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. 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. 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.

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. Delayed (non–IgE-mediated) reactions occur hours to days after exposure.

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. This most often requires the help of an expert in allergy. 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.

A negative result on skin testing with both major and minor determinants has a negative predictive value for an immediate hypersensitivity reaction nearing 100%. 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. For patients who tolerate this graded challenge, penicillin can be prescribed. 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. Skin testing can be safely performed in pregnancy.

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%. 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. 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. Desensitization can be safely performed in pregnancy.

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. Currently, it is believed that the rate of cross-reactivity is closer to 1%. 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. Patients with a prior history suggestive of IgE-mediated penicillin allergy have
only a 2% risk of IgE-mediated reaction to carbapenems. Aztreonam does not cross-react with other β-lactam agents except for ceftazidime. 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.

**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.

**References**

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