Drug allergy

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Outline

1. Background
2. SCAR
3. Mechanism of action
4. Assessment on history
5. Investigations
6. Drug desensitisation
7. Specific drugs
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Adverse drug reactions

- WHO 1966 definition\(^1\)
  - An adverse drug reaction is any noxious, unintended, undesired effect of a drug
  - Occurring at doses used in humans for prevention, diagnosis or treatment

Hospitalised patients

- 15.1% of patients
- Nearly half being serious in nature\(^1\)
- Fatal ADRs in 0.32%

Outpatients

- 17-25% of patients
- More than half being serious in nature\(^2,3\)

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Epidemiology
IgE mediated drug allergy

- Penicillin allergy
  - Self-reported versus post-assessment
    - Rate of self-reported penicillin allergy is 10%\(^1\)
    - Following evaluation > 90% are able to tolerate drug \(^2,3\)
  - Why bother?
    - More likely to be treated with expensive, broad-spectrum antibiotics \(^4\)
    - This can lead to development and spread of multi-drug resistant bacteria


1. National database analysis of anaphylaxis deaths and hospital admissions in Australia over 8 years (1998-2005)
2. Peak age-specific hospital admissions rates were for the 55-84 year age group
1. Most deaths (73%) occurred in adults > 55 yo; all penicillin-induced deaths occurred between persons 35-74 years of age.

2. Significant co-morbidities included: a) ischaemic heart disease or dysarrhythmias (n = 21), b) obstructive airway disease (n = 11), c) mastocytosis (n = 1) and d) hypogammaglobulinemia (n = 1).

Department of Allergy and Immunology

Drug-induced anaphylaxis admissions
1. Estimated multiplicative rate increase of 1.06 per year (P < 0.0001)

Food-induced anaphylaxis admissions
Estimated multiplicative rate increase of 1.12 per year (P < 0.0001)

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# Adverse drug reactions

## Table 1

**Classification of adverse drug reactions**

<table>
<thead>
<tr>
<th>Reactions</th>
<th>Example</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predictable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overdosage</td>
<td>Acetaminophen</td>
<td>Hepatic necrosis</td>
</tr>
<tr>
<td>Side effect</td>
<td>Albuterol</td>
<td>Tremor</td>
</tr>
<tr>
<td>Secondary effect</td>
<td>Clindamycin</td>
<td><em>Clostridium difficile</em> pseudomembranous colitis</td>
</tr>
<tr>
<td><strong>Drug–drug interaction</strong></td>
<td>Terfenadine/erythromycin</td>
<td>Torsade de pointes arrhythmia</td>
</tr>
<tr>
<td><strong>Unpredictable</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intolerance</td>
<td>Aspirin</td>
<td>Tinnitus (at usual doses)</td>
</tr>
<tr>
<td>Idiosyncratic</td>
<td>Chloroquine</td>
<td>Hemolytic anemia in G6PD-deficient patient</td>
</tr>
<tr>
<td><strong>Allergic</strong></td>
<td>Penicillin</td>
<td>Anaphylaxis</td>
</tr>
<tr>
<td>Pseudoallergic</td>
<td>Radiocontrast material</td>
<td>Anaphylactoid reaction</td>
</tr>
</tbody>
</table>

*Predictable, or type A, reactions occur in otherwise normal patients, are generally dose-dependent, and related to the known pharmacologic actions of the drug.*

*Unpredictable, or type B, reactions occur only in susceptible individuals, are dose-independent, and not related to the pharmacologic actions of the drug.*
<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Mechanisms</th>
<th>Clinical Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (immediate)</td>
<td>IgE mediated</td>
<td>Urticaria, Angioedema, Anaphylaxis, Anaphylactic shock, Bronchial asthma, Rhinitis, conjunctivitis</td>
</tr>
<tr>
<td>Type II (cytotoxic)</td>
<td>Antibody mediated</td>
<td>Immune hemolytic anemia, Thrombocytopenia, Blood cell dyscrasias, Organ-specific reactions</td>
</tr>
<tr>
<td>Type III (immunocomplex)</td>
<td>Immunocomplex mediated</td>
<td>Serum sickness-like syndrome, Vasculitis, Organ-specific reactions</td>
</tr>
<tr>
<td>Type IV (delayed)</td>
<td>T cell mediated</td>
<td>Maculopapular exanthema, SJS, TEN, Organ-specific reactions, AGEP, DRESS/DHIS, Fixed drug eruption, Contact eczema, Delayed urticaria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IV a</th>
<th>Type IV b</th>
<th>Type IV c</th>
<th>Type IV d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune reactant</strong></td>
<td>IgE</td>
<td>IgG</td>
<td>IgG</td>
<td>IFNγ, TNFα (T_{H1} cells)</td>
<td>IL-5, IL-4/IL-13 (T_{H2} cells)</td>
<td>Perforin/Granzyme B (CTL)</td>
<td>CXCL-8 GM-CSF (T-cells)</td>
</tr>
<tr>
<td><strong>Antigen</strong></td>
<td>Soluble antigen</td>
<td>Cell-or matrix-associated antigen</td>
<td>Soluble antigen</td>
<td>Soluble antigen presented by cells or direct T cell stimulation</td>
<td>Soluble antigen presented by cells or direct T cell stimulation</td>
<td>Cell-associated antigen or direct T cell stimulation</td>
<td>Soluble antigen presented by cells or direct T cell stimulation</td>
</tr>
<tr>
<td><strong>Effector cells</strong></td>
<td>Mast-cell activation (phagocytes, NK cells)</td>
<td>FcR⁺ cells</td>
<td>Complement immune complex</td>
<td>Macrophage activation</td>
<td>Eosinophils</td>
<td>T cells</td>
<td>Neutrophils</td>
</tr>
</tbody>
</table>

![Diagram](image)

**Example of hypersensitivity reaction**
- Allergic rhinitis, asthma, systemic anaphylaxis
- Hemolytic anemia, thrombocytopenia
- Serum sickness, Arthus reaction
- Tuberculin reaction, contact dermatitis (with IVc)
- Chronic asthma, chronic allergic rhinitis, maculopapular exanthema with eosinophilia
- Contact dermatitis, maculopapular and bullous exanthema, hepatitis
- AGEP Behçet disease

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SCARs
Severe cutaneous adverse reactions

- Comprises of:
  1. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)
  2. Acute generalised exanthematous pustulosis (AGEP)
  3. Hypersensitivity syndrome (HSS)
    - Drug reaction with eosinophilia and systemic symptoms (DRESS)
    - Drug-induced hypersensitivity syndrome (DiHS)

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SJS

- **Time course**
  - Prodromal illness of fever, sore throat and conjunctivitis for 1-3 days.
  - Mucosal lesions appear, followed by cutaneous lesions.

- **Cutaneous lesions**
  - AKA Erythema multiforme (target lesions)
  - Begin as erythematous macules with dusky centres
  - Flacid blisters then appear as the necrotic epidermis detaches from the dermis

SJS

- Prominent mucosal lesions
  - Conjunctiva
  - Oral mucosa
  - Genital mucosa
  - Trachea, bronchi
  - Gastrointestinal tract

- Systemic features
  - High fevers
  - Lymphadenopathy
  - Arthralgia
  - Arthritis

Spectrum of SJS and TEN

**SJS**
< 10% of BSA

**SJS/TEN**
10-30% of BSA

**TEN**
> 30% of BSA

**MORTALITY**

10%

30%

50%


SJS and TEN

**Culprit ‘high-risk’ drugs**

1. Anti-infective sulphonamides: cotrimoxazole, sulfasalazine, sulfadiazine, sulfadoxine, sulfafurazole
2. Allopurinol
3. Antiepileptics: carbamazepine, lamotrigine, phenytoin, phenobarbital
4. Oxicam-NSAIDs: meloxicam, piroxicam, tenoxicam
5. Nevirapine

**Not associated**

1. Beta-blockers
2. ACE inhibitors
3. Calcium channel blockers
4. Sulphonamide-relate diuretics
5. Sulfonylurea anti-diabetics
6. Insulin
7. Propionic acid NSAIDs

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Acute generalised exanthematous pustulosis (AGEP)

- Also known as
  - Toxic pustuloderma
  - Pustular drug rash
  - Pustular psoriasiform eruption with leukocytosis

- Characterised by
  - Acute appearance of dozens of pustules, on the background of oedematous erythema
  - Pustules are sterile, non-follicular, pinhead-sized

Acute generalised exanthematous pustulosis (AGEP)

- Clinical features (cont)
  - Accentuated in main folds
  - Facial oedema
  - Rarely mucous membrane involvement
  - Systemic symptoms e.g. fever, leucocytosis

Acute generalised exanthematous pustulosis (AGEP)

- **Typical time course**
  - Skin symptoms arise rapidly (hours)
  - Resolve quickly (within days) without treatment

- **Time of onset**
  - Antibiotics: 1 day
  - All other associated drugs: 11 days

Acute generalised exanthematous pustulosis (AGEP)

- **Aetiology**
  - Antimicrobials: pristinamycin, aminopenicillins, quinolones, sulphonamides, terbinafine
  - Hydroxychloroquine
  - Diltiazem

- **Complications**
  - Rare
  - Usually in elderly or patients with poor medical health
  - Amongst 97 patients with validated cases of AGEP, death rate was 4%

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  2. Acute generalised exanthematous pustulosis (AGEP)
  3. Hypersensitivity syndrome (HSS)
     - Drug reaction with eosinophilia and systemic symptoms (DRESS)
     - Drug-induced hypersensitivity syndrome (DiHS)

Hypersensitivity syndrome (HSS)

• Traditionally used to summarise numerous severe drug reactions $^{1,2}$
• More recently, 2 other denominations were created $^{3,4}$

Drug rash with eosinophilia and systemic symptoms (DRESS)

Drug induced Hypersensitivity Syndrome (DiHS)

HSS/DRESS/DiHS

- Clinical features
  - Diagnosis of exclusion
  - Variable presentation
  - High fever is usually first noted
  - Then widespread skin rash: erythematous, papular and pustular
  - Also
    - Multi-organ involvement
    - Eosinophilia
HSS/DRESS/DiHS

- **Timing**
  - Onset usually later: 2-8 weeks after therapy started
  - Duration usually longer
  - This makes recognition of drug as a cause difficult

- **Culprit drugs**
  - Aromatic anticonvulsants: carbamazepine, phenytoin, phenobarbitone
  - Others: minocycline, allopurinol, thalidomide, sulfonamides, anti-retrovirals

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4. Khan et al. 2010; Journal of Allergy and Clinical Immunology 125:S126-37
SCARs
Severe cutaneous adverse reactions

- Take home points
  - Important to recognise these conditions
  - Although rare, high morbidity and mortality
  - Presents as a contraindication to skin testing and drug provocation testing
### Pharmacogenetics

**TABLE I.** Recent HLA associations with DIHS/DRESS and SJS/TEN

<table>
<thead>
<tr>
<th>Drug toxicity syndrome/drug</th>
<th>Ethnicity</th>
<th>Allele</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SJS/TEN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Han Chinese, Japanese, Thai</td>
<td>HLA-B*5801</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>White subjects</td>
<td>HLA-B*1502</td>
<td>4</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Han Chinese, Thai</td>
<td>HLA-B*1502</td>
<td>5-7</td>
</tr>
<tr>
<td></td>
<td>Malaysians</td>
<td>HLA-B*1511</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Indian</td>
<td>HLA-B*5901</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Japanese</td>
<td>HLA-B*1511</td>
<td>Ikezawa (Yokohama)</td>
</tr>
<tr>
<td>DIHS/DRESS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir</td>
<td>Highest risk in Caucasians but generalizable across ethnicity</td>
<td>HLA-B*5701</td>
<td>12-15</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Han Chinese</td>
<td>HLA-B*5801</td>
<td>1</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>White subjects</td>
<td>HLA-DRB1*0101</td>
<td>16</td>
</tr>
<tr>
<td>Rash associated hepatitis with CD4+ T cells 25% or greater</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIHS/DRESS</td>
<td>Sardinian</td>
<td>HLA-Cw8-B14 haplotype</td>
<td>17</td>
</tr>
<tr>
<td>DIHS/DRESS</td>
<td>Japanese</td>
<td>HLA-Cw8</td>
<td>18</td>
</tr>
<tr>
<td>DIHS/DRESS</td>
<td>Thai</td>
<td>HLA-B*3505</td>
<td>19</td>
</tr>
<tr>
<td>DIHS/DRESS with rash (no liver function tests done)</td>
<td>HLA-B*3505</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>DIHS/DRESS with rash</td>
<td>White subjects</td>
<td>HLA-B*3501</td>
<td>20</td>
</tr>
</tbody>
</table>

**FIG 2.** Number needed to test (NNT) to prevent 1 case of specific drug reaction. Numbers shown are for abacavir hypersensitivity, allopurinol-associated SJS/TEN/drug hypersensitivity, CBZ-associated SJS/TEN, and fluvoxacillin-associated drug-induced liver disease. Adapted from Phillips and Mallal.24

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Pathogenesis

**Low molecular weight drugs**
- Metabolised or bioactivated

**High molecular weight drugs**
- Spontaneously degrade e.g. penicillin

**Drug reaction via:**
1. Binding to nucleic acids → produce altered gene product
2. Binding to macromolecules → cause direct cellular damage
3. Binding covalently to larger macromolecules → form immunogenic complex and induce immune response (haptenization)

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History

- What was the name of the medication?
  - Penicillin vs amoxycillin vs augmentin

- Underlying illness
  - E.g. Cellulitis versus viral upper respiratory tract infection

- Time course and duration of symptoms

- Rash appearance
  - Mucous membrane involvement?
  - Urticarial vs bullous vs exfoliative vs morbiliform?

- Systemic involvement
  - Gastrointestinal, respiratory, arthropathy, fever

History

- Concurrent medications prescribed?
  - E.g. Narcotics, NSAIDs

- Previous course of same/similar medication?
  - May suggest past sensitisation

- Previous episodes of similar symptoms in the absence of drug treatment?
  - Suggestive of idiopathic urticaria

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Investigations

- **Commonly performed**
  1. Skin prick test
  2. Intradermal test
  3. Drug provocation test (challenge)

- **Less commonly used**
  1. Serum sIgE
  2. Basophil activation assay
  3. Patch testing
Investigations (less used)

1. Serum sIgE
   - Detects antigen-specific IgE antibodies in subject’s serum
   - Most are not adequately validated
   - Unclear specificity and sensitivity
   - Difficult to bind drug allergens to solid-phase matrices

2. Basophil activation test

- Uses flow cytometry to quantify the expression of activation markers (CD63 or CD203C) on basophils after stimulation with an allergen\(^1\)
- Currently there is only limited data using this method to evaluate patients with possible drug allergies\(^1\)
- Diagnostic sensitivity and specificity is poor when directly compared to skin testing\(^2\)

3. Drug patch testing\textsuperscript{1,2}

- Patches placed on the upper back
- Read at 20 minutes, with delayed readings at 48 hours, 96 hours and (if negative) 7 days.
- Might be useful for presumed non-IgE delayed cutaneous drug reactions e.g. maculopapular exanthems, AGEP, fixed drug eruptions
- Not helpful for SJS or urticarial reactions

\textsuperscript{1} Khan DA and Solensky R. Drug allergy. JACI 2010;125:s126-37.
Investigations (common)

- Skin prick test
- Intradermal skin test
- Drug challenge
Intradermal skin testing

- A tuberculin, 0.5 mL insulin syringe or 1mL syringe with a 25- to 27-gauge needle is used
- 0.02-0.05 mL of allergen is injected into the dermis, producing a 2- to 3-mm-diameter bleb
- Test is performed over the volar aspect of the forearm

2. Figure: Kranke B and Aberer W. Skin testing for IgE-mediated drug allergy. Immunol Allergy Clin N Am 2009;29:503-516.
Intradermal skin testing

- Scoring method
  - European Network for Drug Allergy (ENDA) position paper in 2003
    • Read at 15-20 minutes after performance of test
    • Positive if wheal increased by > 3 mm with an associated flare, when compared to initial wheal
  - Alternate scoring system
    • Positive intradermal test when any wheal diameter is > 5 mm
    • This method has been used in a number of European studies 2,3,4,5

Intradermal skin testing

- University Hospital of Montpellier, France
  - 8.8% (13/998) of patients developed systemic reactions to skin tests performed for beta-lactams between 1996-2004

### TABLE I. Description of the patients with generalized reactions during positive skin tests*

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Type of reaction in clinical history</th>
<th>Chronology in clinical history</th>
<th>ST</th>
<th>Reactive concentration</th>
<th>Positive ST</th>
<th>Type of reaction after ST</th>
<th>Delay after ST</th>
</tr>
</thead>
<tbody>
<tr>
<td>51</td>
<td>M</td>
<td>A shock</td>
<td>&lt;1 h</td>
<td>Prick (1/1)</td>
<td>PPL, Cfr</td>
<td>Anaphylaxis</td>
<td>&lt;30 min</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>F</td>
<td>Anaphylaxis</td>
<td>&lt;1 h</td>
<td>ID (1/10)</td>
<td>Amp, MDM, PPL, PG</td>
<td>A shock</td>
<td>&lt;1 h</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>M</td>
<td>A shock</td>
<td>&lt;1 h</td>
<td>Prick (1/1)</td>
<td>Amx, Amp</td>
<td>Anaphylaxis</td>
<td>&lt;30 min</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>F</td>
<td>Anaphylaxis</td>
<td>&lt;1 h</td>
<td>Prick (1/10)</td>
<td>Amx, Amp, MDM, PPL, PG, Cfr, Cfla</td>
<td>A shock</td>
<td>&lt;15 min</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>F</td>
<td>A shock</td>
<td>&lt;1 h</td>
<td>ID (1/10)</td>
<td>Amx, Amp, Amx+cclav, PG</td>
<td>A shock</td>
<td>&lt;1 h</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>Urticaria</td>
<td>NA</td>
<td>ID (1/1)</td>
<td>Amx, Amp</td>
<td>G urticaria</td>
<td>14 h</td>
<td></td>
</tr>
<tr>
<td>58</td>
<td>F</td>
<td>Urticaria</td>
<td>12 h</td>
<td>ID (1/1)</td>
<td>PPL</td>
<td>G urticaria</td>
<td>&lt;1.5 h</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>F</td>
<td>Anaphylaxis</td>
<td>&lt;1 h</td>
<td>ID (1/1)</td>
<td>Amx</td>
<td>Anaphylaxis</td>
<td>&lt;1.5 h</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>M</td>
<td>A shock</td>
<td>&lt;1 h</td>
<td>Prick (1/10)</td>
<td>Amx, MDM, PG</td>
<td>Anaphylaxis</td>
<td>&lt;15 min</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>F</td>
<td>Anaphylaxis</td>
<td>&lt;1 h</td>
<td>ID (1/1)</td>
<td>Amx, PPL, MDM</td>
<td>A shock</td>
<td>&lt;1.5 h</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>F</td>
<td>Anaphylaxis</td>
<td>&lt;1 h</td>
<td>ID (1/10)</td>
<td>Amx, Amp, PPL, MDM, PG, Cfr</td>
<td>Anaphylaxis</td>
<td>&lt;1 h</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>M</td>
<td>Anaphylaxis</td>
<td>&lt;1 h</td>
<td>ID (1/1)</td>
<td>Amx</td>
<td>Anaphylaxis</td>
<td>&lt;1.5 h</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>F</td>
<td>Macular eruption</td>
<td>NA</td>
<td>Prick (1/1)</td>
<td>Amx, Amp, PPL, PG</td>
<td>G urticaria</td>
<td>&lt;30 min</td>
<td></td>
</tr>
</tbody>
</table>

*Amx, Amoxicillin; Amp, ampicillin; A shock, anaphylactic shock; Cfla, cefalotin; Cfrd, cefradine; Cfm, cefotaxime; Cfr, ceftriaxone; Cfur, cefuroxime; G urticaria, generalized urticaria; ID, intradermal test; MDM, minor determinant mixture; NA, not available; PG, penicillin G; PPL, penicilloyl polyclysine; ST, skin tests.

*Chronology: time between last drug intake and clinical reaction; delay: time between the first prick test and reaction after ST.

Co Minh et al. JACI 2006; 117:466-468
Drug challenge

- Gold standard for determining if a patient is tolerant or allergic to a particular drug
- Patient is admitted to hospital for 4 hours
- Graded doses of the index drug is administered, starting typically at 1/100th of the final treatment dose
- Patient then completes the medication course at home
- Contraindications: SJS, TEN, DRESS

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Drug desensitisation

- New term is ‘drug tolerance induction’, as procedure is used for both IgE and non-IgE mediated drug allergies
- Indicated where there is an absolute need for a particular drug and no suitable alternative exists
- Aim is to allow the patient to temporarily tolerate the drug in a safe manner (through immunologic or other non-immunologic mechanisms)

Drug desensitisation

- General principles
  - The amount of drug tolerated by patient during the skin test determines a safe initial dose (usually 1/10,000th of the final treatment dose)
  - Double dose every 15 minutes until final dose
  - Mild reactions occur in about 1/3 of patients, but no fatal reactions have been reported
  - In order for patient to remain desensitised, it is necessary to continually administer medication

Table 7
Penicillin intravenous desensitization protocol with drug added by piggyback infusion

<table>
<thead>
<tr>
<th>Step</th>
<th>Penicillin (mg/mL)</th>
<th>Amount (mL)</th>
<th>Dose given (mg)</th>
<th>Cumulative dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>0.2</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>0.4</td>
<td>0.04</td>
<td>0.07</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>0.8</td>
<td>0.08</td>
<td>0.15</td>
</tr>
<tr>
<td>5</td>
<td>0.1</td>
<td>1.6</td>
<td>0.16</td>
<td>0.31</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0.32</td>
<td>0.32</td>
<td>0.63</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>0.64</td>
<td>0.64</td>
<td>1.27</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>1.2</td>
<td>1.2</td>
<td>2.47</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>0.24</td>
<td>2.4</td>
<td>4.87</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>0.48</td>
<td>4.8</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>1</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>2</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>13</td>
<td>100</td>
<td>0.4</td>
<td>40</td>
<td>80</td>
</tr>
<tr>
<td>14</td>
<td>100</td>
<td>0.8</td>
<td>80</td>
<td>160</td>
</tr>
<tr>
<td>15</td>
<td>100</td>
<td>1.6</td>
<td>160</td>
<td>320</td>
</tr>
<tr>
<td>16</td>
<td>1000</td>
<td>0.32</td>
<td>320</td>
<td>640</td>
</tr>
<tr>
<td>17</td>
<td>1000</td>
<td>0.64</td>
<td>640</td>
<td>1280</td>
</tr>
</tbody>
</table>

Observe patient for 30 minutes, then give full therapeutic dose by the desired route.

a Interval between doses is 15 minutes.

Outline

1. Background
2. SCAR
3. Mechanism of action
4. Assessment on history
5. Investigations
6. Drug desensitisation
7. Specific drugs
Specific drugs

1. Beta-lactams
   • Penicillins
   • Cephalosporins
2. Sulfonamides
3. Perioperative
4. Radiocontrast media
5. Aspirin & NSAIDs
Specific drugs

1. Beta-lactams
   - Penicillins
   - Cephalopsorins
2. Sulfonamides
3. Perioperative
4. Radiocontrast media
5. Aspirin & NSAIDs
Beta-lactams: Penicillins

Beta-lactams: Penicillins

Penicillins

Thiazolidine ring

Beta-lactams: Penicillins

R1 side chain

Penicillins

### Structural similarities and differences of penicillin side-chains

<table>
<thead>
<tr>
<th>R⁻</th>
<th>R⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Benzylpenicillin" /></td>
<td><img src="image" alt="Ampicillin" /></td>
</tr>
<tr>
<td><img src="image" alt="Phenoxy methylpenicillin" /></td>
<td><img src="image" alt="Amoxicillin" /></td>
</tr>
<tr>
<td><img src="image" alt="Ticarcillin" /></td>
<td><img src="image" alt="Azlocillin" /></td>
</tr>
<tr>
<td><img src="image" alt="Oxacillin" /></td>
<td><img src="image" alt="Mezlocillin" /></td>
</tr>
<tr>
<td><img src="image" alt="Cloxacillin" /></td>
<td><img src="image" alt="Piperacillin" /></td>
</tr>
<tr>
<td><img src="image" alt="Dicloxacillin" /></td>
<td></td>
</tr>
<tr>
<td><img src="image" alt="Flucloxacinil" /></td>
<td></td>
</tr>
</tbody>
</table>

Baldo BA. Penicillins and cephalosporins as allergens – structural aspects of recognition and cross-reactions. Clinical and Experimental Allergy 199;29:744-749
Beta-lactams: Penicillins

Penicillins

Penicilloate

Penilloate

~ 95%

Suggested reagent panel

• Classical penicillin reagents: PPL, MDM and benzylpenicillin
• Semi-synthetic penicillins: Amoxycillin and ampicillin

Investigations

Skin prick test → Intradermal skin test → Drug challenge
NPV of Penicillin testing

- Generally considered to be very high
- Large scale studies show that only 1-3% of skin test-negative patients develop a mild, self-limiting reaction when challenged to the drug
  - Gadde et al. *JAMA* 1993; 270: 2456-63 (n = 775)
  - Mendelson et al. *JACI* 1984; 73: 76-81 (n = 240)

Cephalosporin cross-reactivity

Cephalosporin cross-reactivity

Cephalosporin cross-reactivity

R1 side chain: implicated in cross-reactivity

Cephalosporin cross-reactivity

R2 side chain: disappears after beta-lactam ring opens

Cephalosporin cross-reactivity

- Historical “10%” cross-reactivity – a myth?
  - Until 1982, compounds related to penicillin had been produced by using a cephalosporium mould and the cephalosporins included in the analyses were contaminated with penicillin¹
  - Patients were not proven to be penicillin-allergic (either through diagnostic testing or drug challenge)⁴
  - Most 1ˢᵗ gen cephalosporins have similar R-group side chains to benzylpenicillin, and this factor (rather than beta-lactam ring) may have led to cross-reactivity²

1. Preger S and Healy B. BMJ 2007;335:991
Cephalosporin cross-reactivity

- In a recent meta-analysis
  - 6 studies of 2387 patients with penicillin allergy and 44,897 without
  - Cross-reactivity was found to be related to cephalosporin generation
    - 1st generation – OR 4.79 (95%CI 3.71-6.17)
    - 2nd generation – OR 1.13 (95%CI 0.61-2.12)
    - 3rd generation – OR 0.45 (95%CI 0.18-1.13)

- Implications
  - For life-threatening conditions where it is optimal to use a cephalosporin antibiotic in a penicillin-allergic patient
  - Consider use of a 2nd or 3rd generation cephalosporin with a different side chain under suspicion

Specific drugs

1. Beta-lactams
   - Penicillins
   - Cephalosporins
2. Sulfonamides
3. Perioperative
4. Radiocontrast media
5. Aspirin & NSAIDs
Sulfonamides

**Pathogenesis**
- Likely T-cell-mediated mechanism (rather than specific IgE or IgG antibodies)\(^1\)
- Increased risk in HIV-positive patients, due to: altered drug metabolism (slow acetylation), relative glutathione deficiency and viral stimulation of cytochrome p450 and gamma-interferon\(^2\)

**Clinical\(^2\)**
- Mostly causes delayed generalised maculopapular eruptions, associated with fever and pruritus

Fig. 4. Structure of sulfamethoxazole—the prototype sulfonamide antibiotic. Nonantibiotic sulfonamides lack an N4 aromatic amine group and N1 substituted ring, which are important for allergic reactions to sulfonamide antibiotics.


<table>
<thead>
<tr>
<th>Table 1. Sulfonamide Nonantibiotic Drugs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetazolamide</td>
</tr>
<tr>
<td>Acetohexamidine</td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
</tr>
<tr>
<td>Benzthiazide</td>
</tr>
<tr>
<td>Bumetanide</td>
</tr>
<tr>
<td>Chlorothiazide</td>
</tr>
<tr>
<td>Chlorpropamide</td>
</tr>
<tr>
<td>Chlorthalidone</td>
</tr>
<tr>
<td>Clopamide</td>
</tr>
<tr>
<td>Clorestylone</td>
</tr>
</tbody>
</table>

Strom et al. NEJM 2003;349:1628-35
Specific drugs

1. Beta-lactams
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   • Cephalosporins
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3. Perioperative
4. Radiocontrast media
5. Aspirin & NSAIDs
Perioperative anaphylaxis

• **Background**
  - Occurs in 1 every 1250 to 10,000 anaesthetics

• **Causes**
  - Neuromuscular blocking agent (NMBA) – 50-70%
  - Latex allergy
  - Antibiotic allergies
  - Uncommon: hypnotic agents, opioids, colloids, aprotinin, protamine
  - Increasingly reported: dyes, chlorhexidine, NSAIDs
Perioperative anaphylaxis

- **NMBA**
  - Occurs in the induction phase of anaesthesia
  - Commonly succinylchloine (depolarising NMBA)
  - Cross-reactivity between NMBA is common (50-70%)
    - ↑ in aminosteroid NMBA: pancuronium, vecuronium, rocuronium
    - ↓ in benzylisoquinolone-derived NMBA: atracurium, cisatracurium (lowerst incidence of anaesthetic anaphylaxis)

- **Latex allergy**
  - Contact urticaria: to latex gloves
  - Anaphylaxis: occurs in the maintenance phase of anaesthesia
  - Risk factors: multiple operations (abdo, gynae, ortho), atopic predisposition, spina bifida (VP shunt)
  - Ix: SPT, sIgE, latex glove challenge
## Local anaesthetics

<table>
<thead>
<tr>
<th>Benzoate esters</th>
<th>Amides</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzocaine</td>
<td>Bupivacaine</td>
</tr>
<tr>
<td>Chloroprocaine</td>
<td>Levobupivacaine</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Lidocaine (lignocaine)</td>
</tr>
<tr>
<td>Procaine</td>
<td>Mepivacaine</td>
</tr>
<tr>
<td>Proparacaine</td>
<td>Ropivacaine</td>
</tr>
<tr>
<td>Tetracaine (amethocaine)</td>
<td>Prilocaine</td>
</tr>
</tbody>
</table>

- Cross-react with other esters
- Does not cross-react with amides.

- Does not cross-react with either other amides or esters.

Specific drugs

1. Beta-lactams
   • Penicillins
   • Cephalosporins
2. Sulfonamides
3. Perioperative
4. Radiocontrast media
5. Aspirin & NSAIDs
Radiocontrast media (RCM)

- **Anaphylactoid reactions**
  - 1-3% of patients receiving ionic RCM
  - <0.5% of patients receiving non-ionic RCM

- **Severe life-threatening reactions**
  - 0.22% of patients receiving ionic RCM
  - 0.04% of patients receiving non-ionic RCM

- **Fatality rate**
  - 1-2 per 100,000 procedures

Radiocontrast media (RCM)

Anaphylactoid versus anaphylaxis

• Reaction not mediated by specific IgE antibodies
• RCM likely has direct effects on mast cells and basophils → leads to direct degranulation and systemic mediator release
• Complement activation may also account for some reactions

Radiocontrast media (RCM)

Management

1. Determine if the study is essential
2. Explain risks to patient
3. Ensure proper hydration
4. Use a non-ionic, iso-osmolar RCM
5. Pretreatment with corticosteroid and antihistamine
Specific drugs

1. Beta-lactams
   - Penicillins
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5. Aspirin & NSAIDs
<table>
<thead>
<tr>
<th>Type of reaction</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Aspirin-exacerbated respiratory disease (AERD)        | • Occurs in up to 20% of adult asthmatic patients, more common in women, has an average onset of around 30 yo\(^1\)  
• Usually starts with rhinitis, progressing to sinusitis and nasal polyposis\(^1\)  
• Pathogenesis: aspirin leads to inhibition of COX-1 $\rightarrow$ decrease PGE2 levels $\rightarrow$ reduced inhibition of 5-lipoxygenase $\rightarrow$ increased cysteinyi leukotrienes\(^2\)  
• Management: avoid both aspirin and NSAIDs; aggressive management of asthma and rhinitis\(^2\) |
| Exacerbation of chronic urticaria & angiodema         | • Ingestion of NSAIDs that inhibit COX-1 can exacerbate chronic urticaria & angioedema\(^2\)  
• Most patients tolerate COX-2 inhibitors\(^2\)                                                                                                                                                           |
| Anaphylaxis                                           | • Typically drug-specific and able to tolerate other NSAIDs\(^3\)                                                                                                                                 |

Summary points

1. Severe cutaneous drug reactions
   - SJS, TEN, AGEP, HSS (DRESS)
   - Can cause significant morbidity and mortality
   - Important to exclude these conditions as they present as contraindications for IDT and drug challenge

2. Investigations
   - Commonly used: SPT, IDT and drug challenge
   - Less useful: serum specific IgE, basophil activation assays and patch testing
3. Penicillin allergy

- Majority (90%) of self-reported penicillin allergic patients are actually tolerant following evaluation and drug challenge
- IDT is performed to the
  - Major determinant: benzylpenicilloyl
  - Minor determinant
  - Side chains: amoxycillin and ampicillin
- NPV for intradermal skin testing is good (97-99%)
Summary points

4. Penicillin and cross-reactivity with cephalosporins

- Previous 10% cross-reactivity rates are likely overestimated
- Cross-reactivity with cephalosporins are most likely due to similarities of R1-side chains (rather than sensitisation to beta-lactam ring)
- If skin testing is negative, patients have a high likelihood of tolerating a 3rd generation cephalosporin