Information for Clinicians

Department of Immunology

Drug Allergy and Hypersensitivity: Assessment and Management in Adults and Children

Introduction

All drugs have the potential to cause side effects, also known as 'adverse drug reactions', but not all of these are allergic in nature. The mechanism at presentation may not be apparent from the clinical history and it cannot always be established whether a drug reaction is allergic or non-allergic without investigation.
This document is based on NICE guidance CG183. This guideline, as with the NICE guidelines, defines drug allergy as any reaction caused by a drug with clinical features compatible with an immunological mechanism.

Contents

Assessment of possible drug allergy in adults and children

NICE guidance 183 suggests the following symptoms and signs as a guide when deciding whether to suspect drug allergy:

Immediate, rapidly evolving reactions

Anaphylaxis – a severe multi-system reaction characterised by:

- erythema, urticaria or angioedema
  and
- hypotension and/or bronchospasm
- Onset usually less than 1 hour after drug exposure (previous exposure not always confirmed)
  See page 4 for anaphylaxis treatment algorithm

Other immediate reactions including:

- Urticaria or angioedema without systemic features
- Exacerbation of asthma (for example, with non-steroidal anti-inflammatory drugs)

Non-immediate reactions without systemic involvement

Widespread red macules or papules (exanthema-like)

Fixed drug eruption (localised inflamed skin)

Onset usually 6–10 days after first drug exposure or within 3 days of second exposure

Non-immediate reactions with systemic involvement

Drug reaction with eosinophilia and systemic symptoms (DRESS) or drug hypersensitivity syndrome (DHS) characterised by:

- Onset usually 2–6 weeks after first drug exposure or within 3 days of second exposure
- widespread red macules, papules or erythroderma
- fever
- lymphadenopathy
- liver dysfunction
- eosinophilia

Toxic epidermal necrolysis or **Stevens-Johnson syndrome** characterised by:

- Onset usually 7–14 days after first drug exposure or within 3 days of second exposure
- painful rash and fever (often early signs)
- mucosal or cutaneous erosions
- vesicles, blistering or epidermal detachment
- red purpuric macules or erythema multiforme

Acute generalised exanthematous pustulosis (AGEP) characterised by:

- Onset usually 3–5 days after first drug exposure
- widespread pustules
- fever
- neutrophilia

Other disorders, which can rarely be caused by drug allergy but are often unrelated:

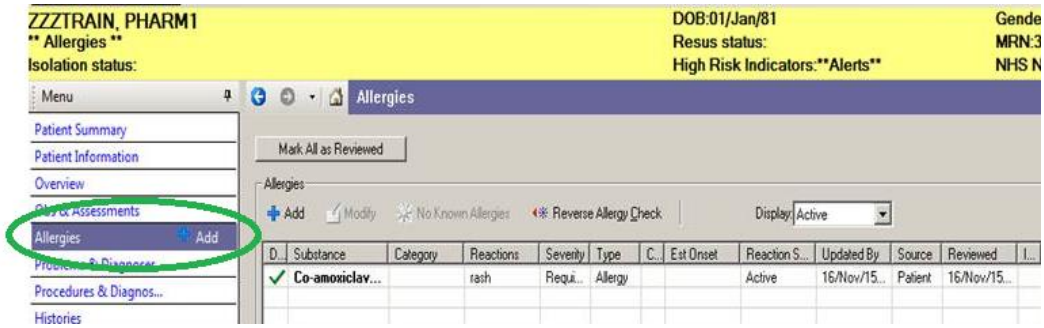
- eczema
- hepatitis
- nephritis
- photosensitivity
- vasculitis

Consider drug reactions as a cause but look for other causes as well. The time of onset in relationship to drug exposure is variable

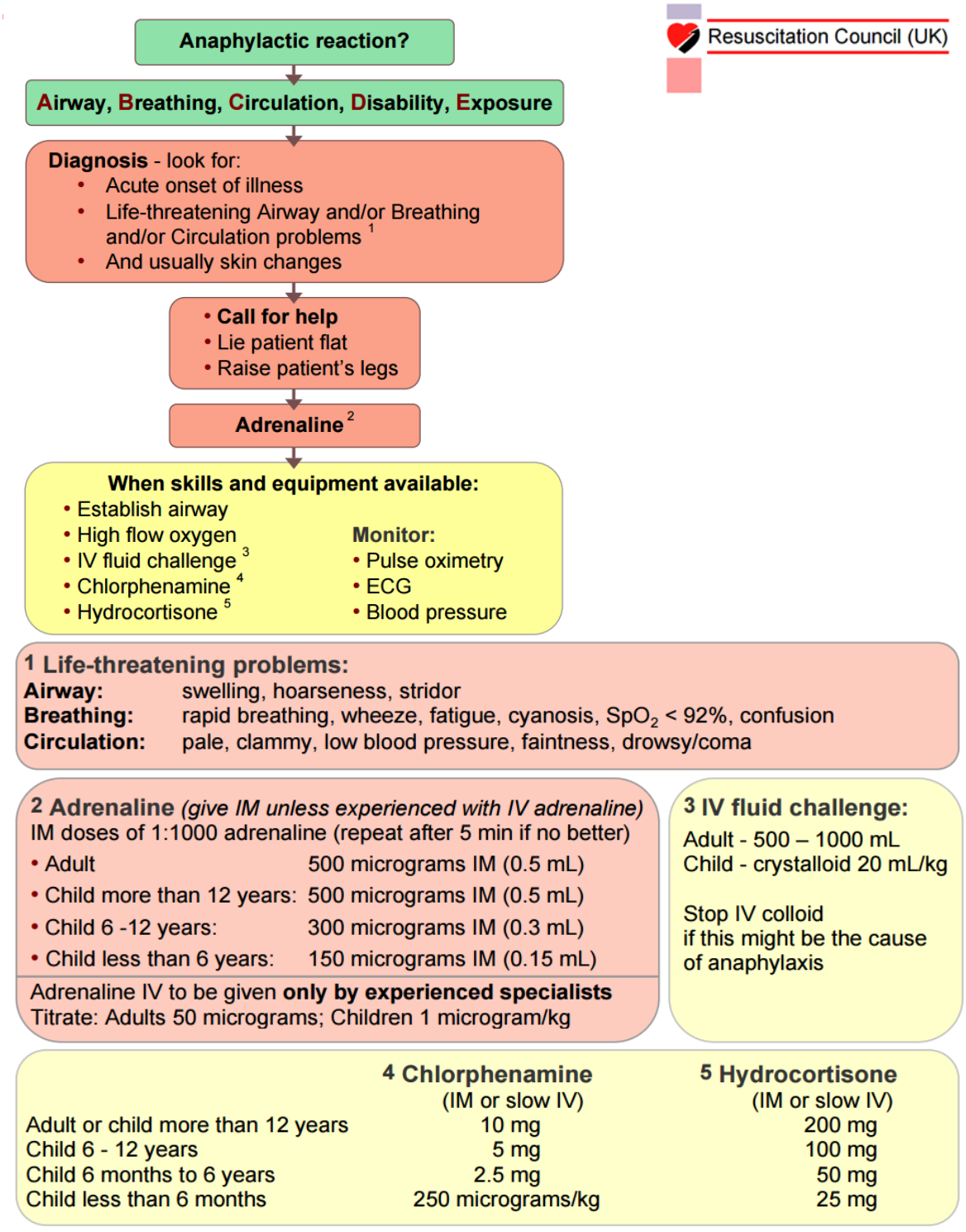
The reaction is less likely to be caused by drug allergy if there is a possible non-drug cause for the person's symptoms (for example, they have had similar symptoms when not taking the drug) or if the person only has gastrointestinal symptoms

Outline of action if drug allergy is suspected:

- Stop the drug suspected to have caused the allergic reaction
- Advise the person to avoid that drug or drug class in future
- Treat the symptoms of the acute reaction if needed
- For anaphylaxis reactions take blood for tryptase (see below)
- Ensure that the patients GP and any other medical teams are informed
- Provide the person with written information eg alternative medication, over the counter preparations, future investigations etc.
- The Anaphylaxis Campaign and Allergy UK charities have good general and drug allergy information
  http://www.anaphylaxis.org.uk/
  www.allergyuk.org
- Report the allergic reaction using the yellow card system (see specific section below)
- Document the details of the suspected drug allergy in the person's medical records
    - ♦ this should include the paper notes; the drug chart AND the electronic medical record (millennium- see picture below)



Treatment of Anaphylaxis



If oral antihistamine is required **cetirizine** is preferable as it is fast acting, long lasting and non-sedating (rather than chlorphenamine / Piriton® which is sedating and wears off quickly).

Documentation of anaphylaxis

Document the acute clinical features of the suspected anaphylactic reaction:
A Airway e.g. pharyngeal or laryngeal oedema
B Breathing eg bronchospasm with tachypnoea
C Circulation eg hypotension and/or tachycardia
Record associated skin and mucosal changes).
Record the time of onset of the reaction.
Record the circumstances immediately before the onset of symptoms to help to identify the possible trigger.

Measurement of mast cell tryptase after suspected anaphylaxis

After a suspected drug-related anaphylactic reaction, take 2 blood samples for mast cell tryptase (SST tube)
Record the exact timing of both blood samples taken for mast cell tryptase in the person's medical records and on the pathology request on ICE.

- Take a sample **as soon as possible** after emergency treatment has started
- Take a second sample ideally **within 1–2 hours** (but no later than 4 hours) from the onset of symptoms
- Additional sample **after 24 hours** or at follow-up for a baseline level to also be considered.

(further information in NICE clinical guideline on anaphylaxis CG134)

Skin eruptions related to drugs

There are several different types of drug eruption, which range from a clinically mild and unnoticed rash to a severe cutaneous adverse reaction (SCAR) that may be life threatening. On average, about 2% of prescriptions for a new medication lead to a drug eruption.

- Allergic reactions to some drugs are more common in females than in males.
- There are genetic factors that predispose people to drug eruptions. These may include differences in drug metabolism.
- Underlying viral infections and diseases can influence reactions.
- Previous allergic drug reaction or drug intolerance increases the risk of reaction to another drug. The more drugs are prescribed, the higher likelihood of allergy.
- Cross-reactions can occur relating to previous sensitivity to different medications, sunscreens, cosmetics, foods or insect bites.

What is the treatment for drug related skin eruptions?

- Identify and stop the responsible drug as soon as possible.
- Severe reactions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) will need specialist advice for their management which may include high dependency or intensive care. Many different medications can cause SJS including virtually all antibiotics. Stop antibiotics and ask for microbiology advice.
- The use of systemic steroids for drug eruptions, eg prednisone, is controversial. They are unnecessary if the rash is mild. Get advice from a dermatologist if the rash is severe.
- Topical corticosteroids, eg betamethasone valerate 0.1% cream, are safe short-term, and may reduce symptoms.

- Emollients should be applied liberally and frequently.
- Urticaria may respond to antihistamines. A long acting, non-sedating antihistamine such as **cetirizine** is preferable to short-acting chlorphenamine (Piriton®) except in the rare situation when IV or IM preparations are needed. Antihistamines are rarely useful for other eruptions. Doses above the adult licensed dose of cetirizine 10mg may in some cases be required, up to a maximum of 40mg daily depending on sedation.
- Further information and photographs of different skin reactions can be found at: http://www.dermnetnz.org/reactions/drug-eruptions.html

Drug Fevers

Many drugs can cause fever as a side effect. The fever most commonly occurs after 7 to 10 days of drug administration but can occur within 24 hours. It persists as long as the drug is continued, disappears soon after stopping the drug, and will rapidly reappear if the drug is restarted. Fever can be the sole manifestation of an adverse drug reaction in an estimated 3 to 5 percent of cases.

The agents most commonly associated with causing fever include the penicillins, cephalosporins, antituberculars, quinidine, procainamide, methyldopa, and phenytoin. The risk of developing drug fever increases with the number of drugs prescribed, especially in older adult patients. Patients with HIV infection also appear to have an increased susceptibility to drug reactions of all types, including fever. Failure to recognize the etiologic relationship between a drug and fever often has undesired consequences including extra testing, unnecessary therapy, and longer hospital stays.

Drug fever is usually a diagnosis of exclusion. In the majority of patients, the only way to know if a patient has a drug fever is by stopping the drug(s). The usual approach is to discontinue the most probable offending drug first, followed sequentially by cessation of other drugs if fever persists.

Investigation following a suspected drug reaction

Investigation of drug allergies can be difficult and is an evolving field.

For those who have had a severe reaction standard blood tests should be done as needed to monitor and manage the symptoms eg renal function. A full blood count to look for eosinophilia while symptoms are still present may be helpful if further investigations are done in the future. Do not use blood testing for serum specific immunoglobulin E (IgE) to diagnose drug allergy in a non-specialist setting.

The British Society for Allergy and Clinical Immunology (BSACI) has produced several guidelines giving detailed advice about the investigation and management drug allergies http://www.bsaci.org/

Referral to specialist services following a drug reaction

Refer people to a specialist drug allergy service if they have had:

- A suspected anaphylactic reaction.
- A severe non-immediate cutaneous reaction for example, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson Syndrome, toxic epidermal necrolysis.

Local contacts for referrals and advice:

Dr Sarah Johnston, Consultant immunologist can advise re the investigation and management of drug reactions in adults. Clinics are held at Southmead Hospital. Contact at the RUH (Wednesdays only): 01225 821406 or via Southmead Hospital, Bristol (all other times): 0117 323 5629 (secretary).

The dermatology team are happy to see patients for management of severe skin reactions such as DRESS. Phone: 01225 825658.

Children and young people under 18 years old can be discussed with Dr Natasha Zurick and Dr Ellie Augustine who run the RUH Paediatric Allergy Clinic (Extn 1545). Complex patients will be referred to Bristol Children's Hospital or in specific cases to other specialist allergy centres.

Essential information required when referring a patient with suspected drug allergy

Information required when referring suspected drug allergy:

1. Detailed description of reaction
2. Symptom sequence and duration
3. Treatment provided and response to treatment
4. Timing of symptoms in relation to drug administration
5. Has the patient had the suspected drug before this course of treatment?
6. How long had the drug(s) been taken before onset of reaction?
7. When was/were the drug(s) stopped? How did stopping the drug alter symptoms?
8. Is there a photograph of any skin rashes or swelling etc? (ideally get the patient or a relative to take this with their own phone camera to take to any appointments, alternatively cameras are held at the RUH by MEMS and photos can be uploaded to millenium)
9. Back ground medical history
10. Illness for which suspected drug was being taken, i.e. underlying illness (this may be the cause of the symptoms, rather than the drug)
11. Other drug reactions
12. Other allergies (foods, environmental allergens, atopic conditions)
13. List of all drugs taken at the time of the reaction (including regular medication, 'over the counter' and 'alternative' remedies)

Information about specific drug groups

Non-steroidal Anti-inflammatory Drugs (including selective cyclooxygenase 2 inhibitors)

For people who have had a mild allergic reaction to a non-selective NSAID but need an anti-inflammatory:

- Discuss the benefits and risks of selective cyclooxygenase 2 (COX-2) inhibitors (including the low risk of drug allergy).
- Consider introducing a selective COX-2 inhibitor at the lowest starting dose with only a single dose on the first day.
- **Do not offer** a selective COX-2 inhibitor to people in a non-specialist setting if they have had a severe reaction, such as anaphylaxis, severe angioedema or an asthmatic reaction, to a non-selective NSAID.
- Be aware that people with asthma who also have nasal polyps are likely to have NSAID-sensitive asthma unless they are known to have tolerated NSAIDs in the last 12 months.

Beta-Lactam Antibiotics

A beta-lactam structure is found in penicillins, cephalosporins, carbapenems, and monobactams.

Most people with reactions to beta-lactams will not need investigation but must be informed about which antibiotics to avoid and which groups are safe (see below).

Discuss with microbiology to determine the best antibiotic for penicillin allergic patients dependent on clinical situation. Further guidance in next section.

***NB* Patients who have had Stevens-Johnson syndrome, toxic epidermal necrolysis or other exfoliating dermatoses following beta-lactam exposure should not receive any beta-lactam antibiotic under any circumstance. (**Note that any antibiotic as well as other non- antibiotic drugs can cause SJS)

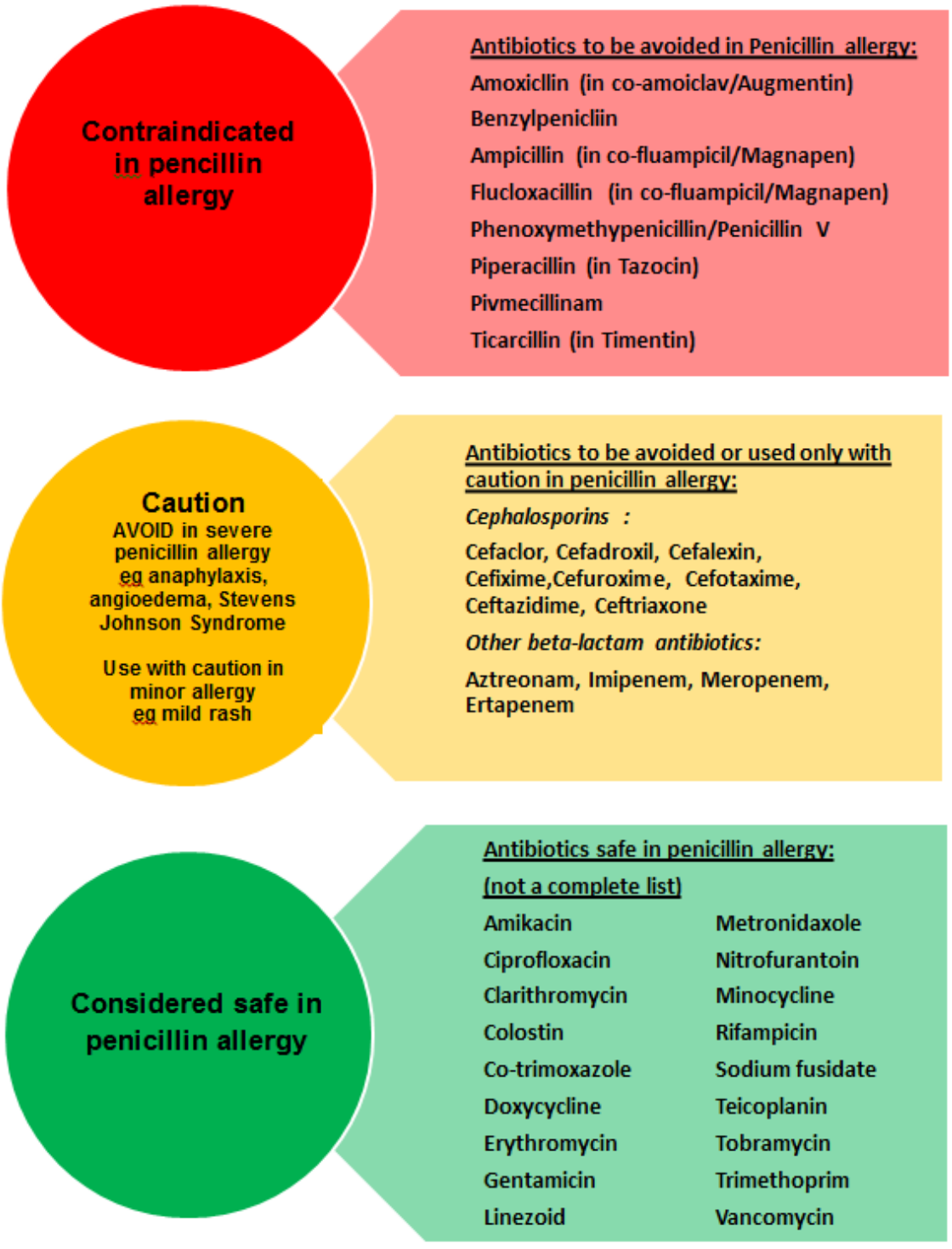
Refer people with a suspected allergy to beta-lactam antibiotics to a specialist drug allergy service <u>only</u> if they:

- Need treatment for a disease or condition that can only be treated by a beta-lactam antibiotic
  or
- Are likely to need beta-lactam antibiotics frequently in the future (for example, people with recurrent bacterial infections or immune deficiency)

- Consider referral for those with allergies to multiple antibiotic groups

See below for ‘traffic light’ advice for antibiotics in penicillin allergy and further information about cephalosporins.

Antibiotic considerations in Penicillin Allergy



See section below for further information about the 'amber/caution' group.

Should Cephalosporins be avoided in a patient who gives a history suggestive of penicillin allergy?

Most people who give a history of a penicillin-related rash are not allergic to cephalosporins, particularly third generation cephalosporins such as cefotaxime, ceftazidime, ceftriaxone and cefixime (available orally)**. However, there are many suitable alternatives to cephalosporins and penicillins so in most situations it is advised to avoid cephalosporins, particularly first generation cephalosporins eg cephalexin.**

The **overall** hypersensitivity rate between penicillins and cephalosporins is between 0.5% and 6.5%. Cross reactivity is more common with aminopenicillins, amoxicillin and ampicillin and first- and second-generation cephalosporins (eg cephalexin and cefuroxime) as opposed to third or fourth generation.

For penicillin-allergic patients, particularly those who have had minor reactions only, the use of third generation cephalosporins eg ceftriaxone (or fourth or fifth generation where microbiologically relevant), carries an extremely small risk of cross allergy. For example the use of ceftriaxone in meningococcal sepsis may be appropriate.

Aztreonam is a monobactam but has been shown to be safe in most penicillin allergy so may be used if there are no other more suitable antibiotics, and can be considered even if there is a history of severe penicillin allergy.

NB Patients who have had Stevens-Johnson syndrome, toxic epidermal necrolysis or other exfoliating dermatoses following beta-lactam exposure should not receive any beta-lactam antibiotic under any circumstance.

Skin testing in penicillin-allergic patients cannot reliably predict an allergic response to a cephalosporin. However, skin testing may be useful in planning care if the patient is likely to need further beta-lactam antibiotics or is allergic to multiple antibiotic groups.

General Anaesthesia

- Refer people to a specialist drug allergy service if they have had anaphylaxis or another suspected allergic reaction during or immediately after general anaesthesia. This is the responsibility of the attending anaesthetist. A copy of the relevant anaesthetic and drug chart are required for full assessment.
- Specific centres in the UK are experienced with investigating anaesthetic allergy including the Immunology Department at Southmead (referral to Dr Sarah Johnston as above)

For more information see the Association of Anaesthetists of Great Britain and Ireland Guidelines (AAGBI) www.aagbi.org

Local Anaesthetics

True local anaesthetic allergy is very rare. Reactions are often due to inadvertent intravenous injection or associated adrenaline.

Refer people to a specialist drug allergy service if they need a procedure involving a local anaesthetic that they are unable to have because of suspected allergy to local anaesthetics.

Information for Patients and Families

Provide the person and family with verbal and written information eg alternative medication, future investigations etc. Advise about over the counter preparations. Ensure they know to always mention their allergy whenever medication is prescribed, advise them not to assume people will know or will have checked their record.

The Anaphylaxis campaign and Allergy UK charities have information and factsheets about drug allergy which can be downloaded from
www.anaphylaxis.org.uk/our-factsheets/
http://www.allergyuk.org/drug-allergy/drug-allergy

Engraved allergy-bracelets such as those provided by Medic Alert (http://www.medicalert.org.uk/) are particularly useful when there is a risk of intravenous drug administration in an emergency, e.g. muscle relaxants, opiates or penicillin

Reporting a suspected Drug Reaction

The yellow card scheme should be used to report suspected drug reactions. This can be done online or by post:

- Report is online at mhra.gov.uk/yellowcard
- Use the Yellow Card mobile app from iTunes Yellow Card or PlayStore Yellow Card for iOS or Android devices
- Complete a paper Yellow Card form which you can post to FREEPOST YELLOW CARD. Yellow Cards can be found in the BNF or obtained by calling the freephone Yellow Card reporting line on 0800 731 6789

References

Suspected anaphylactic reactions associated with anaesthesia 2009
www.aagbi.org/sites/default/files/anaphylaxis_2009.pdf

Resuscitation Council UK : www.resus.org.uk/anaphylaxis/

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http://www.nice.org.uk/guidance/cg183

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