**Introduction**

Penicillin belongs to the broad class of antibiotics called beta (ß)-lactam antibiotics which are generally effective at eradicating common bacterial infections and are relatively inexpensive and therefore widely used to treat skin, ear, sinus and upper respiratory tract infections. Included in this class of antibiotics are the penicillin derivatives such as ampicillin and amoxicillin as well as cephalosporins, monobactams, carbapenems and β-lactamase inhibitors. As with most drugs, penicillin exhibits common side effects and adverse reactions (Table I). However, true drug allergy, which is IgE-mediated, accounts for very few of all reported adverse drug reactions.

There are two clinical pictures that can result from penicillin allergy, namely acute and sub-acute reactions mediated by IgE and IgG antibodies respectively. The acute allergic reaction arises immediately or rapidly within a matter of minutes to an hour or two and includes sudden anaphylaxis with hypotension, bronchospasm, angioedema and urticaria. Acute reactions result from reaction with preformed IgE to penicillin as a result of previous exposure. The resulting release of histamine and other mediators from mast cells produce the signs and symptoms typical of a true anaphylactic reaction. A less dramatic picture may occur 7 to 10 days after penicillin treatment starts or 1–2 days after repeat therapy. In this setting the picture is sub-acute and can include urticaria, fever and arthralgias or arthritis. The sub-acute reaction is caused by preformed IgG to penicillin as a result of previous penicillin treatment. The IgG antibody results in the activation of the complement reactions producing inflammation resulting in the symptoms mentioned earlier.

Many patients say they are allergic, but then list symptoms that do not coincide with an anaphylactic response as described above. So, it is currently considered relatively safe to administer the same antibiotic, and related ones if indicated, as long as it has been confirmed that the initial reaction was not IgE-mediated. This is, however, difficult to confirm in a pharmacy setting without the use of skin sensitivity testing.

**Table I: Adverse drug reactions associated with the use of penicillin**

| Common adverse drug reactions | Diarrhoea, nausea, rash, neurotoxicity, urticaria, and/or superinfection (including candidiasis) | Experienced in ≥ 1% of patients |
| Infrequent adverse effects | Fever, vomiting, erythema, dermatitis, angioedema, seizures (especially in epileptics), and/or pseudomembranous colitis | Experienced in 0.1% of patients |
| True anaphylaxis | Hypersensitivity with hypotension, angioedema, bronchospasm and urticaria | Experienced in 0.01% of patients |

True penicillin allergy is rare with the estimated frequency of anaphylaxis at 1 – 5 per 10 000 courses of penicillin administered. Hypersensitivity is however the antibiotic’s most important adverse reaction resulting in nausea, vomiting, pruritus, urticaria, wheezing laryngeal oedema and ultimately, cardiovascular collapse. Identification of patients who erroneously carry a label of β-lactam allergy leads to improved utilisation of antibiotics and slows the spread of multiple drug-resistant bacteria. Cross-reactivity between penicillin and second and third generation cephalosporin is low and may be lower than the cross-reactivity between penicillin and unrelated antibiotics.
associated with any other class of antibiotics and are as
much at risk of an allergic reaction as the general population.
Thus, use of skin testing can increase the number of in-
stances in which penicillin can be safely used rather than
alternative broad-spectrum antibiotics, thereby helping to
reduce the development of antibiotic resistance. Ideally,
penicillin skin testing should be done in all persons with a
history of penicillin allergy. Unfortunately, because of the
lack of commercial penicillin skin test reagents, this is not
possible. It should be noted that any skin sensitivity testing
should be done by specially trained professionals with
access to a complete panel of penicillin skin test materials.
There are times when doctors try to weaken and eventually
overcome a patient’s sensitivity to the penicillin allergen
through desensitisation. They do this by administering small
but gradually increasing doses of penicillin orally or intrave-
nously. Note that because desensitisation can trigger a life-
threatening reaction, it is only attempted in a controlled
hospital setting — and only when penicillin therapy is
absolutely necessary.

Anaphylaxis

Risk management
As mentioned before, documentation or reporting of allergies
may be inaccurate and many patients may report that they
have an allergy to an antibiotic whereas they may have in
fact experienced effects of the infection such as fever and
diarrhoea. If a patient has exhibited signs of a true allergic
reaction, re-exposure to penicillin or related antibiotics can
trigger life-threatening anaphylaxis. It has been estimated
that up to 60% of penicillin-allergic patients will experience
another allergic event if given the drug again. However, new
data suggest that this rate is less than 2%. Researchers
analysed data from more than 3 million patients on the UK
General Practice Research Database, who had received at
least one prescription for penicillin. Of this group, 6 212
(0.18%) patients had experienced an allergic-like reaction
after their initial penicillin prescription. Although these
patients were 19-times less likely than others to receive a
repeat prescription for penicillin, the percentage of allergic
patients who received such prescriptions was high (48.5%).
With repeat penicillin use, those with an allergy were 11.2-
times more likely than others to experience an allergic event.
Despite this relative difference, the absolute risk of such
events in the penicillin-allergic group was reported to be just
1.89%. The management of such an event therefore needs to
focus on awareness to prevent re-exposure, knowledge of
initial signs and symptoms such as wheezing, light-head-
edness, slurred speech, rapid or weaker pulse rate, blue-
ness of skin – lips and nail beds, diarrhoea, nausea and
vomiting along with emergency medical assistance and drug
therapy to cope with the situation, particularly corticosteroids.

In addition, the pharmacist must be alert with respect to the
use of combination products such as co-amoxiclav (Augmen-
tin®) piperacillin/tazobactam (Tazocin®) and ticarcillin/
clavulanic acid which all contain a penicillin. Serious
medication errors can occur where doctors prescribe these
medicines (often by brand name) and do not recognise that
they contain penicillin.

Signs and symptoms of anaphylaxis
Anaphylaxis, characterised by symptomatic hypotension with
associated dyspnoea, urticaria, and possibly gastrointestinal
(GI) symptoms, is the most severe manifestation of IgE-
mediated drug allergy. It is most common after parenteral
drug administration and is rare with oral or cutaneous
exposure. Anaphylaxis results when antigen-specific IgE is
present on mast cells and a systemic exposure to antigen
occurs, cross-linking the IgE. This results in the simultaneous
degranulation of large numbers of mast cells. Mast cells
contain histamine and other vasoactive mediators. Their
sudden release, due to either an IgE-mediated anaphylactic
reaction or a similar non-IgE-mediated reaction (referred to
as an “anaphylactoid” reaction), results in a sudden drop in
blood pressure and blood volume, flushing, itching, and
potentially respiratory compromise, bowel oedema, and
potential death (Table II).

Drug therapy and emergency medical care
A mild allergic reaction can be treated with an antihistamine
like diphenhydramine, which helps relieve itching and skin
 rash. However, serious anaphylactic reactions require the
urgent administration of adrenaline to counter the cardiac
collapse as well as corticosteroids to counter the effect of the
mediators released from the mast cell. In the case of a true
anaphylactic hypersensitivity reaction, a patient may die
unless controlled with adrenaline and their airway is main-
tained.

Cross sensitivity
Until recently it has been accepted that there was up to a
10% cross-sensitivity between penicillin-derivatives, cepha-
losporins, and carbapenems, due to the sharing of the β-
lactam ring. Recent papers have shown that the major
determinant in the immunological reaction is the similarity
between the side chain of first generation cephalosporins
and penicillins, rather than the β-lactam structure that they

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share. This means that the risk of an allergic reaction to cephalosporins in those with an established IgE-mediated allergy to penicillin may be low or non-existent, as long as the side chains are not similar. The cephalosporin medications that are likely to cross-react after penicillin allergies have been established and include:

- Cephalexin
- Cefadroxil
- Cefaclor
- Cephadine
- Cefprozil
- Ceftriaxone
- Cefpodoxime

Among those that lack the β-lactam side chain, and would therefore be safer, are:

- Cefazolin
- Cefuroxime
- Cefdinir
- Cefixime
- Cefitubutin

Pharmacists should be aware that cephalosporin cross-reactivity in a penicillin-allergic patient is not necessarily a class effect. Dispensing of a prescription in a penicillin-allergic patient should be evaluated based on the type of allergic manifestations and the drug prescribed.

The other side of the discussion is whether those allergic to cephalosporins can safely receive penicillin. Anaphylactic reactions to cephalosporins are much less common than anaphylaxis associated with penicillin. Persons who make IgE in response to cephalosporins seem to produce it only in response to a particular cephalosporin, whereas persons who make clinically significant IgE in response to penicillin tend to react to core penicillin break-down products. Thus, in a patient with a history of a serious, potentially IgE-mediated reaction to a cephalosporin, it is critical to avoid re-exposure to the same cephalosporin, to a cephalosporin that shares the same side chain, and even to other β-lactams that share the same side chain (such as ceftazidime and aztreonam). Another thing to remember when thinking about medication for patients with a penicillin allergy is that there is a three-fold increased coincidental risk of adverse reactions to even an unrelated drug. Penicillin-allergic patients are more likely to react to any class of drug, so extra care is required.

Conclusion
Clinicians commonly encounter patients with a history of allergy to penicillin and other β-lactam antibiotics. However, it is known that about 90% of these patients are not truly allergic and could safely receive β-lactam antibiotics. The seriousness of the problem posed by drug allergies is perhaps overblown in part because of the loose use of the word “allergy,” to refer to all immunologically-mediated reactions. When assessing an allergy to penicillin the first issue is to establish whether or not a true allergic IgE-mediated reaction has taken place. Instead, these patients are often treated unnecessarily with an alternate broad-spectrum antibiotic, which could increase costs and contribute to the development and spread of multiple drug-resistant bacteria.

The frequently cited figure of 10% cross reactivity between penicillin and cephalosporin is an overestimate. The degree of cross-reactivity between cephalosporins and penicillins depends on the generation of cephalosporins, being higher with earlier generation cephalosporins. Cross reactivity between penicillin and second and third generation cephalosporin is low and may be lower than the cross reactivity between penicillin and unrelated antibiotics. In addition, the frequency of immediate allergic reactions to cephalosporins is considerably lower compared to penicillins, and cross-reactivity among cephalosporins is lower compared to cross-reactivity between penicillin and cephalosporins.

References:
5. Pichichero, ME Drug topics Jul 25, 2005

South African Association of Pharmacists in Industry
15th Annual General Meeting

Notice in terms of the Constitution – Section 22
To: All members of the South African Association of Pharmacists in Industry

You are hereby notified that the 15th Annual General Meeting of the South African Association of Pharmacists in Industry will take place at:

52 Glenhove Road, Melrose Estate, Johannesburg
on 10 March 2009
Commencing at 12:30 pm

Issued by:
Jackie Dring – Chairperson
South African Association of Pharmacists in Industry
January 2009