Definitions

Drug hypersensitivity reactions (DHRs)

Drug allergy
Definitions

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- Any adverse effect of a drug
- May resemble an allergic reaction

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- Any adverse effect of a drug
- May resemble an allergic reaction

Drug allergy
- A type of drug hypersensitivity reaction that has definite immunologic mechanism
- Only 5-10% of adverse reactions to drugs are allergic
Definitions

Predictable reaction (80%)
Related to known pharmacological action of the drug: may occur in any host

- Side-effect - undesirable effect at recommended dose
- Drug interaction – enzyme inducers and inhibitors affect efficacy/toxicity
- Toxic effect – due to excess dose

Unpredictable reaction
Not dose dependent: occurs in susceptible host

- Intolerance – low threshold for normal physiological action of drug
- Idiosyncratic – unexpected due to metabolic or enzymatic deficiency
- Allergic – immune mediated
- Non-allergic (pseudo-allergic/anaphylactoid)
Mechanisms of drug allergy

Gell-Coombs classification (1968)

• Useful in its time

• However it doesn’t account for many common clinical problems such as
  
  erythema multiforme
  AERD
  anticonvulsant hypersensitivity syndrome
  drug-induced lupus, hypersensitivity vasculitis
Gell-Coombs

Type 1 – immediate hypersensitivity

- Minutes – hours

- IgE-drug complex binds to mast cells releasing inflammatory mediators

- Anaphylaxis, urticaria, angioedema, bronchospasm
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Type 2 – antibody-mediated cytotoxic

- Hours – days

- IgM or IgG binds to drug-hapten coated cells

- Autoimmune haemolytic anaemia, thrombocytopenia, interstitial nephritis
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Type 3 – immune complex mediated

• 1-3 weeks

• Drug-antibody complexes deposited in tissues leading to complement activation

• Serum sickness, nephritis, arthralgia, hepatitis, lymphadenopathy, fever, urticaria
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Type 4 – delayed hypersensitivity

- T-cell mediated
- 48-72hrs
- Contact dermatitis, Mantoux
Gell-Coombs

Type 4 - modification

- IVa: monocytes – eczema/dermatitis
- IVb: eosinophils – DRESS/morbilliform rash
- IVc: CD4+ and CD8+ cells – SJS and TEN
- IVd: neutrophils - AGEP

DRESS= drug rash, eosinophilia and systemic symptoms
AGEP= acute generalised exanthenatous pustulosis
# Gell-Coombs

## Antibody (I-III) and T-cell-orchestrated hypersensitivity reactions (IVa-d)

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
<th>Type IVa</th>
<th>Type IVb</th>
<th>Type IVc</th>
<th>Type IVd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune reactant</td>
<td>IgE</td>
<td>IgG</td>
<td>IgG</td>
<td>IFNγ, TNFα, TH1 cells</td>
<td>IL-5, IL-4/IL-13 (TH2 cells)</td>
<td>Perforin/ granzyme B (CTL)</td>
</tr>
<tr>
<td>Antigen</td>
<td>Soluble antigen</td>
<td>Cell-or matrix-associated antigen</td>
<td>Soluble antigen</td>
<td>Antigen presented by cells or direct T-cell stimulation</td>
<td>Antigen presented by cells or direct T-cell stimulation</td>
<td>Cell-associated antigen or direct T-cell stimulation</td>
</tr>
<tr>
<td>Effector</td>
<td>Mast cell activation</td>
<td>FcR+ cells (phagocytes, NK cells)</td>
<td>FcR+ cells complement</td>
<td>Macrophage activation</td>
<td>Eosinophils</td>
<td>T-cells</td>
</tr>
</tbody>
</table>

### Example of hypersensitivity reaction
- Allergic rhinitis, asthma, systemic anaphylaxis
- Hemolytic anemia, thrombocytopenia (e.g., penicillin)
- 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
- Behcet’s disease

Classification

Immediate
Delayed
Classification

Immediate

- Occur within 1-6 hours after the last drug administration
- Typically within 1st hour
- Typical symptoms include urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, nausea, vomiting, diarrhoea, abdominal pain, anaphylaxis
- Possibly induced by IgE mechanism
- The term "anaphylactoid" is better known as non-allergic DHR
Classification

Delayed

• Non-immediate DHRs occur at any time from 1 hour after the initial drug administration.

• Typical symptoms include maculopapular exanthems and delayed urticaria, blistering diseases, fixed drug eruptions

• Often due to a delayed T-cell dependent mechanism
Immediate and delayed drug reactions

Immediate type:
- Urticaria
- Fixed drug eruption
- Angioedema

Immediate and Non-immediate:
- Recurrent Urticaria

Delayed type:
- Serum sickness
- Exanthema macular, papular, bullous
Risk factors

Drug factors

Chemical properties
- High molecular weight (insulin)
- Specific structures (β lactam ring)

Duration
- Prolonged administration
- Frequent/repeated administration especially topical local anaesthetic, topical anti-histamines

Route
- IV/IM/topical > oral
Risk factors

Host factors

Genetics

- HLA-DR3 – gold/penicillamine
- HLA-B1502 – SJS+carbamazepine
- HLA-B5701 - Abacavir

Viral illness

- EBV, HIV
- HHV6 & 7

Sex/Age

- Females>males
- Young and middle aged adults
Diagnosis

History

- Current and previous use
- Dose
- Frequency
- Route of administration
- Temporal sequence of events from initiation of treatment to onset of symptoms
- Intercurrent illness, esp viral infections/HIV
- Previous medical history
Diagnosis

Examination

- Skin most commonly and prominently affected organ
- Important to characterise the skin lesions
Diagnosis

Skin manifestations may include:
- Maculopapular eruptions
- Urticaria, angioedema
- Fixed drug eruptions
- Photosensitivity
- Bullous lesions
- Vasculitis
- Erythema multiforme
- DRESS, SJS, TEN
Diagnosis

Vasculitis

Mucus membrane involvement

Fixed drug eruption
Diagnosis
Diagnosis

- Rubella
- Roseola
- EBV
- Phenytoin DHR
Diagnosis

Investigations depend on clinical picture

- General investigations
- Drug-specific tests
Diagnosis

General investigations:

- **Full blood count** - Type II reactions: haemolytic anaemia, thrombocytopenia or neutropenia, eosinophilia
- **ESR/CRP** - vasculitis
- **U&E/dipstix** – serum sickness/nephritis/vasculitis
- **C3/ANA/cANCA/pANCA** – vasculitis, drug-induced lupus, Churg-Strauss
- **Coombs** – haemolytic anaemia
- **Skin biopsy**
Diagnosis

Drug-specific investigations:

- Tryptase
- Skin prick test
- Intradermal test
- Patch test
- Immunocap/Specific IgE
- Basophil activation test
- Drug provocation test
Diagnosis

Tryptase

Histamine is the major mediator released from mast cells
• Peaks at 5mins, declines rapidly by 15mins

Tryptase is a sensitive and specific marker of mast cell degranulation
• Helpful in the context of anaphylaxis

• Serum levels peak at 1 hour after a reaction and decline thereafter over 6 hours

• Repeat samples taken at 0, 1 and 6 hours after the event may confirm anaphylaxis
Tryptase

% Maximal level of mediator

Time (min) after venom challenge
Diagnosis

Skin prick tests

The most useful test for diagnosing IgE-mediated drug reactions caused by:

- penicillins
- local anaesthetics
- muscle relaxants
- insulin
- monoclonal antibodies
Diagnosis

Intradermal testing

• Inject various dilutions raising a bleb

• More sensitive than SPT

• Greater risk of causing false positives and reactions/side effects
## Diagnosis

### Dilutions for anaesthetic agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>SKIN PRICK</th>
<th>INTRADERMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suxamethonium</td>
<td>1:1000</td>
<td>1:10 000 → 1:1000 → 1:100</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>1:1000</td>
<td>1:10 000 → 1:1000 → 1:100</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>1:100</td>
<td>1:10 000 → 1:1000 → 1:100</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>1:100</td>
<td>1:10 000 → 1:1000 → 1:100</td>
</tr>
<tr>
<td>Atracurium</td>
<td>1:10</td>
<td>1:10 000 → 1:1000 → 1:100</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>1:10</td>
<td>1:10 000 → 1:1000 → 1:100</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>1:10</td>
<td>1:10 000 → 1:1000 → 1:100</td>
</tr>
<tr>
<td>Propofol 10mg/ml</td>
<td>1:100 → 1:10 → 1:1</td>
<td>1:1000 → 1:1000 → 1:10</td>
</tr>
<tr>
<td>Alfentanil 0.5mg/ml</td>
<td>1:100 → 1:10 → 1:1</td>
<td>1:10 000 → 1:1000 → 1:100</td>
</tr>
<tr>
<td>Fentanyl 0.05mg/ml</td>
<td>1:100 → 1:10 → 1:1</td>
<td>1:10 000 → 1:1000 → 1:100</td>
</tr>
<tr>
<td>Remifentanil 0.05mg/ml</td>
<td>1:100 → 1:10 → 1:1</td>
<td>1:10 000 → 1:1000 → 1:100</td>
</tr>
</tbody>
</table>
Diagnosis

Patch testing

- For delayed hypersensitivity reactions - contact dermatitis

- Allergen-containing patch applied to the skin for 24-48 hours and then removed

- Results read at 72 hours

- For suspected photoallergic or phototoxic reactions a photopatch may be performed
Diagnosis

Immunocap – measures IgE antibody levels (Not a RAST!)

• Safe

• Available for small range of drugs
  
  penicilloyl G  
  penicilloyl V  
  cefaclor  
  insulin  
  suxemethonium  
  morphine
Diagnosis

**Basophil activation tests (CAST)**

- Measures the *in-vitro* production of leukotrienes by the patient’s white blood cells on exposure to the drug

- Sensitivity low

- Value: diagnosis of non-IgE mediated reactions
## Available CAST tests

<table>
<thead>
<tr>
<th>Penicillin G</th>
<th>Ciprofloxacin</th>
<th>Phenylbutazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin V</td>
<td>Ampicillin</td>
<td>Propylphenzone</td>
</tr>
<tr>
<td>Cephalosporin C</td>
<td>Amoxycillin</td>
<td>Dipyrrone</td>
</tr>
<tr>
<td>Benzylpenicilloyl</td>
<td>Rifampicin</td>
<td>Atracurium</td>
</tr>
<tr>
<td>Minor determinants</td>
<td>Clarithromycin</td>
<td>Mivacurium</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>Aspirin</td>
<td>Pancuronium</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Diclofenac</td>
<td>Suxamethonium</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Ibuprofen</td>
<td>Rocuronium</td>
</tr>
<tr>
<td>Sulphomethoxazole</td>
<td>Indomethacin</td>
<td>Vecuronium</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Paracetamol</td>
<td>Lignocaine</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Mefenamic acid</td>
<td>Propofol</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Bupivicaine</td>
<td>Mepivacaine</td>
</tr>
</tbody>
</table>
Diagnosis

Drug provocation test (DPT)

- Gold standard
- Administer drug at incremental doses
- Observe for signs and symptoms of allergy
- Safety precautions – resuscitation equipment

DPT is most often useful for:

- NSAIDS
- Local anaesthetics
- Antibiotics other than B-lactams
Diagnosis

DPT indicated for:
• Exclude allergy when history not suggestive
• Definitively diagnose allergy where history suggestive but tests negative/equivocal
• To exclude cross-reactivity of related drugs in proven allergy

DPT contraindicated for:
• Systemic reactions (DRESS, anaphylaxis, haematologic, organ involvement)
• Severe skin reactions (SJS, TEN, DRESS)
# Drug challenge doses for common drugs

<table>
<thead>
<tr>
<th>DRUG</th>
<th>1/100 (mg)</th>
<th>1/10 (mg)</th>
<th>2/10 (mg)</th>
<th>8/10 (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxil 125mg</td>
<td>1,25</td>
<td>12,5</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Flucloxacillin 125mg</td>
<td>1,25</td>
<td>12,5</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Penicillin V 125mg</td>
<td>1,25</td>
<td>12,5</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Erythromycin 125mg</td>
<td>1,25</td>
<td>12,5</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Clarithromycin 125mg</td>
<td>1,25</td>
<td>12,5</td>
<td>25</td>
<td>100</td>
</tr>
<tr>
<td>Cefalexin 250mg</td>
<td>2,5</td>
<td>25</td>
<td>50</td>
<td>200</td>
</tr>
<tr>
<td>Ibuprofen 100mg</td>
<td>1</td>
<td>10</td>
<td>20</td>
<td>80</td>
</tr>
<tr>
<td>Paracetamol 120mg</td>
<td>1,2</td>
<td>12</td>
<td>24</td>
<td>96</td>
</tr>
<tr>
<td>Codeine 8mg</td>
<td>0,08</td>
<td>0,8</td>
<td>1,6</td>
<td>6,4</td>
</tr>
</tbody>
</table>
DHR

History & examination

Suspect allergy?

Yes

No

Is testing available?

Yes

No

Immediate reaction

Delayed reaction

SPT/Immunocap

Patch Test/CAST

Positive?

Positive?

Consider cross-reacting drugs

Non-immune mediated DHR

- toxicity
- side effect
- drug interaction

Management

- reduce dose
- alternative drug
- ? graded challenge
- ? premed
- patient education

Management

- avoid drug
- desensitise if drug required
- consider graded challenge
- future prudent use of drugs
- no challenge if previous severe reaction such as SJS/TEN/DRESS
- patient education

Does it have high NPV?

No

Yes

May still be allergic

Not allergic
Management

Prevent

• Determine host risk factors

• Avoid cross-reacting drugs

• Prudent prescription of drugs known to commonly cause ADRs

• Use oral drugs where possible

• Document previous ADRs clearly in medical record
Management

Acute

• Discontinue offending agent

• May be enough for mild reactions

• Treat symptoms and signs of anaphylaxis, urticaria, angioedema and wheeze

• SJS, TEN and DRESS etc will require specific medical treatment
Management

Long term

• Educate
• Avoidance
• Medic-alert bracelet
• Desensitise
• Pre-medication with antihistamines and glucocorticosteroids may be useful for non-allergic DHRs but will not reliably prevent IgE mediated anaphylaxis.
Management

Desensitisation

• Indicated mainly for IgE-mediated reactions

• If no acceptable alternative available
  eg insulin, penicillin in endocarditis, chemotherapy, monoclonal antibodies

• The temporary induction of tolerance

• Done in ICU
Management

Desensitisation

- Principle: start with minute dose, increase every 15 minutes until a full therapeutic dose is reached

- Oral or intravenous (oral preferred)

- Mild reactions occur in 1/3

- Mechanisms are not clearly defined; although cytokines and mast cells do play a role
Management

Desensitisation

• Temporary tolerance – maintained only as long as patient continues to take the drug

• Begin therapy immediately after desensitisation or tolerance may be lost (24-36hrs)

• Should same drug need to be given in future, desensitisation must be repeated

• Successful in 58-100% of cases
Example of a desensitisation protocol

<table>
<thead>
<tr>
<th>Penicillin V Suspension dose</th>
<th>Amount (units/mL)</th>
<th>mL</th>
<th>Units</th>
<th>Cumulative dose (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,000</td>
<td>0.1</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>1,000</td>
<td>0.2</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>3</td>
<td>1,000</td>
<td>0.4</td>
<td>400</td>
<td>700</td>
</tr>
<tr>
<td>4</td>
<td>1,000</td>
<td>0.8</td>
<td>800</td>
<td>1,500</td>
</tr>
<tr>
<td>5</td>
<td>1,000</td>
<td>1.6</td>
<td>1,600</td>
<td>3,100</td>
</tr>
<tr>
<td>6</td>
<td>1,000</td>
<td>3.2</td>
<td>3,200</td>
<td>6,300</td>
</tr>
<tr>
<td>7</td>
<td>1,000</td>
<td>6.4</td>
<td>6,400</td>
<td>12,700</td>
</tr>
<tr>
<td>8</td>
<td>10,000</td>
<td>1.2</td>
<td>12,000</td>
<td>24,700</td>
</tr>
<tr>
<td>9</td>
<td>10,000</td>
<td>2.4</td>
<td>24,000</td>
<td>48,700</td>
</tr>
<tr>
<td>10</td>
<td>10,000</td>
<td>4.8</td>
<td>48,000</td>
<td>96,700</td>
</tr>
<tr>
<td>11</td>
<td>80,000</td>
<td>1.0</td>
<td>80,000</td>
<td>176,700</td>
</tr>
<tr>
<td>12</td>
<td>80,000</td>
<td>2.0</td>
<td>160,000</td>
<td>336,700</td>
</tr>
<tr>
<td>13</td>
<td>80,000</td>
<td>4.0</td>
<td>320,000</td>
<td>656,700</td>
</tr>
<tr>
<td>14</td>
<td>80,000</td>
<td>8.0</td>
<td>640,000</td>
<td>1,296,700</td>
</tr>
</tbody>
</table>

Observation period: 30 minutes before parenteral administration of penicillin.

Interval between doses, 15 minutes; elapsed time, 3 hours and 45 minutes; cumulative dose, 1.3 million units.

The specific amount of drug was diluted in approximately 30 ml of water and then administered orally.
Desensitisation vs graded challenge

- Both involve administration of the drug at incremental doses in a controlled environment.
- Depends on history of previous reaction and likelihood that patient is allergic.
- Goal of induction of tolerance is to modify immune response to allow safe treatment.
- Goal of graded challenge is to cautiously administer drug to a patient who is unlikely to be allergic.
- A graded challenge does not alter immune response.
Specific drugs

- Penicillin
- NSAIDS
- TMP-SMX
- Local anaesthetics
- Insulin
- Opiates
- Radiocontrast media
Penicillin allergy

- Penicillin and its derivatives are still the most commonly used antibiotics

- Most likely to cause allergic reactions
  - Systemic reactions 2%
  - Anaphylaxis 0.05%
  - 500-1000 deaths per yr

- 10% report being penicillin allergic

- On testing, 80-90% of these are not
- Most will lose their penicillin allergy over time
Penicillin allergy

Alternative antibiotics are often unnecessary

- higher costs
- increased drug resistance
- more side effects
- may compromise optimal care
Penicillin allergy

Patients with penicillin allergy:

- Longer hospital stays
- 23% more likely to have *C. difficile* than controls
- 30% more likely to have vancomycin resistant *enterococcus*
- Mean antibiotic costs 63x greater
Penicillin allergy

• Less common in children than in adults
• Frequently develop maculopapular or urticarial rashes
• Most are due to viral infections
• Frequently over-diagnosed
• Only 10% are found to be truly allergic if offered investigations
Penicillin allergy - diagnosis

- History
- Examination
- Investigations
  - Tryptase (0, 1 and 6hrs)
  - Immunocap
  - Skin prick test
    (Intradermal test)
  - Drug provocation test
Penicillin allergy - diagnosis

- Diagnostics tests are useful for immediate reactions

- If history consistent with serum-sickness, SJS or TEN, penicillins should be avoided
Penicillin allergy - diagnosis

**Immunocap**
- Not a substitute for skin tests
- Insensitive - 54%
- Specificity up to 95%

Penicillin G
Penicillin V
Amoxycillin
Ampicillin
Penicillin allergy - diagnosis

Skin prick tests

- Specificity +/- 100%
- Sensitivity +/- 50-70%
- Safe, but small possibility of systemic reaction (0.7-11%)
- Should be done in environment where resuscitation is possible
Penicillin allergy - diagnosis

Skin prick tests

- Do while patient is well and not in immediate need of antibiotic
- Not indicated for non-IgE mediated reactions such as Stevens-Johnson syndrome or serum sickness
Penicillin allergy - diagnosis

Skin prick tests

- Histamine (positive control)
- 0.9% saline (negative control)
- major determinants
- minor determinants
- amoxycillin 20-25mg/ml
- other implicated drug, NPV unknown
Penicillin allergy - diagnosis

Drug provocation test

- Performed when IgE and skin prick tests are negative
- Not done if history of anaphylaxis
- Suggestive history and positive skin prick tests and/or Immunocap is usually sufficient for diagnosis
Penicillin allergy

Child presents with a history of reacting to a beta-lactam

Immediate reaction ≤1 hour following ingestion of first dose of antibiotic
- Skin test with PPL, MDM, benzylpenicillin, amoxicillin and suspect drug
  - Negative
    - Drug provocation test in hospital
  - Positive
    - Avoid beta-lactams

Non-immediate / delayed reaction, occurring mid-course of antibiotic AND > 1 hour following ingestion of last dose of antibiotic
- Mild rash or maculopapular reaction only
  - Oral challenge test
    - First dose given under observation then 5 day course completed at home
- Severe or generalised symptoms, EM, TEN, SJS, DRESS, AGEP
  - No further investigation
  - Avoid causative drug and beta-lactams from the same class
Penicillin allergy

Take home message:

• Do not withhold penicillin from a child if a parent is allergic

• Do not investigate patients with a family history of penicillin allergy but no personal history of a reaction

• Penicillin allergy testing should be performed routinely in all self-reported cases

• Children with delayed, mild, maculopapular eruptions, may be safely challenged (1st dose under observation, remainder at home)

• Atopy is not a risk factor for penicillin allergy
Cephalosporin

- Up to 20% cross reactivity reported
- Depends on similarity of R-group side chains, not β-lactam ring
  - i.e. amoxycillin and cephadroxil
  - ampicillin and cephalexin
  - ceftriaxone and cefotaxime
- 1st generation ~ 20%
- 3rd generation ~ 2%
Cephalosporins

- If penicillin allergic – do a cephalosporin SPT
  - if negative; give cephalosporin via graded challenge
  - <1% mild systemic reaction

- If cephalosporin allergic – do penicillin SPT
  - if negative; give penicillin
  - if no penicillin SPT available: give via graded challenge

- If allergic to one cephalosporin
  - use one with different R-side chain
  - give via graded challenge or desensitise
Carbapenems

- Reported 50% cross reaction with imipenem and 10% with meropenem (based on SPT)

- When DPTs done, cross reactivity <1%

- **Recommendation if penicillin allergic:**
  - do meropenem SPT
  - if negative, give via graded challenge
Cross reacting penicillins

| Drug                      | amoxicillin | ampicillin | aztreonam | benzylpenicillin | cefaclor | cefadroxil | cefamandole | cefazolin | cefepine | cefixime | cefmetazole | cefotaxime | cefotetan | cefpodoxime | ceftriaxone | cefuroxime | cephaloridine | cephalothin | cephradine | imipenem | loracarbef | meropenem |
|---------------------------|-------------|------------|------------|------------------|----------|------------|-------------|------------|----------|----------|--------------|------------|-----------|-------------|-----------|------------|-----------|-----------|-----------|----------|----------|
| amoxicillin               | XX          | 1          | 1          |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| ampicillin                |             |            | 1          | 1                |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| aztreonam                 |             |            |            | XX               |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| benzylpenicillin          |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefaclor                  |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefadroxil                |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefamandole               |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefazolin                 |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefepine                  |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefixime                  |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefmetazole               |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefotaxime                |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefotetan                 |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefpodoxime               |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| ceftriaxone               |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cefuroxime                |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cephaloridine             |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cephalothin               |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| cephradine                |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| imipenem                  |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| loracarbef                |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |
| meropenem                 |             |            |            |                  |          |            |             |            |          |          |              |            |           |             |           |            |           |           |           |          |          |

(1 or 2 = identical side chains; XX = same drug)
NSAIDs

- 2\textsuperscript{nd} major cause of ADR after β-lactams
- Prevalence 0.1-0.3%
- Large spectrum of ADR
## NSAIDs

<table>
<thead>
<tr>
<th>Allergic DHR</th>
<th>Non-allergic DHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>Respiratory</td>
</tr>
<tr>
<td>urticaria/angioedema</td>
<td>aspirin-induced asthma</td>
</tr>
<tr>
<td>anaphylaxis</td>
<td>AERD — asthma, polyps, rhinosinusitis</td>
</tr>
<tr>
<td>Delayed</td>
<td>Cutaneous</td>
</tr>
<tr>
<td>fixed-drug eruptions</td>
<td>Non-allergic anaphylaxis</td>
</tr>
<tr>
<td>contact dermatitis</td>
<td>-“anaphylactoid/pseudoallergic”</td>
</tr>
<tr>
<td>SJS/TEN</td>
<td>Side effects</td>
</tr>
<tr>
<td>maculopapular</td>
<td>Nausea, bruising</td>
</tr>
<tr>
<td></td>
<td>Toxic</td>
</tr>
<tr>
<td></td>
<td>Tinnitus, acidosis</td>
</tr>
</tbody>
</table>
NSAIDs

**Diagnosis**
- No blood or skin test (CAST)
- Drug provocation test if history unclear/definite diagnosis required

**Management**
- AERD - aggressive Rx of asthma/rhinosinusitis
  - avoid Cox-1 inhibitors
  - Cox-2 usually safe
- Desensitisation followed by daily aspirin
TMP-SMX

- Account for majority of DHRs in HIV

- Maculopapular eruption & fever 7-21 days after starting

- 25-86% (3-5% in HIV neg)

- **Discontinue immediately if**:  
  - rash/fever > 5 days
  - absolute neutrophil count < 500/mm
  - hypotension/dyspnoea
  - desquamation/mucous membranes involved

- Desensitise
Local anaesthetics

Esters - benzocaine, cocaine, procaine
Amides - lignocaine, prilocaine, bupivacaine, mepivacaine

Esters more commonly implicated
Local anaesthetics

- Immediate Type 1 reactions are extremely rare
- DHRs mainly due to anxiety, vasovagal or toxic reactions
- Many due to additives, preservatives (sulphites and parabens), epinephrine and latex
- Type IV reactions also common – contact dermatitis due to topical application
Local anaesthetics

- No reliable Immunocap

- CAST (sensitivity low)

- Best test is SPT and intradermal followed by a graded challenge

- Patch test for contact dermatitis
## Local anaesthetics

### Skin prick and intradermal tests

<table>
<thead>
<tr>
<th>AGENT</th>
<th>SKIN PRICK</th>
<th>INTRADERMAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacain 2.5mg/ml</td>
<td>neat</td>
<td>1:100 → 1:10</td>
</tr>
<tr>
<td>Lidocaine 10mg/ml</td>
<td>neat</td>
<td>1:100 → 1:10</td>
</tr>
<tr>
<td>Mepivacain 10mg/ml</td>
<td>neat</td>
<td>1:100 → 1:10</td>
</tr>
</tbody>
</table>
Radiocontrast media

- Non-allergic DHR are common but allergic are rare
- Severe immediate reactions as well as delayed cutaneous eruptions
- No evidence to support belief that those who are seafood or iodine allergic are at greater risk
- Pretreatment with antihistamines and corticosteroids may reduce the risk of a repeated reaction
Insulin

• Since introduction of recombinant insulin, allergy has become rare,<1% of diabetics

• Immediate life-threatening reactions and delayed reactions

• May be due to preservatives, latex and protamine

• Diagnosis by Immunocap, SPT, intradermal testing and DPT

• Desensitisation protocols are available
Opiates

- True allergy is rare

- Toxic and pseudoallergic reactions are very common and usually mild

- SPT use is limited as opiates cause direct mast cell degranulation (fentanyl less so)

- For a suspected reactions, a graded challenge with an alternate opioid may be tried
**DHR**

1. History & examination
2. Suspect allergy?
   - Yes
     - Is testing available?
       - Yes
         - Immediate reaction
           - SPT/Immunocap
             - Positive?
               - No
                 - Consider cross-reacting drugs
               - Yes
                 - Management
                   - avoid drug
                   - desensitise if drug required
                   - consider graded challenge
                   - future prudent use of drugs
                   - no challenge if previous severe reaction such as SJS/TEN/DRESS
                   - patient education
           - Delayed reaction
             - Patch Test/CAST
               - Positive?
                 - No
                   - Consider cross-reacting drugs
                 - Yes
                   - Management
                     - reduce dose
                     - alternative drug
                     - ? graded challenge
                     - ? premed
                     - patient education
     - No
   - Non-immune mediated DHR
     - toxicity
     - side effect
     - drug interaction
   - No

**Management**

- does it have high NPV?
  - No
    - May still be allergic
  - Yes
    - Not allergic
AFSA
allergy foundation south africa
- Drug Allergy: an updated practice parameter
Annals of Allergy, Asthma & Immunology
Vol 105, October 2010

- Management of allergy to penicillin and other beta-lactams. Clinical and experimental allergy
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