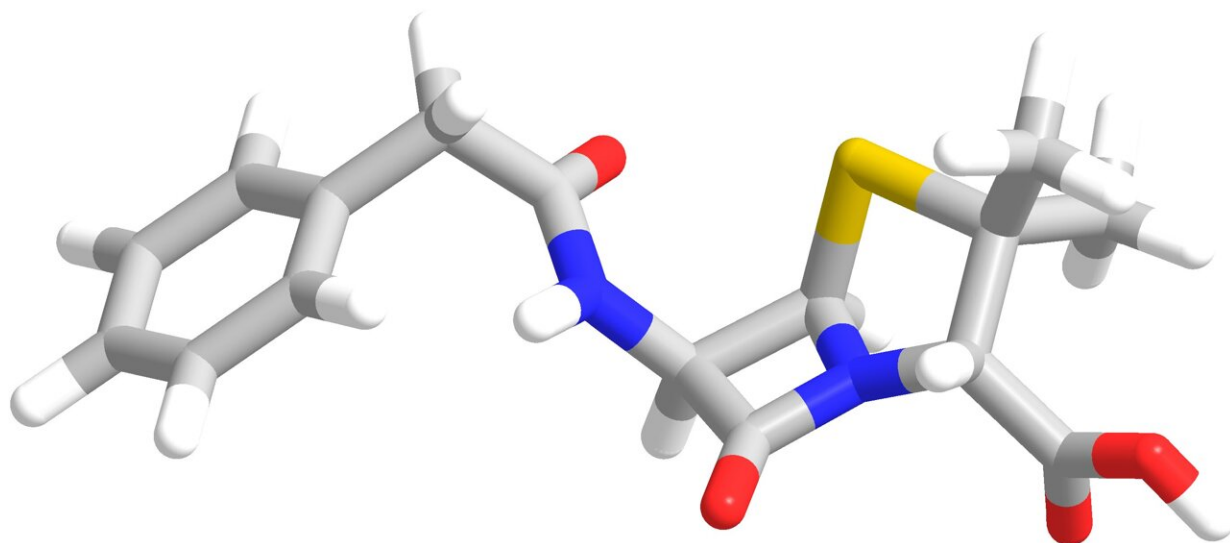


# World-first clinical trial to help millions with penicillin allergies

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Chemical structure of Penicillin G. The sulfur and nitrogen of the five-membered thiazolidine ring are shown in yellow and blue respectively. The image shows that the thiazolidine ring and fused four-membered  $\beta$ -lactam are not in the same plane. Credit: Public Domain

Penicillin allergy affects more than 25 million people in the United States (up to 1 in 10 Americans) and has been shown to lead to particularly poor health outcomes in pregnant women and surgical patients. It is also a public health threat, leading to antibiotic resistance and infections in hospitalized patients that can be life threatening.

Seventy-five percent or more [penicillin allergy](#) labels come on by age 3 due to, for example, confusion with a viral rash. The majority of these rashes were never allergic, but the labels 'stick' into adulthood and carry many adverse consequences."

Many low-risk patients with a penicillin allergy were able to have their penicillin allergy label removed through a simple procedure known as "direct oral challenge" as part of a world-first multicenter randomized control trial known as the Penicillin Allergy Clinical Decision Rule (PALACE) study.

In the PALACE study, investigators randomized low-risk penicillin allergic patients to two different approaches to remove their allergy label. They either underwent the current standard of care to have skin testing followed if negative by oral challenge with a penicillin or they went straight to oral challenge ("direct oral challenge") without preceding skin testing.

"The majority of patients labeled as penicillin allergic, more than 90%, have low-risk histories, meaning they did not have a history to suggest a severe or more recent reaction to a penicillin," said PALACE study protocol member and Vanderbilt University Medical Center principal investigator Elizabeth Phillips, MD, the John Oates Professor of Clinical Research. "We would expect more than 95% of these patients to have negative testing and be able to take penicillin in the future."

The study, published in *JAMA Internal Medicine* and undertaken by a team of researchers from specialized centers in North America and Australia, enrolled 382 adults who were assessed using a specialized risk assessment tool called PEN-FAST. Participants were randomly assigned to receive either a direct oral penicillin challenge or the standard approach (penicillin skin testing followed by an oral challenge).

The primary goal was to determine if the direct oral penicillin challenge was no worse than the standard method of skin testing followed by oral challenge which needs to be performed in an allergist's office.

Only one patient (0.5%) in each group experienced a positive reaction to the penicillin challenge, demonstrating that the direct oral penicillin challenge performs just as well as the standard method. Importantly, there were no significant differences in adverse events between the two groups, and no serious adverse events were reported.

The findings have wide-ranging implications for patients. By accurately identifying low-risk penicillin allergy patients, [health care providers](#) can ensure appropriate antibiotic prescriptions. Patients with a documented penicillin allergy are more likely to be prescribed alternative antibiotics, known as second-line antibiotics, which are often not as effective against certain infections and may have more side effects.

"Patients with penicillin allergy are more likely to get second-line or broader spectrum antibiotics that lead to risk of [antibiotic resistance](#) and serious infections such as antibiotic-associated diarrhea due to *Clostridioides difficile*, which can spread through hospitals and become a major public health problem," Phillips said.

"In the U.S. increasingly we also have a major problem with other antibiotic-resistant 'superbugs' such as multi-resistant gram-negative infections, *Candida auris* and even a resurgence of syphilis for which penicillin is the best treatment and the only treatment that should be used in pregnancy to prevent transmission to an unborn child."

"The evidence provided by the PALACE study will change clinical practice. Many patients in the United States do not have [direct access](#) to an allergist to provide specialized testing such as skin testing. Therefore, the ability to go to direct oral [challenge](#) with a penicillin in low-risk

patients which can be carried out in any observed setting will make it easier for patients in the United States to access health care to safely and effectively remove the label of [penicillin allergy](#)," she said.

**More information:** Elizabeth Phillips et al, Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients with Low-Risk Penicillin Allergy, *JAMA Internal Medicine* (2023). [DOI: 10.1001/jamainternmed.2023.2986](#)

Provided by Vanderbilt University Medical Center

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