrease costs.[2] Daily assessment of the need to broaden or change the antibiotic regimen is also necessary should the clinical condition deteriorate. Once the organism and its susceptibilities have been identified, it is appropriate to de-escalate broad-spectrum coverage to a narrower one. Typically, antimicrobial therapy should be administered for 7 to 10 days.[2] A longer duration of therapy is needed under certain circumstances including, but not limited to, the presence of *Staphylococcus aureus* bacteremia, neutropenia, and a slow clinical response.

According to the Surviving Sepsis Guidelines, if hypotension persists despite initial fluid resuscitation, a central venous catheter should be placed for determination of the intravascular volume status.[2] If the CVP is below 8 mm Hg, adequate fluid resuscitation has not been achieved and continuation of fluids would be appropriate. If the CVP is between 8 and 12 mm Hg, adequate fluids have been infused and vasopressors should be initiated.

In the event that vasopressors are required, therapy should be targeted toward a MAP of 65 mm Hg. Norepinephrine should be the first choice in vasopressor selection with epinephrine as a second-line therapy.[2] Corticosteroids should be used in the management of severe sepsis/septic shock only if hypotension persists despite treatment with fluids and vasopressors.[2] A corticotropin stimulation test has not been proved to predict faster resolution of shock and is not required to judge the need for corticosteroids in these patients.[1,6]

Although use of the 6-hour EGDT bundle has been associated with reduced mortality, it is not currently the standard of care.[1,5] The ARISE (Australasian Resuscitation in Sepsis Evaluation) and ProCESS (Protocolized Care for Early Septic Shock) trials are 2 studies that have argued against the benefit of EGDT. The ProCESS trial found that there is no significant advantage, with respect to mortality or morbidity, of protocol-based resuscitation over bedside care that was provided according to the physician's judgment, as well as no significant benefit of the mandated use of central venous catheterization and central hemodynamic monitoring in all patients as long as the most important elements in management are completed (early recognition, early antibiotic administration, and early adequate volume resuscitation using clinical parameters).[7] The ARISE trial investigators questioned the value of incorporating EGDT into international guidelines as a standard of care because their study found that EGDT did not reduce all-cause mortality at 90 days in critically ill patients presenting to the emergency department with early septic shock.[8] The ProMISe (Protocolised Management in Sepsis) trial will further investigate the clinical and cost effectiveness of EGDT for resuscitation in patients with septic shock, but the results have not yet been published.[9] Nevertheless, EGDT bundles have led to quality improvement in sepsis care and are valuable


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tools in the management of severe sepsis and septic shock, especially for physicians with limited experience in managing these clinical scenarios.

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## REFERENCES

1. Angus DC, van der Poll T. Severe sepsis and septic shock [published correction appears in *N Engl J Med*. 2013;369(21):2069]. *N Engl J Med*. 2013;369(9):840-851.
2. Dellinger RP, Levy MM, Rhodes A, et al; Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39(2):165-228.
3. Myburgh JA, Finfer S, Bellomo R, et al; CHEST Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med*. 2012;367(20):1901-1911.
4. Ramar K, Gajic O. Early recognition and treatment of severe sepsis [editorial]. *Am J Respir Crit Care Med*. 2013;188(1):7-8.
5. Levy MM, Dellinger RP, Townsend SR, et al; Surviving Sepsis Campaign. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med*. 2010;38(2):367-374.
6. Sprung CL, Annane D, Keh D, et al; CORTICUS Study Group. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124.
7. ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683-1693.
8. ARISE Investigators; ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371(16):1496-1506.
9. Power GS, Harrison DA, Mouncey PR, Osborn TM, Harvey SE, Rowan KM. The Protocolised Management in Sepsis (ProMISe) trial statistical analysis plan. *Crit Care Resusc*. 2013;15(4):311-317.

**CORRECT ANSWERS: 1. c. 2. a. 3. b. 4. c. 5. c**