SELF STUDY CME SERIES

Self Study CME Series No.211 (1 CME Point)

Management of Antibiotic Allergy in the Era of Antimicrobial Resistance

Allergy to antibiotics is a commonly encountered condition. This article will briefly discuss on aspects including classification, prevalence, diagnosis and recommended approach in primary care setting.

Classification of antibiotic allergy

There are 4 types of allergic reactions in classical teaching. For practical purpose, we can classify them into type 1 (acute) and non-type-1 (delayed) reactions. Type-1 reactions are mediated by IgE antibodies with a fast onset typically within 1 hour. Hallmark features are urticaria, wheezing, angioedema and anaphylaxis. This is the type of reaction that skin test aims to exclude. Delayed reactions are mediated by other immune mechanisms with a more gradual and variable onset (1-2 days to weeks). Manifestations can be diverse, ranging from mild skin rash to systemic upset like fever, eosinophilia, cytopenia, liver and renal impairment. Except for certain severe delayed reactions such as Steven Johnson Syndrome, hemolysis and acute interstitial nephritis, delayed reactions are not contraindications to further use with care. Certain side effects of antibiotics e.g. headache, GI upset and dizziness are not true allergy and should not be labelled as such. In paediatrics, most skin rashes are due to viral-drug interaction (as in infectious mononucleosis) which do not indicate true allergy. Some antibiotics e.g. vancomycin, amphotericin B may also produce infusion reactions mimicking systemic allergy reactions.

Epidemiology of penicillin allergy

Among all antibiotics, penicillin is the most commonly reported drug to cause allergy. Overseas data show that 10% of the general population have allergy labels, although less than 1% are truly allergic (IgE-mediated). Overall, 80-90% of them eventually can tolerate penicillin treatment. The prevalence of penicillin allergy is falling because of purer penicillin preparations nowadays, and decreased use of intramuscular injections. For any individual, the likelihood of reaction drops by about 10% per year on average, so that most would have lost their reactions in 10 years. The prevalence of anaphylaxis is quoted to be 0.02-0.04% and is also decreasing. Cross-reactivity between penicillins and cephalosporins depend on similarity of their side chains. The frequently quoted figure of 10% cross-reactivity rate is likely an overestimate from contaminated penicillins in the past. Recent systematic review has found that the rate is usually <5%, with negligible rate among 3rd and 4th generation cephalosporins. Carbapenems have universally low cross-reactivity rate of <1%.

Diagnosis of penicillin allergy

A detailed history is the most important step to help characterize the nature of reactions. Questions should cover the name of drug, route, date given, time of onset, indication, time to resolution, symptoms of reaction, concurrent illness and agents tolerated. Routine penicillin skin testing (PST) is recommended by overseas guideline for all cases with reported penicillin allergy. The aim of PST is to exclude type-1 reactions. Personnel suitable to perform PST include allergy specialists and doctors/nurses/pharmacists who have received training. Severe delayed reactions are contraindications to skin test. Patients with known anaphylactic reactions should be referred to allergist centres for testing, while low-risk individuals can usually skip skin test and proceed directly to graded oral drug challenge (DC). DC is performed usually with amoxicillin. Patients are observed for 30 to 60 minutes after the challenge dose (1/10th of full dose) is given. If uneventful, the full dose is given followed by another observation. Although acute reactions are excluded by a negative DC, benign delayed reactions can still develop several days later in about 3% of patients, which is the rate observed in general population.

Effect of penicillin allergy on patient and society

Beta-lactams are considered as the drug of choice for many common or severe infections, such as beta-hemolytic streptococci, staphylococci, listeriosis, gonorrhea and syphilis. Penicillin allergy is associated with adverse patient outcomes, including longer hospital stay, higher rate of infection by resistant organisms e.g. C. difficile, MRSA & VRE, increased adverse effects from the use of alternative antibiotics. Surgical prophylaxis with non-beta-lactam regimen leads to an increased risk of surgical site infection. Significantly higher healthcare cost is noted among penicillin-allergic subjects.

Allergy and Antibiotic Stewardship Programme (ASP)

Evaluation of allergy should be part of ASP. The objective is to maximize the prescription of first-line beta-lactam agents whenever indicated. There is an increasing amount of literature reports highlighting efforts to integrate evaluation by means of history-taking, PST and DC into various ASPs in in-patient and out-patient settings. Many patients were successfully "delabelled" after proper assessment by doctors, nurses or pharmacists. Cost-effectiveness and enhanced use of beta lactams without increase in adverse reactions have been demonstrated.

Suggested approach in Primary Care

After detailed history taking, an 'allergic' patient may be classified into one of the 3 categories: high risk (acute or severe delayed reactions) / low risk (benign delayed reactions) / non-allergy. For the low-risk category, direct DC with amoxicillin may be attempted. The rate of serious reactions or death after DC reported in the literature is extremely low. Ambulatory facilities are considered as ideal settings for DC because patients are usually not very ill without an urgent need of antibiotics. Nevertheless, standard antianaphylaxis medications should be readily available. Occasionally, successful delabelling can be achieved by a detailed history-taking or interview alone without employing PST or DC.

In Hong Kong, the Antibiotic Stewardship Programme in Primary Care by the Centre for Health Protection recommends that for penicillin-allergic patients with potential type-1 or severe reactions, beta lactams should be avoided; whereas cephalosporins (especially the non-cross-reacting agents) can be used for those without these features. This practice echoes overseas recommendations. If further reassurance is required, it is in the author's opinion that the cephalosporin can be given as graded drug challenge. Finally, if a patient subsequently tolerates a beta lactam and completed treatment uneventfully, it is advisable to record the exact details in patient notes to facilitate future use of the drug.

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Summary

1. Type-1 (acute) reactions have a rapid onset typically within 1 hour. It is marked by urticaria, wheezing, angioedema and anaphylaxis. Severe delayed reactions include Steven Johnson Syndrome, hemolysis, organ dysfunction, etc. Both types of reactions are considered absolute contraindications to reuse of the implicated antibiotic.

2. Penicillin is the most common antibiotic associated with allergy. About 10% of the population are reported as penicillin-allergic, but <1% have true allergy (type-1 reactions).

3. History taking is the most important step in diagnosing antibiotic allergy. We should ask about the circumstances of the exposure episode, characteristics of the symptoms, prior evaluation results and name of the tolerated agents.

4. Penicillin allergy is associated with adverse patient outcomes e.g. longer length of hospital stay and infections with resistant microorganisms. Antibiotic Stewardship Programme (ASP) should include allergy assessment to facilitate use of first-line beta lactam antibiotics whenever indicated.

5. In primary care setting, graded oral antibiotic challenge may be attempted for patients without features of type-1 (acute) or severe delayed reactions. 30 to 60-minute observation should follow each dose administered. Antianaphylaxis medications should be readily available.

Questions

1. Which of the following is not a typical sign and symptom of type-1 (acute) reaction?
A. Urticaria
B. Angioedema
C. Wheezing
D. Anaphylaxis
E. Pruritis without rash

2. About ___% of general population is reported to be allergic to penicillin.
A. 1
B. 5
C. 10
D. 20
E. 30

3. Which of the following statement is incorrect?
A. Cross reactivity between penicillin and cephalosporins are determined by similarity of side chains
B. 3rd and 4th generation cephalosporins have very low cross-reactivity rate with penicillin
C. Carbapenems have extremely low cross-reactivity rate with penicillin
D. Amoxicillin and ampicillin have extremely low cross-reactivity rate with penicillin
E. 80-90% of penicillin-allergic individuals can actually tolerate penicillin treatment

4. Penicillin allergy is associated with the following adverse outcomes except:
A. Longer hospital stay
B. Increased risk of infection by drug-resistant organisms e.g. C. difficile, MRSA, VRE
C. Higher healthcare cost
D. Increased risk of surgical site infection
E. Higher risk of tendonopathy

5. Which of the following statements about graded drug challenge (DC) is true?
A. The minimal number of doses is 3 (1/100th, 1/10th, full dose)
B. An observation period of 4 hours is required after administering the challenge doses
C. Test is commonly performed using oral amoxicillin
D. Negative result can effectively rule out all types of allergic reaction
E. Can only be performed in allergy specialist clinics

Answer to Self Study CME Series No. 210 (Jan 2020)

ANSWER: 1) b 2) d 3) c 4) d 5) e

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