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CORE TRAINING FOR DOCTORS

Penicillin allergy diagnosis and desensitization

Penicillin, discovered over 80 years ago by Alexander Fleming at St Mary's Hospital, London, belongs to the beta-lactam group of antibiotics. All beta-lactams share a central ring structure (beta lactam ring) and in addition to penicillins include cephalosporins (e.g. cephalexin), monobactams (e.g. aztreonam) and carbapenems (e.g. meropenem). They are the most widely prescribed antibiotics throughout the world.

Penicillins are effective, inexpensive and well tolerated by most patients. They are also one of the most common causes of perceived and true drug allergy (Bernstein et al, 1999; Yates, 2008). Many patients are mislabelled with the diagnosis of penicillin allergy, as the diagnosis based only on clinical history and without the allergy tests is frequently unreliable (Mendelson, 1998). This can result in use of medication with worse side effects, greater cost and broader spectrum of activity than needed. The patient is then labelled as having penicillin (beta-lactam) allergy for the rest of his/her life, posing a therapeutic challenge for clinicians and potentially contributing to the emergence of multidrug resistant pathogens. Determining a patient's true beta-lactam allergy status can improve his/her antimicrobial treatment and the quality of his/her overall care.

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Drug hypersensitivity reactions to beta-lactam antibiotics can generally be classified as immediate or non-immediate according to the timing of symptoms. Immediate reactions (likely immunoglobulin E (IgE)-mediated) occur within 1 hour of exposure, whereas non-immediate reactions are seen after 1 hour of exposure (usually between 6 hours to weeks) and are caused by other non-IgE-mediated mechanisms. In fact, the longer the interval between the exposure and the reaction, the less likely the reaction is IgE mediated (Torres et al, 2003).

Epidemiology

The estimated prevalance of beta-lactam allergy in the general population, based on patients' reports, ranges between 1–10% (Park and Li, 2005). Interestingly up to 20% of hospital patients claim to be allergic to beta-lactams (Mendelson, 1998). However only 10–20% of patients suspected of beta-lactam allergy test positive on skin testing (Salkind et al, 2001). This discrepancy between reported and confirmed allergy is the result of overdiagnosis of beta-lactam hypersensitivity in general populations where drug side effects (nausea) (Yates, 2008) or the symptoms of the condition for which the patient is treated are attributed to drug allergy.

Additionally as penicillin-specific IgE decreases by about 10% per year to around 30% after 10 years (Blanca et al, 1999) a patient with a childhood history of penicillin allergy may be able to tolerate it in his/her adult life (Bernstein et al, 1999). Penicillin-induced anaphylaxis is rare with an incidence of 1–4 cases per 10 000 administrations and fatal outcomes in 1 in every 50 000–100 000 courses (Idsoe et al, 1968; Markowitz et al, 1991; Napoli and Neeno, 2000).

Diagnosis

Clinical history

Diagnosis of beta-lactam allergy begins with a detailed drug and index event his-

tory. Questions should establish the timing of the reaction (immediate/non-immediate) and characteristics of the signs and symptoms experienced by the patient during the reaction.

Classical IgE-mediated symptoms can be divided into organ or system based: skin, gastrointestinal, respiratory and cardiovascular. Skin reactions include rapidly appearing angioedema, often perioral, periorbital or genital, and urticaria with moderate to severe pruritus. Gastrointestinal symptoms include abdominal pain, diarrhoea and vomiting. Respiratory symptoms can involve any one or all of the following: wheeze, shortness of breath, chest tightness and stridor. Finally, cardiovascular complications include tachycardia, arrhythmia and hypotension. These should be contrasted with symptoms of non-allergic side effects of the drug (gastrointestinal upset) or idiosyncratic events (headache) as well as non-IgE-mediated reactions (maculopapular exanthem). *Table 1* lists some beta-lactam allergy questions which can help to establish the likelihood of true beta-lactam allergy and help to differentiate between immediate and non-immediate allergic reactions.

In-vivo testing

Two basic methods of skin testing are used in drug allergy practice: skin prick test and intradermal test. Histamine and normal saline serve as positive and negative controls for the test. Skin prick testing is more specific, but less sensitive than intradermal testing and should precede it. Skin prick testing is performed by placing a drop of antigen on the forearm and inserting a lancet which is calibrated to pierce the skin to a depth of 1 mm. The lancets are placed at 90° to the skin and the 1 mm calibrated lancet is used to pierce the skin. The intradermal test is performed with a 30 gauge needle: 0.03 ml of antigen solution is injected into the dermis of the skin in order to create a small bleb. This can be marked with a pen. The skin is then observed for 15–20 minutes.

A positive skin prick test is defined as a wheal with the diameter measuring 3 mm more than the negative control (*Figure 1*). A positive intradermal test is defined as a wheal diameter measuring 2–3 mm more than the initial bleb. The reagents used in beta-lactam skin testing include major determinant (penicilloyl-polylysine or PPL) and minor penicillin determinants (penicillenyl and penicillamine or MDM), benzylpenicillin and amoxicillin as well as the index beta-lactam (Torres et al, 2003).

Penicillin skin testing detects the presence of penicillin-specific IgE in the skin and can therefore predict only the likelihood of IgE-mediated penicillin allergy (Yates, 2008). It is not useful for identifying other types of reactions. It should be avoided if the index reaction was very severe and involved bullous or exfoliative skin dermatoses, Stevens–Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms. These patients should avoid penicillins for life.

The positive predictive value of penicillin skin testing is approximately 50%, while the negative predictive value has been estimated at 97–99% (Bernstein et al, 1999).

Some drugs can give rise to a false negative skin testing such as antihistamines and tricyclic antidepressants, so these should be stopped 72 hours before testing.

Penicillin skin testing is safe provided that it is performed correctly (right concentrations and amounts of the drugs, used in a sequential manner) (Bernstein et al, 1999) with a reaction rate of 0.3–1.2% (Lin, 1992; Gadde et al, 1993).

In-vitro testing

In-vitro testing detects the presence of serum IgE antibodies against various beta-lactams. The ImmunoCAP method detects serum IgE antibodies to penicillin V, penicillin G, amoxicillin and ampicillin. This is an attractive way of confirming allergy in an outpatient setting as it can be performed along with other routine blood tests and, unlike skin testing, is not affected by antihistamines. However, in-vitro testing is less sensitive and a negative result cannot exclude penicillin allergy. On the other hand, its specificity is close to 100%, and a positive test is likely to be a true result (Fontaine et al, 2007; Mayorga et al, 2010).

Although most UK allergy centres perform serum IgE antibodies to penicillins, its use in clinical practice is highly varied (Richter et al, 2013). There is no agreed position of serum IgE antibodies testing in

Figure 1. Positive skin prick test to amoxicillin defined as a wheal and flare.

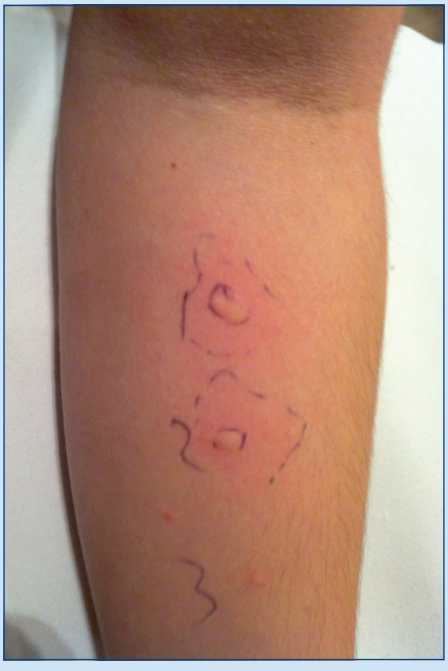

Table 1. Key questions to ask

When? Age at the time of the reaction?
Why? Why was penicillin used (condition treated)? Was the reaction (often skin rash) related to the underlying condition (hepatitis B, coxsackie virus, echovirus, some bacterial infections)?
What? What beta lactam was used and in which form (oral/intravenous)?
How? How did the patient react? What were the characteristics of the reaction? Are there any photographs?
How soon after the start of the course of penicillin did the reaction occur? (immediate/non-immediate)
How soon after taking the dose of penicillin preceding the event did the reaction occur?
What happened when penicillin was stopped?
Was the patient taking any other drugs at the time?
Has the patient taken similar drugs (amoxicillin, co-amoxiclav, cephalosporins) since or before? What happened?

the testing algorithm although often it is performed during the assessment stage by the allergy practitioner. This is reflected in the testing algorithm in *Figure 2*.

Challenge

In order to establish a definite diagnosis and only when skin tests are negative, drug provocation test (challenge) is performed.

Patients should stop antihistamines for at least 72 hours before the challenge as these may mask early signs of an allergic reaction. Beta-blockers should not be taken for at least 24 hours before the challenge as they can interfere with treatment of anaphylaxis.

The challenge is performed in a hospital setting (day unit, ward) with resuscitation equipment available at all times.

A small dose (usually 1/100 of the total dose) of index penicillin is administered to the patient. Provided there is no evidence of an allergic reaction, this is then increased incrementally every 30 minutes until a full therapeutic dose is reached (usually 4 to 5 steps). The challenge is concluded 1 hour after the final dose.

Patients with positive skin tests or positive oral challenge to penicillins should avoid all penicillins. As mentioned, drugs such as cephalosporins may be tolerated provided skin testing and challenge is negative.

In certain cases where treatment with penicillin is necessary (e.g when there are no other alternatives such as in pregnant women with syphilis), penicillin desensitization can be performed.

Desensitization

Drug desensitization induces temporary tolerance to that drug. It is effective for as long as the patient is receiving the drug in question.

The procedure is performed in a specialized allergy clinic in a hospital setting with all resuscitation facilities available in case of anaphylaxis. As with skin testing and oral challenge, desensitization should not be performed in patients with severe exfoliative reactions such as Stevens–Johnson syndrome or toxic epidermal necrolysis.

Desensitization can be performed by oral, intravenous or subcutaneous routes. The oral route is the safest, and is used whenever possible, starting with a small dose (usually 1/10 000 the normal dose). However, in patients with significant allergic reactions to the drug an even smaller dose can be used. The dose for desensitization is doubled every 15 minutes until the full dose is reached (usually in 12 to 15 steps) (*Table 2*).

Allergic reactions may occur in some patients during and after desensitization. However, no fatal reactions have been reported so far. Desensitizations have been performed safely in pregnant women (Wendel et al, 1985).

Figure 2. Diagnostic work up for penicillin testing.

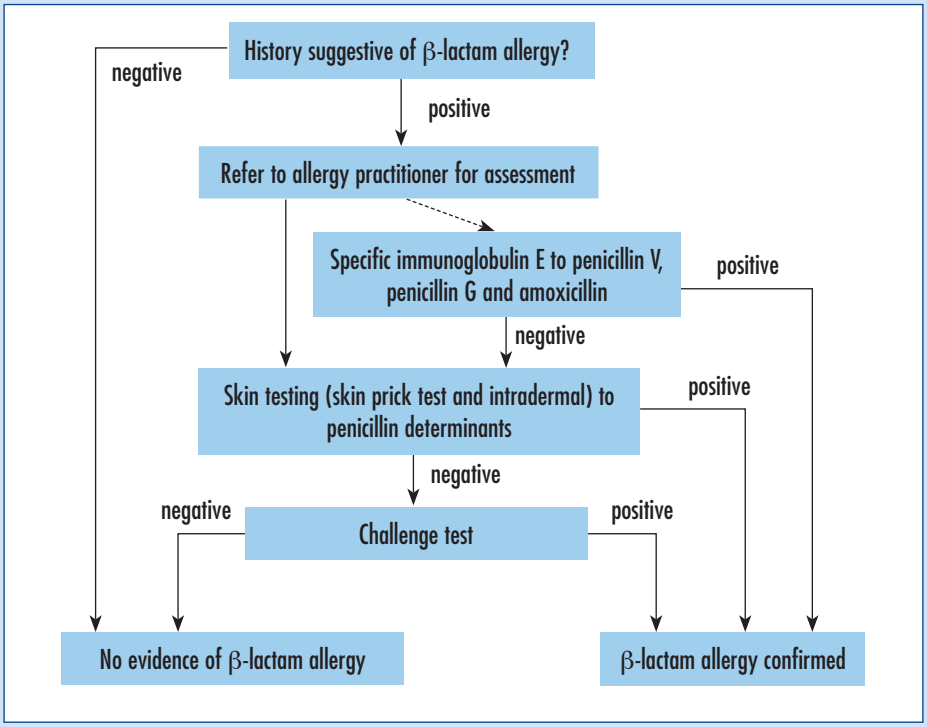

Table 2. Penicillin desensitization protocol

Step	Dose given (mg)	Cumulative dose (mg)	Accumulated time from start
1	0.05	0.05	15 min
2	0.1	0.15	30 min
3	0.2	0.35	45 min
4	0.4	0.75	1 hr 00 min
5	0.8	1.55	1 hr 15 min
6	1.6	3.15	1 hr 30 min
7	3.2	6.35	1 hr 45 min
8	6	12.35	2 hr 00 min
9	12	24.35	2 hr 15 min
10	25	49.35	2 hr 30 min
11	50	100	2 hr 45 min
12	11	200	3 hr 00 min
13	200	400	3 hr 15 min
14	400	800	3 hr 30 min
15	Full dose	Full dose + 800	4 hr 30 min

Modified from Sullivan (1993)

Cross reactivity with cephalosporins

The true incidence of cross reactivity with cephalosporins is still uncertain, with some reports of up to 20% (Kelker and Li, 2001). It is likely to range between 5 and 10% (higher with the first and second generation of cephalosporins and lower with third and fourth) (Saxon et al, 1987). Penicillin-allergic patients who require cephalosporins should therefore undergo skin testing followed by challenge with the cephalosporin in question. Cephalosporin-allergic patients who require penicillin treatment should be skin tested and challenged with penicillin, and provided this is negative can safely receive it (Antunez et al, 2006).

Conclusions

Mislabelling patients as penicillin allergic not only impacts the quality of the individual's care but also has economic and public health consequences (multidrug resistant infections). 'Removing' the label requires a combination of careful history of the index event, with penicillin allergy testing and challenge. Patients who are allergic to penicillin can receive the treatment via desensitization when there is no alternative available. BJHM

Conflict of interest: none.

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KEY POINTS

- Not every patient with infection who develops skin rash while taking penicillin is penicillin allergic.
- Not every patient labelled with penicillin allergy is truly allergic to penicillin.
- A detailed history of the index reaction forms the basis of penicillin allergy diagnosis, but without confirmatory tests it is not diagnostic.
- Skin testing for immediate reactions should be performed if the reaction suggests an immunoglobulin E-mediated process (urticaria, anaphylactic shock) or if the history is vague and future penicillin use is desired.
- False negative results can be seen in patients taking antihistamines or tricyclic antidepressants.
- Services such as preoperative assessment, oncology or microbiology clinics could be used as referral routes for patients who are labelled allergic to penicillin and who require or are likely to require antimicrobial treatment. Refer to the local drug allergy service.
- Desensitization is performed in patients with a definite immediate IgE-mediated allergic reaction where there is no effective alternative antibiotic treatment available. If treatment is discontinued the risk of the allergic reaction will return.
- Anaphylaxis is not the only life-threatening penicillin allergic reaction – delayed reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis, and some organ-specific reactions like acute hepatic failure can also be fatal.