CLINICAL DECISIONS
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Early Administration of Antibiotics for Suspected Sepsis

This interactive feature addresses the approach to a clinical issue. Case vignettes are 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 VIGNETTES

A Man with Hypoxemia and a Woman with Acute Kidney Injury

Michael Y. Mi, M.D.

Mr. Shui is a 35-year-old man who is brought to the emergency department by ambulance after falling from the crest of a tall wave while surfing. He had been in the water for approximately 10 minutes before a lifeguard reached him and brought him to shore. At that time, he was unconscious and coughing and had a palpable pulse. A friend accompanied him to the nearest community hospital, where you work. The friend thinks that Mr. Shui is generally in good health and takes no medications regularly, but earlier in the day, Mr. Shui mentioned to his friend that he had felt slightly fatigued and had had a persistent cough for 2 days. He drinks alcohol occasionally. He does not smoke tobacco but smokes marijuana regularly.

On examination, his temperature is 36.0°C, blood pressure 98/65 mm Hg, heart rate 110 beats per minute, respiratory rate 24 breaths per minute, and oxygen saturation 90% while he is breathing ambient air. He opens his eyes and moves his limbs in response to commands but is confused and disoriented. Breath sounds are diminished at the base of both lungs. There is a 3-cm laceration on the right side of his scalp. The remainder of the physical examination is unremarkable. The complete blood count is notable for a white-cell count of 12,400 per cubic millimeter. Electrolyte levels, renal function, and liver-function tests are within normal limits. Arterial blood gas analysis reveals a pH of 7.37, partial pressure of oxygen (Po_2) of 60 mm Hg, partial pressure of carbon dioxide (Pco_2) of 36 mm Hg, and lactate level of 2.2 mmol per liter. A chest radiograph shows bibasilar air-space opacities. Computed tomography (CT) of the head and neck without administration of contrast material shows no acute intracranial abnormalities and no fractures of the cervical spine.

Ms. Wilkinson is a 72-year-old woman with a history of hypertension and urgency urinary incontinence who presents to the emergency department with a 1-day history of acute-onset abdominal pain in the left lower quadrant. Before the onset of abdominal pain, she had had constipation for 3 days and had not urinated for 1 day despite her efforts to drink plenty of water. She takes extended-release oxybutynin, at a dose of 30 mg daily, and she was recently given a prescription for hydrochlorothiazide, 25 mg daily. She does not smoke or drink alcohol.

Her temperature is 36.7°C, blood pressure 126/75 mm Hg, heart rate 100 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 99% while she is breathing ambient air. On examination, she has tenderness to palpation of the left lower quadrant of the abdomen. She is alert and fully oriented. Cardiac and pulmonary examinations are normal. Laboratory studies show a creatinine level of 2.0 mg per deciliter (180 μmol per liter), anion gap 21 mmol per liter, white-cell count 24,200 per cubic millimeter with a predominance of neutrophils, hematocrit 45.0%, and lactate 3.9 mmol per liter. CT of the abdomen and pelvis with administration of contrast material shows large stool volume in the descending and sigmoid colon without evidence of gastrointestinal wall edema or hypoenhancement. A chest radiograph shows clear lungs without focal consolidations. An indwelling uri-

nary catheter is placed, and 1 liter of urine is drained. Results of urinalysis are within normal limits.

You are the on-call provider caring for both Mr. Shui and Ms. Wilkinson. You suspect that there may be infections underlying the presentations of both patients, but you are not certain. You believe that early administration of antibiotics to patients with sepsis may save lives, but antibiotics can have serious adverse effects. Your task is to decide whether to administer antibiotics in addition to providing supportive care.

TREATMENT OPTIONS

Which one of the following approaches would you recommend for these patients? Base your choice on the published literature, your own experience, guidelines, and other sources of information, as appropriate.

1. **Do not administer antibiotics.**
2. **Administer antibiotics immediately.**

To aid in your decision making, each of these approaches is defended in a short essay by two experts in the field. Given your knowledge of the patients and the points made by the experts, which approach would you choose?

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OPTION 1

Do Not Administer Antibiotics

Michael Klompas, M.D., M.P.H.

These two cases encapsulate a common dilemma for clinicians who are trying to implement the recommendation of the Surviving Sepsis Campaign to administer broad-spectrum antibiotics within 1 hour after a patient's presentation with possible sepsis. Both patients meet Surviving Sepsis Campaign criteria for sepsis and thus immediate administration of antibiotics, because their provider suspects infection and they have organ dysfunction with a Sequential Organ Failure Assessment (SOFA) score of 2 or higher (as defined by the Third International Consensus Definitions for Sepsis and Septic Shock [Sepsis-3][1]). Mr. Shui has a SOFA score of 3 (because of confusion and impaired oxygenation); Ms. Wilkinson has a SOFA score of 2 (because of renal dysfunction). The dilemma, of course, is that the evidence for infection is equivocal in both patients and there are alternative explanations for their organ dysfunction. This is not an uncommon scenario. Fewer than 60% of patients admitted to intensive care units with a diagnosis of sepsis are ultimately confirmed to have definite or even probable infection.[2]

There are good alternative explanations for both patients' presentations. Mr. Shui has confusion, impaired oxygenation, diminished breath sounds, leukocytosis, an elevated lactate level, and bibasilar opacities after a possible viral prodrome. These findings are consistent with pneumonia, but his history of nonfatal drowning makes it more likely that his abnormal signs are due to water inhalation, aspiration pneumonitis, and prolonged anoxia. Patients who have had a nonfatal drowning event are at high risk for development of pneumonia, but evidence-based reviews recommend against antibiotic prophylaxis because case series have found no difference in rates of pneumonia or mortality with and without prophylaxis.[3] When pneumonia does develop in patients who have had a nonfatal drowning event, the patients often have bacteria and fungi that are resistant to common empirical antibiotic choices. This risk of antibiotic-resistant organisms underscores the wisdom of waiting to see how patients' conditions evolve and which organisms grow in culture to inform the selection of antibiotics before they are prescribed.

Ms. Wilkinson's presentation is also not clearly due to infection. Signs that favor infection include tenderness in the left lower quadrant, tachycardia, an elevated lactate level, acute kidney injury, and leukocytosis with a predominance of neutrophils. The history and imaging, however, suggest that these signs are more likely due to constipation and acute urinary retention caused by oxybutynin therapy. Severe constipation and fecal impaction can cause marked inflammatory findings, including fever and leukocytosis, presumably due to bowel-wall compression leading to ischemia.[4] Bacterial translocation across the bowel wall is possible but unusual. The CT scan

is reassuring insofar as there is no inflammation or abscess. Leukocytosis is not specific for infection; approximately 50% of patients presenting to the emergency department with white-cell counts of 12,000 to 25,000 cells per cubic millimeter have noninfectious conditions.[5]

The Surviving Sepsis Campaign recommends that all patients with sepsis and septic shock should receive antibiotics immediately, but two large observational series and a randomized, controlled trial suggest that rapidity of treatment with antibiotics matters most for patients who have septic shock; the data are equivocal for patients who have sepsis without shock.[6-8] The absence of shock in our patients allows us time to gather more data and to observe their clinical trajectories before deciding whether the potential benefits of antibiotics outweigh their risks.[9] In Mr. Shui's case, it will be informative to see whether his pulmonary condition progresses and, if so, whether pulmonary cultures obtained while he is not receiving antibiotics yield pathogenic organisms. If both occur, directed antibiotics will then be warranted. In Ms. Wilkinson's case, it will be informative to see what happens to her leukocytosis and creatinine and lactate levels if oxybutynin is stopped, the bladder is drained, and bowel movements are encouraged. It is very possible that she will get better with these steps alone.

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OPTION 2

Administer Antibiotics Immediately

Laura Evans, M.D.

Both Mr. Shui and Ms. Wilkinson have presented for medical care with signs and symptoms that arouse concern for sepsis; however other explanations are also possible. Thus, the question in these cases is about the diagnostic certainty required to begin therapy — specifically, the potential risks of withholding therapy as compared with the risk of the therapy itself.

Sepsis is defined by Sepsis-3 as "life-threatening organ dysfunction caused by a dysregulated host response to infection."[1] In patients with sepsis, timely initiation of antimicrobial therapy is a cornerstone of treatment. To break the decision down, there are two steps the clinician must take: decide whether infection is present or suspected and assess whether the patient has acute organ dysfunction attributable to the known or suspected infection. I will address both steps in each case.

Whether infection is present is unclear from the presentation of each patient, although it is reasonable to suspect infection in both patients. Mr. Shui had been fatigued and had had a cough for 2 days before his presentation. He has borderline hypothermia and hypotension, tachycardia, tachypnea, and hypoxemia with a mild elevation of his white-cell count, and he has decreased breath sounds at the lung bases and bibasilar opacities. Aspiration without infection is certainly an alternative explanation in the context of a nonfatal drowning event, but infection cannot be ruled out at this stage. Similarly, Ms. Wilkinson presents with abdominal pain, urinary retention while she is taking an antispasmodic agent, and a markedly elevated white-cell count. Despite the negative urinalysis, infection cannot be fully ruled out at this time.

Regarding step two, the Sepsis-3 definition suggests the use of the SOFA score to assess for organ dysfunction, whereas previous definitions used slightly different criteria.[1,10,11] Mr. Shui has hypoxemia and altered mental status. Ms. Wilkinson has acute kidney injury and a creatinine level of 2.0 mg per deciliter. Both patients have elevated lactate levels, which is commonly used as a biomarker of end-organ dysfunction in sepsis even though the lactate level is not included in the SOFA score.[10,11]

The Surviving Sepsis Campaign guidelines strongly recommend initiation of intravenous antimicrobial agents within 1 hour or, if possible, even sooner, both in patients with sepsis and in patients with septic shock.[12] Published data corroborate the studies that were used to inform the guideline recommendation, with the data showing a 4-to-7% increase in the odds ratio for death for each hour delay in the initiation of antimicrobial therapy.[6,13]

Both Mr. Shui and Ms. Wilkinson have pos-

sible infection, and both patients have definite signs of acute organ dysfunction. The potential risk of withholding therapy is high in both patients, whereas the risk of prompt and appropriate antibiotic therapy until more information is available is low. I would give both patients an initial dose of antibiotics while continuing to evaluate for infection. That said, a commitment to antimicrobial stewardship is essential. If further investigations are negative for infection, de-escalation or discontinuation of unnecessary antimicrobial agents is critical to reduce the risk of antibiotic-associated adverse drug effects and antimicrobial resistance.[14]

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