ABSTRACT
Penicillin and penicillin-based antibiotics are the most widely used antibiotics for common infections and are also the antibiotics which most often cause allergic reactions. Penicillins and cephalosporins share a common beta-lactam ring structure as well as similar side chains which could potentially lead to clinical cross-reactivity. IgE-mediated allergy to penicillins and cephalosporins may be due to the beta-lactam ring structure that is common to this group of drugs, or due to the R-group side chain that distinguishes the different penicillins from each other. After administration penicillin undergoes degradation resulting mainly in the formation of benzyl penicilloyl which is the major antigenic determinant to which the majority of allergic patients react. The beta-lactam ring may act as a hapten by covalently binding to tissue or serum proteins. When cephalosporins degrade, the beta-lactam ring as well as the R-group side chain are exposed. It is the R-group that is believed to play a more important role in the cross-reactivity between penicillins and cephalosporins. Most patients with proven penicillin allergy can safely receive cephalosporin antibiotics after a thorough history is taken and skin prick testing and a drug provocation test performed.

BACKGROUND
It is not uncommon for a skin rash to occur during a course of treatment with a penicillin antibiotic. This is often assumed to be due to penicillin allergy. In most cases no testing is performed in order to verify the diagnosis. Many individuals are simply labelled ‘penicillin allergic’.

Penicillin and penicillin-based antibiotics are the most widely used antibiotics for common infections. They are also the antibiotics which most often cause allergic reactions with the frequency of life-threatening anaphylaxis estimated to be 0.01%-0.05%. The incidence of self-reported penicillin allergy is from 1%-10% but more than 80-90% of these have no evidence of IgE antibodies to penicillin on skin-testing.

Penicillin-based antibiotics are usually less expensive and have fewer side effects than alternative broad-spectrum antibiotics. They are also more effective for certain infections. This is especially important among patients on long-term antibiotic prophylaxis or treatment such as those with rheumatic heart disease or bacterial endocarditis.

Patients with penicillin allergy have been shown to have longer hospital stays. They are 23% more likely to have C difficile than controls and 30% more likely to have vancomycin resistant enterococcus. Their mean antibiotic costs have been shown to be 63 times greater than those of non-allergic patients.

Penicillins and cephalosporins share a common beta-lactam ring structure as well as similar side chains which may lead to clinical cross-reactivity.

ANTIGENIC COMPONENTS
It is helpful to review the potential allergenic components of these drugs in order to better understand how they may possibly cross-react in a clinical situation.

IgE-mediated allergy to penicillins and cephalosporins may be due to the beta-lactam ring structure that is common to this group of drugs or due to the R-group side chain that distinguishes the different penicillins from each other. The beta-lactam ring itself is too small to be antigenic but it can act as a hapten by covalently binding to tissue or serum proteins.

After administration penicillin undergoes degradation resulting mainly in the formation of benzyl penicilloyl which is the major antigenic determinant to which the majority of allergic patients react. Penicillin degradation also results in a range of molecules which can act as hapten.

These so-called minor determinants are responsible for allergic reactions in about 15% of allergic patients. When
cephalosporins degrade, the beta-lactam ring as well as the R-group side chain are exposed. It is the R-group that is believed to play a more important role in the cross-reactivity between penicillins and cephalosporins.

**CLASSIFICATION OF ALLERGIC REACTIONS**

There are a number of ways to classify drug allergies. From a clinical perspective a practical method is to classify adverse drug reactions as ‘immediate’ and ‘non-immediate’ based on the time interval between administration of the drug and the reaction.

Immediate hypersensitivity reactions are IgE-mediated and occur within minutes up to 1 hour after administration. Non-immediate reactions are generally non IgE-mediated and manifest from 1-72 hours after exposure. Immediate reactions present with the typical IgE-mediated symptoms and signs which may include anaphylaxis, urticaria, angioedema and bronchospasm. Non-immediate allergic reactions may include contact reactions, serum sickness, haemolytic anaemia, morbilliform eruptions and Stevens-Johnson syndrome. Table 1 shows the classification of allergic reactions.

**RISK FACTORS**

A personal or family history of drug allergies predisposes to penicillin allergy whereas a history of atopy does not. Young adults between 20 and 49 years of age are most likely to be allergic and females report being allergic more than males. Older age predisposes to more serious reactions due to comorbidities and the use of other drugs, such as beta-blockers. Concurrent viral infections such as HIV, EBV, HHV and CMV predispose to non-immediate reactions.

**DIAGNOSIS**

**CLINICAL HISTORY**

The signs, symptoms and severity of the reaction and any prior reactions should be documented. For example, urticaria and bronchospasm would suggest an IgE-mediated immediate drug reaction, whereas a vague history of minor gastrointestinal upset or a non-specific rash is much less suggestive.

The dose and route of administration are important. Prolonged parenteral administration is more likely to cause a hypersensitivity reaction than the oral or topical route, especially in non IgE-mediated allergy. A concomitant viral illness is important as this may cause a rash that is mistaken for penicillin allergy. The maculopapular rash induced by ampicillin or amoxicillin given to a child with Epstein-Barr virus infection is often mistaken for penicillin allergy.

**QUESTIONS TO BE ASKED ABOUT HISTORY:**

- Current and previous use;
- Dose;
- Frequency;
- Route of administration;
- Temporal sequence of events from initiation of treatment to onset of symptoms;
- Intercurrent illness, especially viral infections/HIV.

<table>
<thead>
<tr>
<th>TYPE</th>
<th>MECHANISM</th>
<th>TIME FRAME</th>
<th>CLINICAL CHARACTERISTICS</th>
<th>LIKELY CULPRIT DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>IgE-mediated</td>
<td>IgE-drug complex binds to mast cells releasing inflammatory mediators.</td>
<td>Hours</td>
<td>Anaphylaxis, urticaria, angioedema, bronchospasm.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Penicillins</td>
</tr>
<tr>
<td>Type 2</td>
<td>Cytotoxic</td>
<td>IgM or IgG binds to drug-hapten coated cells.</td>
<td>Hours-days</td>
<td>Haemolytic anaemia, thrombocytopenia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cephalosporins, penicillins, dapsone.</td>
</tr>
<tr>
<td>Type 3</td>
<td>Immune complex-mediated</td>
<td>Drug-antibody complexes deposited in tissues leading to complement activation.</td>
<td>Days–weeks</td>
<td>Serum sickness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Antibiotics, antivenoms, antibiotics.</td>
</tr>
<tr>
<td>Type 4</td>
<td>T-cell mediated</td>
<td>Days–weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 4a</td>
<td>Monocytes</td>
<td>Contact dermatitis</td>
<td></td>
<td>Topical anaesthetics, topical antihistamines.</td>
</tr>
<tr>
<td>Type 4b</td>
<td>Eosinophils</td>
<td>Morbilliform rash, DRESS*</td>
<td>Anti-epileptics, sulfa-based agents, antidepressants, antibiotics.</td>
<td></td>
</tr>
<tr>
<td>Type 4c</td>
<td>CD4+ and CD8+ cytotoxic T-cell activation.</td>
<td>SJS/TEN*</td>
<td>Antibiotics, analgesics, NSAIDS, antiepileptics.</td>
<td></td>
</tr>
<tr>
<td>Type 4d</td>
<td>Neutrophil activation.</td>
<td>AGEP*</td>
<td>Penicillins, cephalosporins, quinolones.</td>
<td></td>
</tr>
</tbody>
</table>

*DRESS: Drug Rash, Eosinophilia and Systemic Symptoms
*SJS: Stevens-Johnson Syndrome
*TEN: Toxic Epidermal Necrolysis
*AGEP: Acute Generalised Exanthematous Pustulosis
The skin is the most commonly and prominently affected organ. Characterising the skin lesion is important. Skin manifestations may include maculopapular eruptions, urticaria, angioedema, fixed drug eruptions, photosensitivity, bullous lesions, vasculitis, erythema multiforme, DRESS, SJS and TEN.

INVESTIGATIONS
Blood tests are done based on the clinical picture (Table II).

<table>
<thead>
<tr>
<th>TEST</th>
<th>HELPFUL IN DIAGNOSING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full blood count</td>
<td>Haemolytic anaemia, thrombocytopenia, eosinophilia</td>
</tr>
<tr>
<td>Chest radiograph</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>ESR/CRP</td>
<td>Vascularitis</td>
</tr>
<tr>
<td>U&amp;E/urine dipstick</td>
<td>Serum sickness/neritis/vasculitis</td>
</tr>
<tr>
<td>Coombs test</td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td>Tryptase</td>
<td>Acute anaphylaxis</td>
</tr>
</tbody>
</table>

Tryptase is a sensitive and specific marker of mast cell degranulation and is helpful in the context of anaphylaxis. Serum levels peak at one hour after a reaction and decline thereafter over hours. Samples taken at 0, 1 and 6 hours after the event may confirm anaphylaxis.

SKIN TESTING
Skin prick testing is the basic diagnostic tool for IgE-mediated reactions to penicillins. Clinical expertise is required in order to perform this test accurately. Skin tests are generally very safe but systemic reactions have been reported. They should, therefore, be done in a suitable setting.

A wheal of ≥3 mm greater than negative control is considered a positive result.

The skin test panel should include a positive and a negative control, benzylpenicillin, major and minor determinant mixture (Diater®, Madrid, Spain) and amoxicillin (20-25 mg/ml). If the offending drug is a cephalosporin, this is added to the above panel with the understanding that the negative predictive value of such a test is unknown. Skin prick tests have a specificity approaching 100% for IgE-mediated allergy. The sensitivity is rather less (≤70%). If the skin prick test is negative, some go on to perform intradermal testing with various dilutions of the drug, injected intradermally on the volar surface of the forearm. Skin prick and intradermal tests are not useful for non-immediate reactions.

IMMUNOCAP
Specific IgE antibodies to amoxicillin, ampicillin, penicillin V, penicillin G and cefaclor can be measured to aid in the diagnosis. This test is highly specific (95%) but less sensitive (54%) than skin prick tests.

OTHER TESTS
Patch testing: Patch testing has been used for investigation of non-immediate reactions. However, their use is not standardised, nor is the sensitivity fully validated. Sensitivity in some studies was only 9%. Delayed reading of intradermal tests has been shown to be slightly more sensitive than patch tests, but less specific.

Cellular Antigen Stimulation Test (CAST): This test measures the in vitro production of sulphidoleukotrienes by leukocytes when stimulated by the specific drug. The sensitivity and specificity are approximately 46% and 85% respectively.

Basophil Activation Test: Limited to research settings.

Lymphocyte Transformation Test: Limited to research settings.

Drug Provocation Test (DPT): If the skin tests are negative and IgE antibody levels normal, a DPT should be performed provided resuscitation equipment and trained staff are available. A strongly suggestive history of immediate allergy coupled with a positive skin test and/or immunoCAP is generally sufficient to make the diagnosis of penicillin allergy without the need to perform a DPT. A DPT is not usually performed if there is a history of anaphylaxis.

RESENSITISATION AFTER INVESTIGATIONS
There is no consensus with regards to the risk of re-sensitisation after performing skin tests and DPT. Recent studies suggest a low risk, however, the International Consensus on Drug Allergy suggests that retesting should be considered in those who have had a previous severe reaction.

CROSS REACTIVITY WITH CEPHALOSPORINS
It was previously believed that up to 20% of patients with a history of penicillin allergy could have an adverse reaction to a cephalosporin, most commonly with the first and second generation cephalosporins. Much of the evidence on cross-reactivity comes from retrospective studies. These studies were limited in that they lacked control groups. Many were based only on clinical history or on skin prick tests rather than on drug provocation challenges. In studies that did perform DPTs, most were carried out in an open fashion, rather than being blinded.

First generation cephalosporins produced prior to 1980 are known to have contained traces of penicillin when they were initially manufactured. This may also have led to a
higher rate of cross-reactivity with these drugs. A meta-analysis from 2007 showed a higher risk of cross-reactivity with first generation but a negligible risk with second and third generation cephalosporins – around 2% overall. There are no reported cases of cross-reactivity with fourth generation cephalosporins.

Cross-reactivity between these drugs is believed to be due to the drugs having similar R-group side chains and not due to the beta-lactam ring. For example, amoxicillin shares a side-chain with cephadroxil, cefotaxime with ceftriaxone and ampicillin with both cephalaxin and cefaclor. Two studies of patients confirmed to be amoxicillin allergic, but not penicillin allergic, showed that up to 38% of patients reacted to cephadroxil as well. Little is known about the cross-reactivity between penicillins and cephalosporins in non-immediate allergy.

RECOMMENDATIONS

For patient with reported, but not confirmed, penicillin allergy:
- Confirm penicillin allergy as above.

For patients allergic to penicillin and requiring a cephalosporin:
- Do a cephalosporin skin prick test;
- If this is negative, give the cephalosporin via graded challenge (see below for an example of a graded challenge);
- If the cephalosporin skin test is positive, the cephalosporin may be administered via a desensitisation protocol (Table III) or alternatively, avoided altogether.

For patients allergic to amoxicillin or ampicillin, but who tolerate penicillin, and require a cephalosporin:
- Avoid cephalosporins with identical side chains;
- If amoxicillin allergic, avoid cefadroxil and cefprozil;
- If ampicillin allergic, avoid cephalaxin, cefaclor and loracarbef;
- Cephalosporins with dissimilar side-chains can be used;
- If a cephalosporin with an identical side chain is necessary, it can be administered via desensitisation.

For patients allergic to a cephalosporin and requiring penicillin:
- Do a penicillin skin prick test;
- If it is negative, give penicillin;
- If it is positive, avoid penicillin or administer penicillin via a desensitisation protocol.

For patients allergic to cephalosporin and requiring a different cephalosporin:
- Use a cephalosporin with a different side chain and administer it via a graded challenge or desensitisation protocol depending on the severity of the previous reaction.

IF SKIN TESTING IS NOT AVAILABLE

If skin testing is not available, the clinical history of penicillin allergy should be carefully assessed and the likelihood of a serious IgE-mediated reaction estimated. If the symptoms are not suggestive, or the reaction was more than 10 years ago, the cephalosporin can be given in the usual way, provided that one with a different side-chain is used.

If there is a high likelihood because the reaction is more recent, or the symptoms are highly suggestive of an IgE-mediated reaction, a cephalosporin with a different side-chain may be given via a graded challenge. If the history of the reaction is consistent with anaphylaxis, rapid desensitisation should rather be performed.

Amoxicillin or ampicillin allergic patients should avoid cephalosporins with identical side chains or receive them via desensitisation. They are able to take cephalosporins with different side chains with no special precautions.

FOR CHILDREN WITH A MILD, NON-IMMEDIATE RASH OR MACULOPAPULAR ERUPTION

The first dose of the oral challenge should be given in hospital, followed by a 2-hour period of observation. The child then completes a 5-day course at home.

| TABLE III: ORAL PENICILLIN DESENSITISATION PROTOCOL (SULLIVAN IN MIDDLETON)|
|-----------------|-------|-------|-------|-------|
| STEP*           | PENICILLIN (MG/ML) | AMOUNT (ML) | DOSE GIVEN (MG) | CUMULATIVE DOSE (MG) |
| 1               | 0.5   | 0.1   | 0.05  | 0.05  |
| 2               | 0.5   | 0.2   | 0.1   | 0.15  |
| 3               | 0.5   | 0.4   | 0.2   | 0.35  |
| 4               | 0.5   | 0.8   | 0.4   | 0.75  |
| 5               | 0.5   | 1.6   | 0.8   | 1.55  |
| 6               | 0.5   | 3.2   | 1.6   | 3.15  |
| 7               | 0.5   | 6.4   | 3.2   | 6.35  |
| 8               | 5     | 1.2   | 6     | 12.35 |
| 9               | 5     | 2.4   | 12    | 24.35 |
| 10              | 5     | 5     | 25    | 49.35 |
| 11              | 50    | 1     | 50    | 100   |
| 12              | 50    | 2     | 100   | 200   |
| 13              | 50    | 4     | 200   | 400   |
| 14              | 50    | 8     | 400   | 800   |

*Interval between doses is 15 minutes. After last dose, observe patient for 30 minutes. If no reaction occurs, the full therapeutic dose may be given.

| TABLE IV: CEPHALOSPORINS WITH IDENTICAL SIDE CHAINS |
|-----------------|-------|-------|
| Cefaclor        | Loracarbef | Cephalaxin |
| Cefadroxil      | Cefprozil  | Cefepime  |
| Cefotaxime      | Cefpodoxime| Ceftriazone|

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GRADED CHALLENGE
A graded challenge does not modify the immune response, but rather is a more cautious method of administering a drug. A typical method for oral drugs is to give a 1/10 of the full dose, followed an hour later by the full dose. More caution is advocated should the drug be administered intravenously. In this case the starting dose is usually 1/100, followed an hour later by 1/10, and then the full dose an hour after that. For example, using cefuroxime give 2.5 mg, 25 mg and then 250 mg at 60 minute intervals.

CONCLUSIONS
Most penicillin allergic individuals are incorrectly labelled. This may result in the unnecessary use of more expensive and less effective antibiotics. It may also lead to the emergence of multi-drug resistant organisms. Accurate diagnosis is essential to avoid the morbidity, mortality and economic cost associated with unnecessarily withholding penicillin in non-allergic patients. A history of penicillin allergy is often unreliable, poorly documented or vague. Skin prick testing remains the standard practice for the evaluation of patients with immediate hypersensitivity reactions to penicillin. This, together with a thorough history, determination of IgE antibodies and a drug provocation test will pick up virtually all cases. Most patients with proven penicillin allergy can safely receive cephalosporin antibiotics.

REFERENCES