Medical News & Perspectives

Overdiagnosis of Penicillin Allergy Leads to Costly, Inappropriate Treatment

Rita Rubin, MA

Penicillin is an oldie but a goodie in the armamentarium for treating bacterial infections.

But, in part because it has been widely used for decades, penicillin is also the most commonly implicated medication when patients report a drug allergy. Approximately 10% of US residents have been labeled as allergic to penicillin, often since childhood. Yet, a growing body of evidence suggests that as few as 10% of people who report they're allergic to the antibiotic really are.

For example, in one retrospective study that included more than 65 000 patients with a history of penicillin allergy who received more than 127 000 courses of cephalosporins (which are beta-lactam antibiotics like penicillins), only 3 cases of anaphylaxis were associated with the drugs. That was not statistically different from anaphylaxis rates in non–penicillin-allergic patients who received cephalosporins.

In many cases, patients labeled as allergic to penicillin might have developed diarrhea or a rash after being treated with the antibiotic as children. Their concerned parents called their primary care physician, who, to be on the safe side, concluded that the symptoms signified a penicillin allergy.

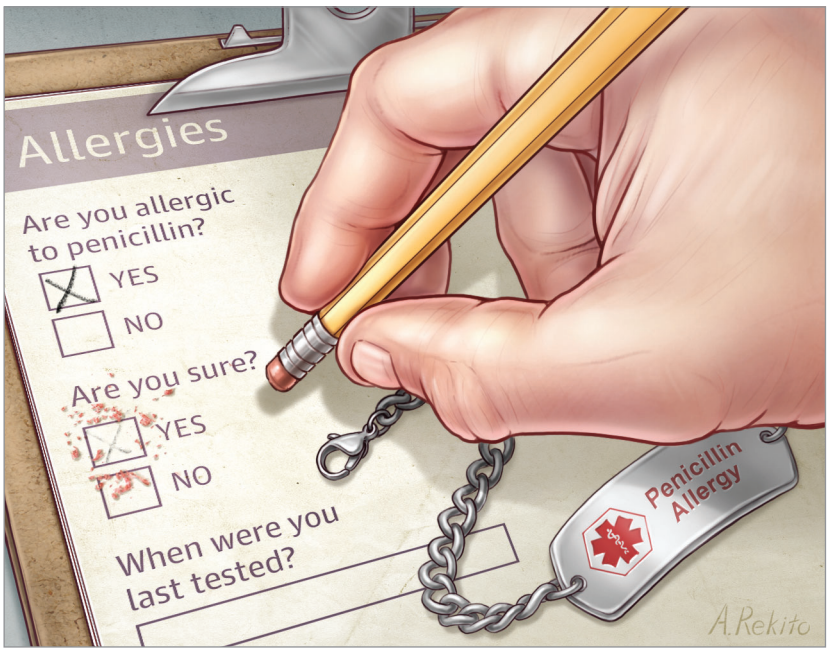
"On the pediatric side, there is a lot of apprehension about a recurrent reaction," said Merin Kuruvilla, MD, an allergist-immunologist at Emory University. "I think that's why a lot of kids end up with this label."

Chances are, though, that the symptoms they developed after receiving penicillin arose from the viral illness for which they mistakenly were treated with the antibiotic and did not represent an immunoglobulin E–mediated reaction. Even those who have experienced a true allergic reaction have about an 80% chance of losing their sensitivity to penicillin within 10 years.

However, once an individual is labeled as having a penicillin allergy, it's rarely questioned, and the label sticks, increasing the patient's risk of receiving suboptimal antibiotic therapy.

"Patients with a label of penicillin allergy invariably get all β-lactams crossed off their list," Kuruvilla said. As a result, she said, "they end up receiving high-cost, broad-spectrum, and sometimes ineffective antibiotics."

George Sakoulas, MD, said it's not unusual for people to assume that they must be allergic to penicillin because a parent or a sibling is. Patients "think that [assumption] is okay because we can use another class of drugs," said Sakoulas, an associate adjunct professor of pediatrics at the University of California, San Diego, School of Medicine. However, using a different class of drugs isn't going to be as effective in treating infection, he noted.



Bigger Risks

To avoid an unlikely risk, ie, an allergic reaction to penicillin, patients might wind up encountering more likely risks when treated with alternative antibiotics.

"Every time you avert a risk, you create another risk," Sakoulas noted. "The question is, which risk is worse? The one you're avoiding, or the one you're creating?"

According to a recent large cohort study, those patients labeled as allergic to penicillin had a 69% greater risk of methicillin-resistant *Staphylococcus aureus* (MRSA) and a 26% greater risk of *Clostridium difficile* than people the same age and sex who were not labeled as allergic to the drug. Increased use of broad-spectrum non-β-lactam antibiotics instead of narrower β-lactam options accounted for a large proportion of the increased risk in those labeled allergic.

Surgery patients suspected of having a penicillin allergy also receive suboptimal β-lactam alternatives prophylactically. That can prolong operations and raise the risk of surgical site infections, which account for 40% of all health care–associated infections among hospitalized patients. A recent retrospective study involving 8385 surgery patients found that those reporting a penicillin allergy had a 51% increased risk of developing a surgical site infection, attributable entirely to inferior antibiotic prophylaxis. Of the 922 who reported a penicillin allergy, 89% received non-β-lactam

antibiotics compared to 18% of patients without a penicillin allergy.

These increased risks associated with the use of alternative antibiotics could in part be due to differences in therapeutic mechanisms. Sakoulas and his coauthors pointed out in a recent review article that β-lactam drugs appear to have benefits not exhibited by other antimicrobial classes. "What I've done in the lab is starting to demonstrate that β-lactam drugs do more than kill bacteria directly," he said. "They're also boosting the activities of our body's immune system."

Debunking Allergies

Some experts suggest that the key to optimizing antibiotic therapy and outcomes in patients labeled as allergic to penicillin is to assess whether they are hypersensitive to the drug before they need it.

In 2016, the American Academy of Allergy, Asthma & Immunology approved a position statement recommending routine penicillin allergy testing in patients who report having the allergy.

And in their recent article, Sakoulas and his coauthors noted that "debunking false penicillin allergies through confirmatory testing may be an important component of antimicrobial stewardship practice."

The question is how and where the testing should be done. The gold standard for confirming a penicillin allergy consists of 3 tests in which patients are administered the drug 3 different ways in this order: by a skin prick, an injection, and an oral therapeutic dose. They progress to the second and third tests only if they're negative on the preceding test. But some people with a positive skin test have no reaction to an oral challenge, whereas some with a negative skin test do.

In a recent article, Eric Macy, MD, an allergist and immunologist at Kaiser Permanente in San Diego, and David Vyles, DO, an assistant professor and pediatric emergency physician at the Medical College of Wisconsin, concluded that an oral challenge is the best way to check whether people labeled penicillin allergic based on a history of low-risk symptoms really are allergic.

"Individuals seen in all healthcare settings can be evaluated for current penicillin tolerance, including the hospital, ICUs [intensive care units], emergency departments, outpatient clinics, and during preoperative evaluations," Macy and Vyles noted.

Primary care physicians can play an important role in delabeling patients who really aren't allergic to penicillin, said Macy, an allergist and immunologist at Kaiser Permanente in San Diego.

Patients labeled as allergic to penicillin in the distant past because of symptoms not likely related to the drug, such as gastrointestinal upset or headache, can safely undergo an oral challenge in less than 1 hour of observation, Macy said. "This should only be done in offices ready and able to deal with a reaction, such as would be expected with vaccinations or any systemic drug administration."

Anyone who visits his allergy department, for whatever reason, and reports having a penicillin allergy is offered an oral challenge, Macy said. "We're trying to make this more part of the culture." However, he said, "if you have [a history of] anything that looks like anaphylaxis, it's probably reasonable to skin test" first.

Not surprisingly, some patients who've lived with the penicillin allergy label for most of their lives become anxious at the thought of an oral challenge, "The ones that are more nervous, we would skin test them first," Macy said.

His department has a team of nurses who are skilled at talking nervous patients through an oral challenge, assuring them that "we do food challenges all the time," Macy said. "Most of them sail right through," he said of patients who undergo an oral penicillin challenge. "They're quite happy that burden's been lifted."

A similar "all comers" approach has caught on in the pediatric emergency department at the Medical College of Wisconsin, where Vyles works. There, parents of patients who reportedly have a penicillin allergy are asked to complete a 17-item questionnaire covering such factors as the child's age when the allergy was diagnosed, the symptoms on which it was based, and how long after the first dose they occurred. If the symptoms that led to the diagnosis do not suggest an allergic reaction, the parents are given the option of having their child tested.

Improving Care, Saving Money

Delabeling people mistakenly thought to be allergic to penicillin is safe and cost-saving, according to a recent study by Vyles and coauthors involving 100 children who had come into the emergency department and whose parents said they had a penicillin allergy. Their allergy had been diagnosed on the basis of symptoms the researchers considered unlikely to be the result of an allergic reaction, mainly rash and itching.

This study was a follow-up to one published in 2017, for which the researchers performed standard 3-tier penicillin allergy testing on these children and found that none was actually allergic.

In their follow-up, the authors reported that 36 of the children received a total of 46 antibiotic prescriptions. Of the 46 prescriptions, 26 were filled by penicillin derivatives. While 1 child developed a rash 24 hours after starting the medication, no child developed a serious reaction. Plus, Vyles and his coauthors estimated, routine penicillin allergy testing could save their pediatric emergency department $192 223 over the course of a year.

"We're doing [penicillin allergy testing] as research right now," Vyles said. But by year's end, he expects the oral challenge will become a quality improvement in his emergency department. "We might be able to make some major changes in health care by giving it to all these people," he said. ■

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