Delayed Sepsis Management Due to Ambiguous Allergy

THE CASE

A 75-year-old man with a history of hemorrhagic stroke, coronary artery disease, and severe aplastic anemia required immunosuppressive therapy and regular blood and platelet transfusions. The patient arrived at the infusion center for a scheduled platelet transfusion but before beginning the infusion, he became unresponsive and hypotensive. The patient was immediately transported to the emergency department (ED) where, after resuscitation, he reported a one-day history of lethargy, abdominal discomfort, diaphoresis, and bloody bowel movements. Additionally, the patient had an allergy to penicillin with a reaction of hives documented in his electronic health record.

In the ED, the patient's vital signs were initially stable. Physical examination found slight abdominal distention without significant tenderness or peritoneal findings. The blood count results were as follows: 8,000 platelets per microliter; 2,300 white blood cells per microliter; and 1,230 absolute neutrophils per microliter. The chemistry panel, liver function, and urinalysis test results were within normal limits.

Soon after the initial evaluation, the patient became hypothermic and hypotensive with a deteriorating mental status. The medical team promptly administered 3 L of IV fluids. Because of the patient's continued instability and the team's concern for septic shock, they also administered vancomycin. However, they did not order gram-negative or anaerobic coverage because of the patient's penicillin allergy and the unknown infection source.

The patient remained hypotensive, and a computed tomography scan of the abdomen and pelvis with contrast suggested colitis as a possible source of infection. The absence of gram-negative coverage went unrecognized for four hours after the patient's initial presentation. The primary admitting team finally ordered aztreonam, but it was not administered for another two hours. Further, the team also ordered anaerobic coverage with metronidazole, which was not administered for another nine hours. Despite the patient's immunocompromised state and sepsis, the medical team's ordering and administration of antibiotics with gram-negative and anaerobic coverage was significantly delayed.

After the patient's prolonged course in the ED, he was admitted to the intensive care unit where his sepsis worsened. Antimicrobial therapy was broadened to include meropenem, caspofungin, azithromycin, and vancomycin. The patient developed anuric renal failure necessitating continuous renal replacement therapy. His providers ultimately transitioned him to comfort care where he died. Autopsy revealed the likely cause of death as septic shock resulting from neutropenic enterocolitis.

The medical team deemed the cause of death as multifactorial (ie, high medical complexity, delayed sepsis recognition, unfamiliarity with antibiotic coverage, prolonged ED stay, multiple involved services). However, according to the data on the relationship between time to antibiotic administration and sepsis mortality, delayed antibiotic administration also likely contributed to the patient's death. Additionally, the documented penicillin allergy may have contributed to the delay by precluding the administration of gram-negative antibiotic treatment with piperacillin-tazobactam or cefepime.

DISCUSSION

Sepsis affects more than 1 million Americans each year and is a leading cause of death in the United States.[1] Sepsis requires rapid recognition and management of infection with beta-lactam antibiotics. Patients may require additional coverage with vancomycin for resistant gram-positive bacteria and, as in this case, they also may need anaerobe coverage for enteric organisms.

http://doi.org/10.1002/aorn.13253
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Mortality from sepsis increases even when the delay before antimicrobial administration is very brief.[2] In this case, the medical team did not provide the patient with gram-negative coverage for six hours. Among patients presenting to the ED with pneumonia, urinary tract infections, bacteremia, and sepsis, patients with a history of penicillin allergy had a longer mean time to first antibiotic dose than patients without a history of penicillin allergy.[3] One study found patients with a history of beta-lactam allergy experienced higher clinical failure for gram-negative bloodstream infections compared with patients with no history of beta-lactam allergy.[4]

Approximately 10% of the US population has reported a penicillin allergy.[5] However, many of these patients are not actually allergic to the medication—formal testing disproves these allergies in patients with historical penicillin reactions more than 95% of the time.[5] Patients may consider adverse effects and intolerances to be allergies, but these reactions may not warrant penicillin avoidance.[6]

In patients with a history of nonsevere penicillin allergy, treatment with cephalosporins without preceding penicillin skin testing leads to a reaction rate lower than the expected new rate of reactions to cephalosporins.[7] Carbapenem use in patients with a history of penicillin allergy also is safe; among 56 acutely infected hospitalized patients with a history of immunoglobulin-E (IgE)–mediated penicillin allergy, none reacted to carbapenems.[8]

Use of non–beta-lactam alternatives in patients reporting penicillin allergies leads to more treatment failures for methicillin-sensitive *Staphylococcus aureus* bacteremia and more surgical site infections.[9,10] Infected hospitalized patients not treated with a beta-lactam had a threefold increase in the odds of experiencing an adverse event that included medication toxicities and *Clostridioides difficile* colitis.[11] Patients who reported penicillin allergies had a 26% increased risk of *C. difficile* colonization or infection and a 69% increased incidence of methicillin-resistant *S. aureus* colonization or infection during a mean follow-up time of six years.[12]

To make better antibiotic choices, it is crucial for providers to perform a systematic evaluation of the history of the patient's penicillin response. Many patients report symptoms that are highly unlikely to reflect a true allergy, such as family history or gastrointestinal intolerance. Physicians can evaluate penicillin allergies that may be IgE-mediated (eg, hives, angioedema, shortness of breath, anaphylaxis) with a penicillin skin test, which takes approximately one hour to perform. If the test is negative, the physician may give the patient one full dose of penicillin (usually amoxicillin) under observation. If there is no reaction, the physician should delete the penicillin allergy from the patient's electronic health record.

PERIOPERATIVE POINTS

- Unverified penicillin allergy can lead to treatment failures in patients with sepsis.
- Patients with a true IgE-mediated penicillin allergy can safely receive most cephalosporins and all carbapenems and monobactams.
- The harms of unverified penicillin allergy labels include increased risk of *C. difficile* infection, surgical site infection, and colonization with antibiotic-resistant organisms.
- System-wide approaches to providing care for hospitalized patients with beta-lactam allergies are needed to improve the quality and safety of care.

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This content is adapted from AHRQ WebM&M (Morbidity & Mortality Rounds on the Web) with permission from the Agency for Healthcare Research and Quality. The original commentary was written by Kimberly G. Blumenthal, MD, MSc, and was adapted for this article by Nancy J. Girard, PhD, RN, FAAN, consultant/owner, Nurse Collaborations, Boerne, TX. (Citation: Blumenthal KG. Delayed sepsis management due to ambiguous allergy. AHRQ WebM&M *[serial online].* https://psnet.ahrq.gov/web-mm/delayed-sepsis-management-due-ambiguous-allergy. *Published June 2019. Accessed August 21, 2020.) Dr Girard has no declared affiliation that could be perceived as posing a potential conflict of interest in the publication of this article.*

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