CLINICAL AND LABORATORY EVALUATION OF ADVERSE REACTIONS TO DRUGS

In hospitalised patients the overall incidence of serious drug reactions is about 6%, and as many as 15 - 20% will suffer some form of adverse reaction to a given medication.

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Reactions to penicillins are the most common, but the fatality rate is low. Radiocontrast media and local anaesthetic agents are also frequently implicated. Because the spectrum of reactions caused by drugs is so broad, and dependent on drug and patient factors, many classifications exist. We may conveniently consider drugs to be chemicals foreign to the biological system.

Adverse drug reactions are undesirable effects of drug treatment occurring at therapeutic doses.

Two types exist:
Type A (75%)
- Part of the normal pharmacological profile of the drug
- Can occur in any patient
- Dose dependent/predictable.

Type B (25%)
- Idiosyncratic responses, unrelated to the conventional pharmacology of the drug
- Occurs in susceptible individuals
- Seldom predictable.

Xenobiotics are chemicals that are foreign to the biological system and include the following:
- naturally occurring compounds (e.g. salicylates in paprika/thyme)
- drugs/medication
- environmental agents/contaminants (e.g. lead)
- food additives (e.g. MSG).

CLASSIFICATION OF ADVERSE DRUG REACTIONS

A simple classification of adverse drug reactions is the following:

Reactions that may occur in anyone:
- side-effect – undesirable pharmacological effect at recommended dose
- drug interaction/cross-reaction – action of a drug on the effectiveness or toxicity of another drug (e.g. enzyme inducers or inhibitors, protein-bound drugs)
- toxic effect – linked to excess dose (e.g. aspirin: tinnitus, nausea/vomiting/tachycardia).

Reactions that occur in susceptible subjects/host effects:
- drug intolerance – a low threshold to the normal pharmacological action of a drug (e.g. the elderly and neonates)
- drug idiosyncrasy – a genetically determined, qualitatively abnormal reaction to a drug related to a metabolic or enzyme deficiency (i.e. genetic polymorphisms cause certain patients to be susceptible to drug metabolites, e.g. slow acetylators more at risk of severe mucocutaneous disease after sulphonamide treatment)
- drug allergy – an immunologically mediated reaction
- hypersensitivity reaction – a reaction with the same clinical manifestations as an allergic reaction (e.g. as a result of histamine release), but lacking immunological specificity at a dose tolerated by a normal subject (e.g. direct release of histamine by opioids).

The elderly and neonates need special consideration as they are more likely to experience a host effect. Drug metabolism plays an important role in adverse reactions.

Elderly
- They oxidise poorly via CP450, but conjugate drugs well
- ↓ renal secretion / ↓ liver mass
- ↓ total body water (TBW) (need to ↓ dose of water-soluble drugs)
- ↓ lean body mass (↓ dose)
- Poor compliance (cost/ confusion/poor nutritional status).

Neonates
- Conjugate poorly but oxidise well (CP450)
- ↓ oral absorption (GIT not well developed)
- ↑ cutaneous absorption (thin skin)
- ↑ % TBW, therefore initial dose of drugs needs to be ↑
- ↓↓ protein binding; therefore ↑↑ competition for binding sites
- Renal excretion relatively poor, as urine is more acidic.

Practically one can consider the following in an attempt to classify drug allergies:
- clinical reaction
- immune mechanism
- drug structure.

Clinical reaction
- Systemic: anaphylaxis
- Cutaneous: majority of reactions
- Visceral: GIT symptoms
- Predilection for various tissues or organ systems.

Limitations: some drugs induce heterogeneous immune responses/tissue reaction. Penicillin may cause anaphylaxis, morbiliform rashes, serum sickness, drug fever, cytotoxic effects (e.g. haemolytic anemia), hypersensitivity vasculitis, interstitial nephritis, or severe contact dermatitis.

The temporal relationship to the onset of symptoms may constitute another type of clinical classification, ranging from immediate (minutes to an hour), accelerated (1 - 3 days) to delayed (> 3 days).

Immune type
- The majority of allergic reactions to drugs are classified according to the old Gell and Coombs classification although specific T-cell activation can also occur.

Gell and Coombs (1968)
Immediate IgE-mediated (skin prick test/radioallergosorbent (RAST)) testing:
- anaphylaxis
- urticaria
- laryngeal oedema
- bronchospasm.

Cytotoxic complement-mediated IgM or IgG antibodies which are formed in response to drug-altered cell surface membranes, e.g.
- autoimmune haemolytic anaemia secondary to α-methyldopa/penicillin
- thrombocytopenia – quinine
- interstitial nephritis.

Immune complex (formed in slight antigen excess):
- fever, macular papular rash, urticaria, lymphadenopathy and arthralgias
- typically 1 - 3 weeks after the last dose of the drug
- subsides when drug/metabolite is completely eliminated (e.g. penicillin, sulphonamides, phenytoin).

Delayed hypersensitivity mediated by cellular immune mechanism (CD4/CD8):
- local contact dermatitis (parabens/metals) – topical induction (confirm with patch testing)
- systemic – sensitised T cells – pro-inflammatory cytokines → lymphocytic infiltrates, granulomas, hypersensitivity pneumonitis (e.g. gold).

Specific T-cell activation
- A number of reactions are associated with specific T-cell activation; the immunopathogenesis is not fully established.
- Examples of these reactions include maculopapular rashes, erythroderma, eczematous rashes, exfoliative dermatitis, drug fever, and fixed drug reactions (Figs 1 - 4) (barbiturates and sulphonamides are often implicated).
- The presence of CD8+ T lymphocytes has been demonstrated in the peripheral blood and involved skin of patients with drug-induced, delayed, cutaneous hypersensitivity reactions (i.e. morbiliform and bullous exanthematous lesions).

Structural characteristics of drug/biological product
- Peptides/proteins: often IgE mediated or form immune complexes
- Topical exposure to essential oils: contact dermatitis (e.g. camphor oil)
- Low molecular weight (< 1000 D): may cause mixed immune responses due to hapten formation.

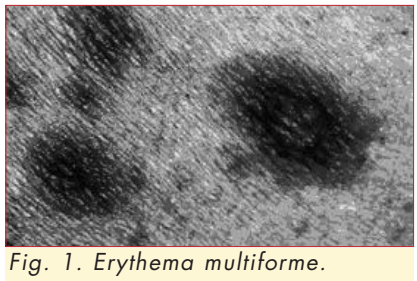


Fig. 1. Erythema multiforme.


Fig. 2. Fixed drug eruption.

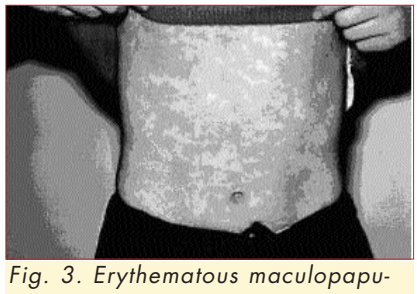


Fig. 3. Erythematous maculopapular eruption.

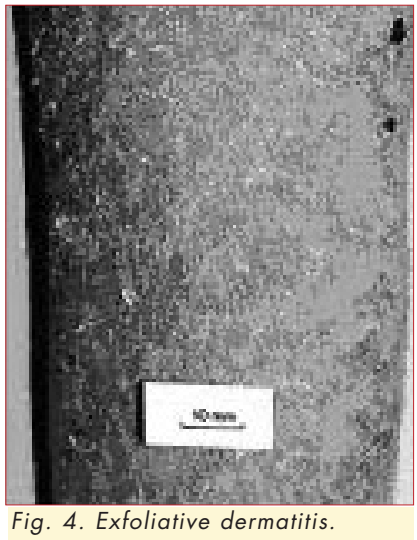


Fig. 4. Exfoliative dermatitis.

RISK FACTORS FOR DRUG ALLERGY

One needs to consider drug factors and host factors when attempting to predict an increased risk of an adverse reaction to a medication.

Drug factors

Chemical properties

- Large molecular mass agents are more likely to induce antibody-mediated reactions, especially in atopic individuals.
- Specific structures (β-lactam ring) may result in cross-sensitivity.

Duration/dose

- Prolonged parenteral administration of a drug is more sensitising than a bolus dose.
- Frequent repetitive courses increase risk of reactions.
- The oral route is less sensitising than the intravenous route.
- Frequent topical applications (e.g. Emla patches/lignocaine) are sensitising (remember local anaesthetics should be used with caution in subjects allergic to aspirin).

Host factors

- True drug allergy is less common in infants and the elderly (immaturity or involution of the immune system).
- Atopic individuals are at a greater risk.
- Women have a 35% ↑ risk of cutaneous reactions.
- Allergy to multiple structurally unrelated antibiotics is more common in women.
- Infants of parents allergic to one antibiotic have a 15-fold risk of reactions to antibiotics.

Genetics

- HLA-DR3 – if treated with gold/penicillamine the risk of drug-induced nephritis is high.
- Systemic lupus erythematosus patients experience more frequent drug reactions.
- HLA-B1502 is found in 100% of Stevens-Johnson syndrome (SJS) patients sensitive to carbamazepines, compared with 3% of carbamazepine-tolerant patients.

Viral illness

- In the case of a viral illness in conjunction with antibiotics there is a higher risk of an adverse cutaneous reaction:
  - Epstein-Barr virus
  - $HHV_{6/7}$ (human herpesvirus)
  - HIV/AIDS.

MORE ABOUT HIV/AIDS

Adverse reactions to drugs are frequently encountered in patients with HIV/AIDS, particularly those on prophylaxis for *Pneumocystis carinii* pneumonia.

Adverse drug reactions (e.g. sulphonamides)

- The exact pathogenesis is unknown.
- Drug reactions are common and may be related to the degree of immunodeficiency. They cause significant morbidity and mortality.
- Adverse reactions to sulphonamides may complicate treatment/prophylaxis of *Pneumocystis carinii* pneumonia.
- Adverse reactions to sulphonamides may decline with HIV disease/progression (unlike reactions to amoxicillin and TB medications).

In the following cases sulphonamides should be discontinued immediately:

- persistent rash/fever > 5 days
- absolute neutrophil count < 500/mm^3
- hypotension/dyspnoea
- blistering desquamation/mucous membrane involvement.

Patients with adverse cutaneous reactions may tolerate the drug after interruption of treatment/lowering of the dose.

Cross-reactivity between sulphonamides and dapsone is unknown, and patients who react to sulphonamides will usually tolerate dapsone. (Do not rechallenge with sulphonamides if SJS has occurred.)

Common reactions to sulphonamides

- A morbiliform maculopapular rash with/without fever 7 - 12 days after start of therapy.

Less common reactions to sulphonamides

Immediate:

- anaphylaxis
- urticaria/angioedema.

Delayed:

- erythema multiforme – major/minor
- SJS
- toxic epidermal necrolysis
- hepatic/renal
- haematological/immune complex.

Why do HIV/AIDS patients display these reactions?

- The broad spectrum of reactions suggests that most are not IgE mediated
- Possibly:
  - ↑ prevalence of slow acetylation
  - altered activity of oxidative metabolic pathways
- Acute illness may partly explain these reactions (as with any medication).

Adverse drug reactions (other drugs)

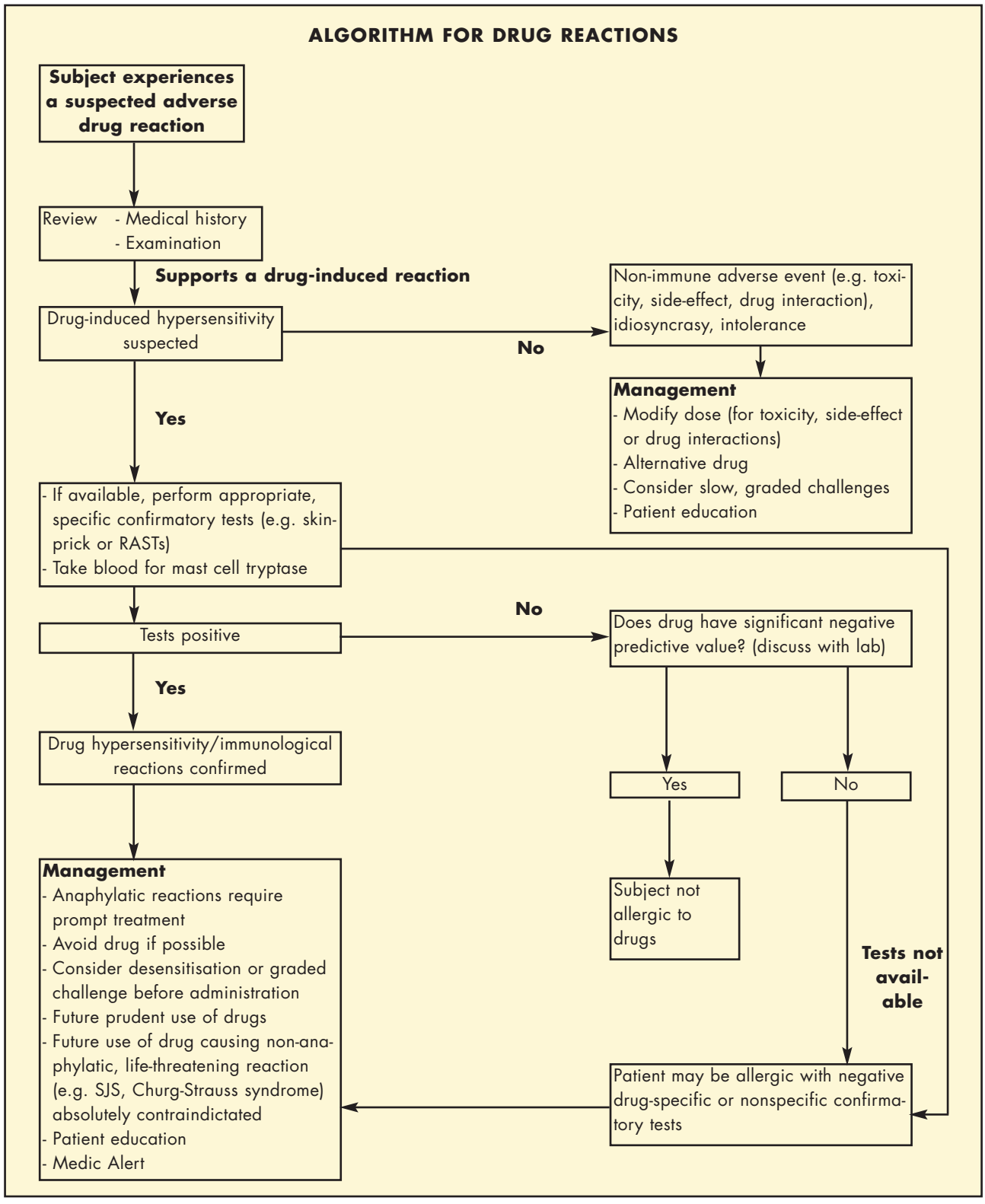
- Anti-TB agents
- Pentamidine
- Amoxicillin/clavulanic acid
- Clindamycin
- Primaquine
- Carbamazepine
- Phenytoin.

ANAPHYLAXIS/MAST CELL TRYPTASE AND DRUGS

- Anaphylaxis refers to a life-threatening syndrome featuring hypotension, bron-

Table I. **Cutaneous reactions to drugs**

Manifestation	Examples
Pruritus, urticaria or angioedema, maculopapular rash	Most drugs (also food additives/colourants) – Cellular Antigen Stimulation Test (CAST)
Contact dermatitis	Antibiotics, ethylenediamine
Photodermatitis	Griseofulvin, sulphonamides
Fixed drug eruption	Metronidazole, penicillin
Toxic epidermal necrosis (potentially life-threatening)	Sulphonamides, phenytoin, carbamazepine, barbiturates, allopurinol



chospasm, angioedema and upper-airway collapse after mast cell degranulation.

- Upon mast cell activation, a variety of mediators are released, including histamine and tryptase.
- Histamine peaks at 5 minutes and declines rapidly within 15 minutes – therefore it is not practical to measure.
- Tryptase is a serine protease which peaks at 1 hour and remains elevated for 4 - 6 hours. It is a sensitive and specific measure of mast cell degranulation.
- The increased levels of tryptase can normally be detected up to 3 - 6 hours after the anaphylactic reaction. Levels return to normal within 12 - 14 hours after release. It is imperative that at least 2 samples are sent as baseline values need to be established.

Fig. 5 demonstrates the tryptase and histamine levels after anaphylaxis.

MORE ABOUT PENICILLIN AND CEPHALOSPORIN (Figs 6 and 7)

- Only 15% of patients with a history of penicillin allergy will have a positive penicillin test.
- Ninety-eight per cent of the above patients will tolerate a cephalosporin.
- Of the 2% who do not tolerate a cephalosporin, 1% may have fatal anaphylaxis.
- If doubt exists about the diagnosis and a suitable alternative first-line antibiotic is available, rather use the *alternative drug*.

MORE ABOUT ASPIRIN/SALICYLATE

Drugs that cross-react with aspirin

All non-steroidal anti-inflammatory agents have the potential to cross-react with aspirin:

- COX inhibitors (e.g. diclofenac)
- selective COX-2 inhibitors (e.g. meloxicam)
- specific cyclo-oxygenase-2 inhibitors (e.g. valdecoxib).

Complications of aspirin ingestion

- Toxicity
  Gastrointestinal: heartburn, epigastric pain, vomiting, bleeding
  Renal: cells, casts, albumin in the urine
  Reye's syndrome

- Intolerance
  Asthma
  Rhinitis
  Nasal polyposis
  Urticaria
  Laryngeal oedema

- Allergy
  Anaphylaxis (rare)
  Note: be aware of naturally occurring salicylates in foods (e.g. paprika).

DRUG REACTIONS AND THE SKIN

Drug-induced rashes are the commonest side-effect of many drugs. Only about 10% of such reactions result from true allergic mechanisms. Typical examples of drug-induced rashes include erythe-

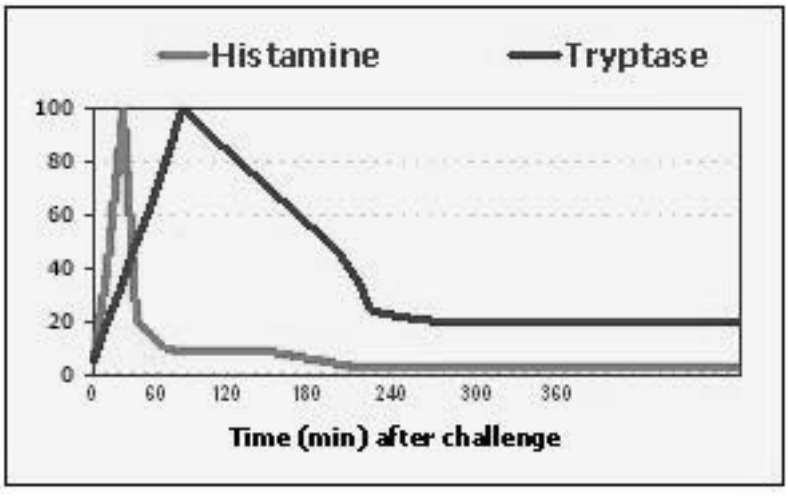


Fig. 5. Tryptase and histamine levels after anaphylaxis.

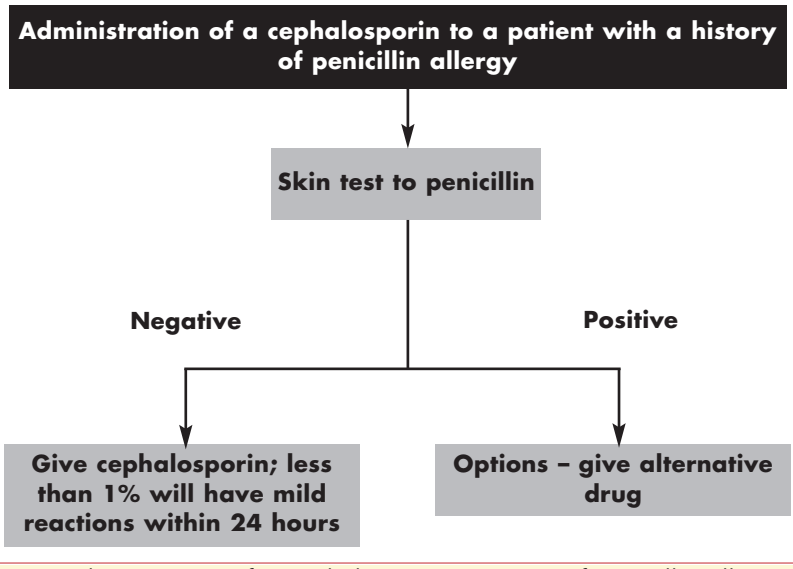


Fig. 6. Administration of a cephalosporin in a case of penicillin allergy.

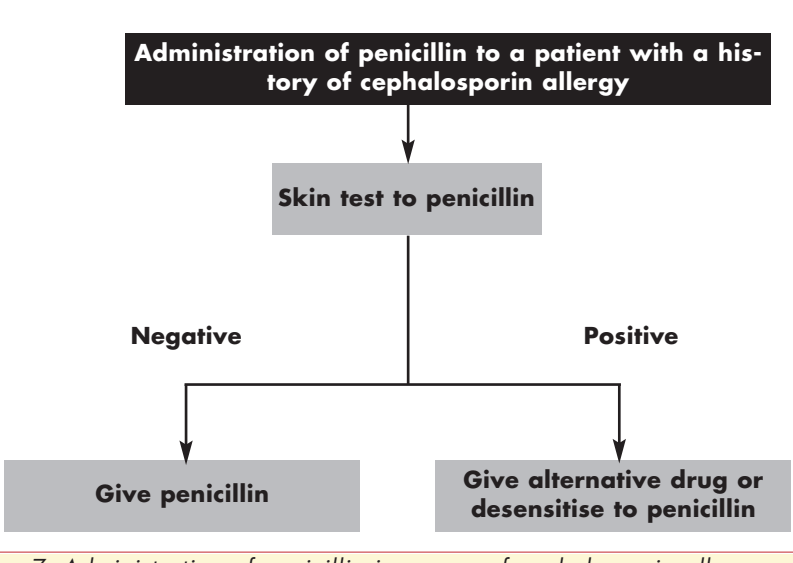


Fig. 7. Administration of penicillin in a case of cephalosporin allergy.

matous maculopapular eruptions, fixed drug eruptions, erythema multiforme, and exfoliative dermatitis (Table I).

CONFIRMATORY TESTS FOR SUSPECTED ALLERGIES

Skin tests

- Available for penicillins and local anaesthetics – only at specialist centres.
- By special arrangement other drugs, e.g. insulin, anaesthetic agents, can be tested. All testing should be performed at a centre with resuscitation facilities.

RAST

- Penicillin and cephalosporin available (2 ml clotted blood).

CAST (Sulphido Leukotriene Release)

- Cellular antigen stimulation test
- Available for some antibiotics, anaesthetic agents, and food additives.

Mast cell tryptase

- To confirm mast cell degranulation
- Nonspecific test
- Serial bloods (5 ml clotted) are informative.

Patch testing

- Available at specialist dermatology centres.

CONCLUSION

Drug allergies are often difficult to confirm and for the majority of drugs no confirmatory tests are available. The diagnosis can often be made by a careful history of every drug taken, including prescription drugs, OTC preparations and herbal medicines or supplements.

Further reading available on request.

IN A NUTSHELL

Adverse reactions to drugs are common, and almost any drug can cause an adverse reaction.

True drug allergies occur when there is an allergic/hypersensitivity reaction with an immune basis. There is usually antibody production and/or histamine release (or sulphido-leukotriene release).

Most adverse reactions to drugs cause minor skin rashes.

The drug that most commonly causes reactions is penicillin. Penicillin reactions may affect most organs or systems and may cause a range of pathologies.

In suspected anaphylaxis, serial tryptase measurements may confirm the diagnosis.

There is no laboratory test to confirm SJS. It is diagnosed clinically and the drugs should not be reintroduced.