

Allergy to penicillins

The penicillin antibiotics are an important group of life-saving drugs that were first derived from *Penicillium* moulds around 80 years ago. All penicillins have the same basic structure, a β -lactam ring (essential for antibacterial activity) and a side chain (determines, in part, the antimicrobial spectrum and pharmacological properties). They prevent cross-linkage between linear peptidoglycan polymer chains that make up bacteria cell walls, thus causing to cell death. Penicillins are one of the most common drug-related causes of allergic reactions and anaphylaxis. The aim of this bulletin is to provide an overview of penicillin allergy.

Prevalence and types of reactions

The true prevalence of penicillin allergy in the general population is unknown, but is self-reported by at least 10% of patients. However, when formally studied, 85-90% of these are found not to be allergic. Therefore, when patients report penicillin allergy it is important to explore the symptoms that occurred. Significant numbers of patients with various side effects such as nausea, vomiting and diarrhoea, are often mislabelled as 'penicillin allergic'. Individuals with asthma or other allergic conditions appear to be more likely to be allergic to penicillins.

Penicillin allergy can present in several forms (see table below):

- **Skin reactions** are the most common allergic reactions with penicillins. These typically present as maculopapular rash, which is an erythematous, symmetrical rash on the legs, buttocks and trunk. It is a cell-mediated hypersensitivity reaction (type IV) that can occur after more than three days of therapy. This is usually labelled as 'mild' penicillin allergy. More serious skin reactions, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, occur rarely. These are caused by a cell-mediated cytotoxic reaction against epidermal cells leading to widespread cell death and subsequent skin loss. These are usually labelled as 'severe' penicillin allergies.
- **Life-threatening anaphylaxis** is estimated to occur in 0.01% to 0.05% of patients. It usually starts within 30 minutes and is more likely to occur following IV rather than oral administration. However, there are reports of anaphylaxis following oral use and a few associated with skin testing. Anaphylaxis is an IgE mediated hypersensitivity reaction (type I). This is usually labelled as 'severe' penicillin allergy.
- **Serum sickness-like reactions** are characterised by a raft of symptoms (fever, cutaneous eruptions, oedema, arthralgia, lymphadenopathy) and have been reported in association with penicillins. The reaction usually occurs within seven to 10 days (up to one month) of initiation of therapy and resolves following withdrawal. Serum sickness-like reactions are mediated by immune complexes (type III). This is usually labelled as 'severe' penicillin allergy.

Cross-reactivity with other penicillins

Generally, all patients who have had an allergic reaction to one penicillin should be considered to be allergic to all penicillins.

Table of allergic reactions to penicillins

Expected prevalence	Allergic reaction	
One or more of 100 treatment courses (>1%)	- maculopapular rash	
Once in 100-1,000 treatment courses (0.1-1%)	- urticaria - angiooedema	- eosinophilia - drug fever
Once in 1000-10,000 treatment courses (0.01-0.1%)	- anaphylactic shock - thrombocytopenia - vasculitis	- bronchospasm & acute severe dyspnoea - serum sickness-like reaction
Less than once in 10,000 treatment course (<0.01%)	- haemolytic anaemia - erythema multiforme - interstitial nephritis	- Stevens-Johnson syndrome - toxic epidermal necrolysis - erythema nodosum

However, there are degrees of cross-reactivity between the penicillins, and patients may have an allergic reaction to one penicillin but not to another. In certain circumstances, re-trial of a penicillin in a penicillin allergic patient might be justified.

Cross-reactivity with other β -lactams e.g. cephalosporins

Data regarding the cross-reactivity of penicillins with other β -lactams are conflicting. The reported cross-reactivity varies between 3% and 9% and it is not entirely clear that this is true cross-reactivity or merely identification of individuals with a predisposition to drug allergy. Cephalosporins are contraindicated in patients who have developed a severe penicillin allergy. However, they can be used in patients with mild penicillin allergy.

Diagnosis

In patients with suspected penicillin allergy, reconciliation of drug history, symptoms and rechallenge is essential to determine a diagnosis. In those who have had a suspected IgE mediated reaction, skin testing may be helpful. However, this should only be undertaken under specialist guidance (Immunologist or Infectious Diseases consultant), and some patients with IgE mediated reactions can still get a negative result.

Desensitisation

Desensitisation can be undertaken in patients who have a history of IgE mediated reactions to penicillins (e.g. anaphylaxis). Small incremental doses are given over a period of time (hours to days) to convert the patient from a highly sensitive state to a state where the drug is tolerated. This technique should only be undertaken under the guidance of an Immunologist.

Acute management

Suspected allergic reactions to penicillins should be managed by stopping the drug followed by symptomatic treatment of the reaction. In the case of anaphylaxis, this may require the use of adrenaline, antihistamines and corticosteroids (see Blue Book for guidelines).

Summary

Many patients report penicillin allergy, but most of these have simply had penicillin-related side effects. Claims of allergy should be explored, as it is important that patients are not unnecessarily denied access to this important group of drugs.