

DECISIONS

A 25-year-old woman reporting an allergy to penicillin

Lucas R. Castellani MBBS, Wayne L. Gold MD, Derek R. MacFadden MD

During routine antenatal screening of a 25-year-old woman in her first trimester of pregnancy, positive results are obtained on serologic testing for syphilis, and after investigation, late latent syphilis is diagnosed. Standard treatment for this stage of syphilis in pregnancy consists of three weekly intramuscular injections of penicillin G benzathine.¹ The patient reports that her mother told her she had an allergic reaction to penicillin as a child, the details of which neither can recall.

On the basis of her history, is this patient likely to have an allergy to penicillin?

Allergy to penicillin is self-reported by about 10% of the general population, but only 10% of those reporting an allergy have a positive result on penicillin skin testing.^{2,3} When assessing a patient with reported penicillin allergy, the clinician must obtain a detailed history. Important questions to be asked are listed in Box 1. Commonly, as in this patient, the history of allergic reactions is remote and difficult to recall.²

Features of hypersensitivity reactions mediated by immunoglobulin E (IgE) (i.e., type 1 reactions) include urticaria, angioedema, gastrointestinal symptoms and bronchospasm. These reactions usually occur within one hour of exposure and can lead to anaphylaxis. Some IgE-mediated reactions may occur 1–72 hours after administration.² Delayed (non-IgE-mediated) reactions occur hours to days after exposure.³

How can a type 1 allergic reaction to penicillin be excluded in this patient?

When a clear history cannot be elicited, skin testing is currently the method of choice for excluding type 1 reactions to penicillin.^{3,4} This most often requires the help of an expert in allergy.³ Penicillin skin testing consists of prick testing followed by intradermal instillation of small quantities of major (penicilloyl–polylysine) and minor (penicillin G, penicilloate and penilloate) determinants and observation for a wheal.³

A negative result on skin testing with both major and minor determinants has a negative

predictive value for an immediate hypersensitivity reaction nearing 100%.³ For safety reasons, a negative skin test result is typically followed by a graded challenge, which involves administration of several incremental, subtherapeutic doses of penicillin.^{3,4} For patients who tolerate this graded challenge, penicillin can be prescribed.³ Skin testing or graded challenges should not be performed in patients with a history suggestive of severe delayed hypersensitivity reactions such as Stevens–Johnson syndrome.³ Skin testing can be safely performed in pregnancy.^{5,6}

If this patient has a positive result on skin testing for penicillin allergy, can she still be treated safely with penicillin?

The positive predictive value of a penicillin skin test ranges from 40% to 100%.³ Therefore, if a patient has a positive skin test result, penicillin can still be administered through a carefully observed desensitization process, which would be performed by an allergy expert.^{3,4} Desensitization involves administering incremental doses of the drug in a monitored setting until the therapeutic dose is achieved. The purpose of desensitization is to induce tolerance without triggering adverse effects, and this is maintained only if the drug is administered continually.⁴ Desensitization can be safely performed in pregnancy.^{5,6}

If this patient has a positive result on skin testing, can she be treated with other β -lactam antibiotics in the future?

It was previously believed that individuals with penicillin allergy had a 10% risk of immediate hypersensitivity with the administration of cephalosporins. However, this belief was based on studies in which the cephalosporin administered contained trace amounts of penicillin.^{3,4} Currently, it is believed that the rate of cross-reactivity is closer to 1%.³ Data suggest that characteristics of the side chains, and not the β -lactam ring itself, are most responsible for cross-reactivity between various β -lactam antibiotics.^{3,4} Patients with a prior history suggestive of IgE-mediated penicillin allergy have

Competing interests:
None declared

This article has been peer reviewed.

Correspondence to:
Derek MacFadden,
derek.macfadden@mail.utoronto.ca

CMAJ 2015. DOI:10.1503/cmaj.141123

Box 1: Questions to ask when eliciting a history of IgE-mediated penicillin allergy²⁻⁴

Questions	Rationale
Age: How long ago did the patient's reported allergic reaction to penicillin occur? How old was the patient at the time of the reported allergic reaction?	The longer the time elapsed since the reaction, the lower the likelihood that the patient will experience an IgE-mediated reaction, as patients can outgrow hypersensitivity reactions with time. If the patient was very young at the time of the reaction, he or she may have learned of it through information relayed by family members, which increases the risk of historical inaccuracies.
Administration of penicillin: How was the penicillin administered?	The parenteral and cutaneous routes are thought to confer greater risk of sensitization than oral administration.
Symptoms: Did the reaction include hives, throat swelling, diarrhea, vomiting or shortness of breath? Were other organ systems involved? If the only symptom was a rash, what was its distribution and pattern?	It is important to differentiate symptoms reflecting a true IgE-mediated allergy from less serious or sometimes more severe (e.g., Stevens–Johnson syndrome) non-IgE-mediated reactions. If the reaction consisted solely of a rash, non-IgE-mediated causes should be carefully considered.
Timing: How long after the penicillin was administered did the onset of symptoms occur?	It is important to identify the temporal relationship between drug administration and onset of the reaction. Most IgE-mediated reactions occur immediately (within one hour), whereas substantial delays between administration and reaction suggest a non-IgE-mediated drug reaction or another alternative cause for the symptoms.
Other medications: Was the patient taking other medications when the penicillin was administered? If so, what were they, and when were they taken in relation to the reaction?	Penicillins are often given in conjunction with other medications, and it may be one of the other medications that is the real precipitant of the reported reaction.
Previous reactions: Has the patient had previous reactions to other medications?	Some patients may have documented reactions to related drugs (e.g., cephalosporins, carbapenems), which may indicate that they are at risk of a severe reaction if penicillin is administered.
Exposure to β -lactam antibiotics: Has penicillin or any other β -lactam antibiotic been safely administered to the patient either before or after the reported reaction to penicillin?	Subsequent exposure to penicillin without a reaction suggests that the patient does not have an IgE-mediated allergy. It is also important to determine whether other β -lactam antibiotics have been safely administered.
Note: IgE = immunoglobulin E.	

only a 2% risk of IgE-mediated reaction to carbapenems.⁷ Aztreonam does not cross-react with other β -lactam agents except for ceftazidime.³ If a patient has a positive result on penicillin skin testing and treatment with a cephalosporin or carbapenem is indicated, he or she can undergo a graded challenge.³

The case revisited

The patient was referred to an allergist for penicillin skin testing, the result of which was negative. This was followed by a graded challenge, which was tolerated. The patient was subsequently treated with intramuscular penicillin G benzathine for her late latent syphilis, without adverse event. Her allergy history was updated in her clinic records to indicate that she did not have an allergy to penicillin.

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Affiliations: Department of Medicine (Castellani, Gold, MacFadden), University of Toronto, Toronto, Ont.; Division of Infectious Diseases (Gold, MacFadden), University Health Network, Toronto, Ont.

Contributors: Wayne Gold and Derek MacFadden were responsible for the concept for this article. All authors contributed to the literature review. Lucas Castellani was responsible for writing the initial draft of the manuscript. All authors contributed to revising the manuscript, responding to reviewers and approving the final version for publication, and all agree to be guarantors for the work.

Acknowledgement: The authors would like to thank Dr. Neil Shear for his critical (presubmission) review of the manuscript.