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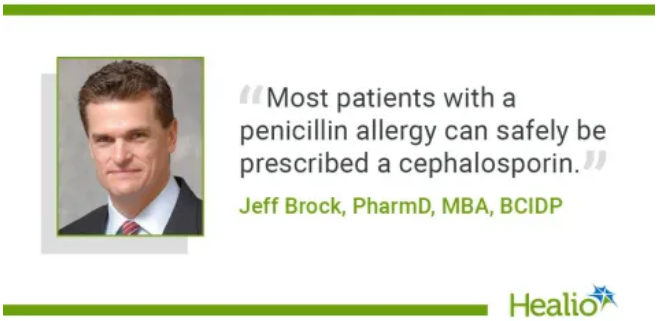
Navigating cephalosporin prescribing in patients allergic to penicillin

I routinely see prescribers avoid prescribing cephalosporin antibiotics for patients with a penicillin allergy.

One of the drivers of this is that our electronic health record systems often warn prescribers that there is a risk for cross-reactivity. Where does this warning come from, and how much risk is there of using cephalosporins in patients with a penicillin allergy?



Penicillin allergies are the most common drug allergy that patients report. Studies done within EHR systems have shown an incidence of 6% to 25%, depending upon the geographical region and patient population. Many penicillin allergies are self-reported and often not accurate. Multiple studies have shown more than 95% of patients reporting a penicillin allergy ultimately can tolerate penicillin antibiotics.

Most penicillin allergies occur during childhood, and unfortunately, these patients often carry this allergy label with them for decades. It is common for true IgE-mediated hypersensitivity to penicillin to wane over time, with approximately 80% of patients becoming tolerant to penicillin over 10 years. It is also common for patients to be labeled as penicillin allergic unnecessarily because of common side effects such as gastrointestinal intolerance, headaches, concomitant viral rashes and other benign symptoms. Although penicillin allergy testing is available, only a small fraction of patients with a penicillin allergy undergoes confirmatory testing.

A myth is born

Cephalosporin allergies are not uncommon, with approximately 2% of patients reporting an allergy. Cephalosporin allergies have largely been attributed to an antigenic response to the R1 or R2 side chains rather than the core beta-lactam portion of the molecule. Aminopenicillins such as ampicillin and amoxicillin do share a common R1 side chain with the first-generation oral cephalosporins cefuroxime and cephalexin, so patients with a confirmed allergy to those may have a higher risk of cross-reactivity. However, cefazolin, which is used widely in hospitalized patients and for surgical prophylaxis, has a unique R1 side chain and is not like penicillin, so the risk of cross-reactivity is extremely low. This is important because the use of alternative perioperative antibiotics for surgical prophylaxis has been shown to result in higher rates of surgical site infection.

The avoidance of cephalosporins in patients with a penicillin allergy dates to the 1960s and concerns of increased reactions. In the 1970s, there were anecdotal reports of increased reactions when using cephalosporins in patients with penicillin allergy, but these were small selective case series. In the mid- and late 1970s, other papers also suggested avoiding cephalosporins in patients with a penicillin allergy because some patients appeared to have an increased incidence of allergic reactions to cephalosporins, despite any clear evidence that these allergies were due to cross-reactivity vs. a new independently acquired allergy. These papers stated patients with a penicillin allergy could also have an increased rate of reactivity to immunologically unrelated drugs. From this, the practice of avoiding cephalosporins in patients with a penicillin allergy became common.

The myth that 10% of patients with a penicillin allergy will have cross-reactivity to cephalosporins was also born despite the lack of supporting data.

Removing EHR warnings

As previously stated, the EHR warning when prescribing a cephalosporin in a patient with a penicillin allergy can prompt prescribers to use a non-beta-lactam antibiotic. What happens to prescribing practices if this warning is removed?

A retrospective study by Macy and colleagues examined the removal of the warning. Their results showed that removal was associated with a change in dispensing or administration of a cephalosporin antibiotic. This study was carried out in the Kaiser Permanente Southern California and Northern California health systems. The Kaiser Southern California site was the intervention site, whereas the Northern California site was the comparison site that did not remove the warning.

There were more than 10 million antibiotic courses in the analysis, with over half occurring after removal of the alert. Most of the courses of antibiotics were oral, with 18% being parenteral courses. The researchers found that cephalosporin use increased from 17.9% to 27% among patients with a penicillin allergy after removal of the alert. The administration or dispensing of cephalosporins increased by 47% among patients with penicillin allergy at the intervention site compared with those in other groups. Additionally, use of other antibiotics decreased: clindamycin from 13.7% to 11.4%, and fluoroquinolones from 12.8% to 10.5%. First-generation cephalosporins were used the most (71.7%), followed by third-generation agents (22.3%). Importantly, there was not a significant difference in antibiotic-associated adverse reactions or serious cephalosporin-associated morbidities before or after removal of the warnings.

When evaluating whether to start a cephalosporin in a patient with a penicillin allergy, the following approach is suggested by the current drug allergy guidelines. Stratifying patients based on anaphylactic vs. nonanaphylactic histories as well as verified vs. nonverified or unconfirmed penicillin allergies is recommended. Patients with a history of an unverified nonanaphylactic penicillin allergy may be administered any cephalosporin without allergy testing or additional precautions. In the rare circumstance of a patient with a history of anaphylaxis to penicillin, a non-cross-reactive cephalosporin, such as cefazolin, can be administered routinely without prior testing. Several charts have been published that can help practitioners choose antibiotics based on similarities of their side chains to minimize the risks of cross-reactivity.

Safe for most patients

Many clinicians will cite the risk of litigation as a reason to avoid prescribing cephalosporins in patients with a penicillin allergy. In 2018, a systematic review evaluated the medical malpractice and negligence cases when a cephalosporin or a carbapenem was prescribed for a patient with a penicillin allergy. The authors concluded that, although there was an increase in cases over the past 2 decades, overall, there was little legal risk when prescribing these agents to patients with a penicillin allergy.

In clinical practice, it is essential to evaluate each patient's allergy history. Penicillin allergies have been associated with increased health care costs, increased risks for drug-resistant infections, longer hospital stays and *Clostridium difficile* infections. Patient-reported allergies can be unreliable, so a thorough history should be obtained before prescribing. Allergic reactions with penicillin and cephalosporins can cause a range of allergic reactions. Although many allergic reactions are often overstated, it is important to differentiate mild to moderate reactions from more serious reactions. Penicillin allergy testing or referral to allergy professionals is important to identify which patients have true allergies and which do not. However, most patients with a penicillin allergy can safely be prescribed a cephalosporin.

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For more information:

Jeff Brock, PharmD, MBA, BCIDP, is a Healio | Infectious Disease News Editorial Board Member and infectious disease pharmacy specialist at MercyOne Medical Center in Des Moines, Iowa. He can be reached at jeff.brock@mercyoneiowa.org.

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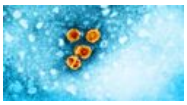

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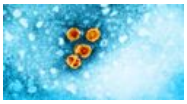

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