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AMPATHCHAT

Dr Louise Murray, Chemical Pathologist, Immunology Department
Dr Cathy van Rooyen, Clinical Virologist, Immunology Department

Endorsed by the Immunology Peer group

Penicillin allergy

Penicillin allergy is the most commonly reported antibiotic allergy. However, very few patients ever have their penicillin allergy confirmed. Furthermore, less than 20% of patients who report a positive history of a prior reaction to penicillin are found to be allergic to penicillin upon skin prick testing. Avoidance of penicillin based on self-reported allergic history alone often leads to the use of an alternate antibiotic with greater cost or side effect profile.

Penicillin is metabolised into benzyl penicilloyl (95%), which is the major determinant (PPL), as well as penilloate, penicilloate and benzyl-n-propylamine, which are the minor determinants (MDM). Both PPL and MDM play an important role in allergic reactions to penicillin. A minority of patients will also react to a specific side chain, for example amoxicillin. Testing only for the major determinant will miss approximately 10% of penicillin-allergic patients. Testing only for minor determinants will miss approximately 30% to 60% of patients.

Approach to diagnosing drug allergy

A detailed history should be obtained to establish if it is a true drug allergy (an immunological mediated reaction that is specific to penicillin and reoccurs on subsequent exposure to that drug). Establish if it is an immediate or delayed reaction to predict which mechanism is involved (Figure 1). Different immunological mechanisms include IgE (immediate reaction), basophil (immediate or delayed reactions), complement mediated, immune complexes (delayed reactions) and T-cell mediated reactions (delayed reactions).

Risk factors for a true penicillin allergy include a history of sensitivity to other drugs, increased frequency of administration of penicillin antibiotics, the intravenous route of administration and a history of atopy.

Available in vitro tests

Immediate reaction:

- Penicilloyl G and V, amoxycilloyl and ampicilloyl IgE (Immunocap)
- CAST (Cellular antigen stimulation test/basophil mediated): PPL, MDM, Pen V, Pen G, amoxicillin, ampicillin and clavulanic acid. The minimum diagnostic combination is PPL, MDM, amoxycillin with clavulanic acid.

Delayed reaction:

- CAST: PPL, MDM and clavulanic acid with amoxicillin.
- Lymphocyte transformation tests (LTTs) or MELISA: Pen V, Pen G, PPL, MDM ampicillin, clavulanic acid and amoxycillin. The minimum diagnostic combination is PPL, MDM, amoxycillin with clavulanic acid.

Skin prick testing (SPT) is generally reserved for patients who test negative in the above assays, but where an allergy is still suspected. SPT is optimally performed using the penicillin major determinant, as well as a mixture of the minor determinants, but this is not widely available in South Africa due to the high cost and lability of test reagents. When both SPT to the major and minor determinants are negative, the negative predictive value is 99%. An alternative, but less sensitive approach, is to do SPT using the specific penicillin drug (tablet or vial); this can be performed at the Ampath Allergy Clinic in Pretoria and by other allergy specialists in South Africa. A drug challenge can be done if all of the above-mentioned tests are negative. Specific protocols for drug challenges are available in the literature (www.aaaai.org/penicillinallergy). SPT or challenge to penicillin is not indicated in patients with Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN) if there is a reasonable suspicion that penicillin is the cause.

If the diagnosis of drug allergy is confirmed, it is important to identify a safe alternative. If no alternative can be found and the patient requires the drug, in-patient desensitisation can be done. There are many different protocols available for desensitisation to different drugs (Chang et al., 2012).

Cross-sensitivity between penicillin and penicillin derivates like cephalosporins and carbapenems are thought to be around 10% due to the shared beta-lactam ring. However, a lower risk of cross-reactivity between penicillins and third- or later generation cephalosporins has been demonstrated (2% to 5%). Carbapenems like imipenem, meropenem, doripenem and ertapenem share a common beta-lactam ring with penicillins, but 99% of patients with a penicillin allergy will be able to tolerate carbapenems.

Currently the American Academy of Allergy, Asthma and Immunology (AAAAI) has stated that, in low-risk individuals with penicillin reaction histories that are unlikely to be IgE-mediated, a direct oral amoxicillin challenge test should be done to confirm current tolerance.

Due to the paucity of allergists or clinicians with knowledge of allergies in South Africa, the European allergy approach is followed, where basophil activation tests are increasingly popular for testing beta-lactam allergies. Penicillin allergy testing is currently recognised as an important part of antibiotic stewardship, due to the improved outcomes when penicillin is used as first-line agent for many infectious disease processes.

References

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AN APPROACH TO PENICILLIN ALLERGY DIAGNOSIS