Approach to Drug Allergy

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Monday Seminar 15/2/16
Overview

- Classification & mechanism of drug allergy
- Clinical Approach & Investigation
- Specific drug reactions
  - Penicillin & Cephalosporin
  - Peri-operative anaphylaxis
- Severe Cutaneous Adverse Reactions
- Cases
Drug Reactions

- Adverse reaction = reaction which is noxious & unintended which occurs at dosages normally used in man; 80% of drug reactions

- Drugs can induce several different types of immunological reactions

- Drug Hypersensitivity Reactions:
  - Adverse effect of drugs that clinically resemble allergic reactions
  - Dose-independent, unpredictable, noxious & unintended response to drug taken at a dose normally used in humans

- Drug allergy: DHRs for which a definite immunological mechanism is demonstrated (antibody or T cell mediated)

- DHRs affect > 7% of general population
  - Underdiagnosis (under-reporting) & overdiagnosis (overuse of term ‘allergy’)
  - Limit therapeutic options
  - Can lead to more expensive, potentially less-effective drugs
  - One drug allergy may lead to misconception that patient is allergic to all drugs
### Mechanisms of Drug Allergy

<table>
<thead>
<tr>
<th>Type of immune response</th>
<th>Pathophysiology</th>
<th>Clinical symptoms</th>
<th>Typical chronology of the reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>IgE</td>
<td>Anaphylactic shock, Angioedema, Urticaria, Bronchospasm,</td>
<td>Within 1 to 6 h after the last intake of the drug</td>
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<tr>
<td></td>
<td>Mast cell and basophil degranulation</td>
<td>Cytopenia</td>
<td></td>
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<tr>
<td>II</td>
<td>IgG and complement</td>
<td>Serum sickness, Urticaria, Vasculitis, Eczema, Maculopapular exanthema, DRESS</td>
<td>5–15 days after the start of the eliciting drug</td>
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<tr>
<td></td>
<td>IgG and complement-dependent cytotoxicity</td>
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<td></td>
<td>Deposition of immune complexes</td>
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<tr>
<td>III</td>
<td>IgM or IgG and complement or FcR</td>
<td></td>
<td>7–8 days for serum sickness/urticaria</td>
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<td></td>
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<td>7–21 days after the start of the eliciting drug for vasculitis</td>
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<tr>
<td>IVa</td>
<td>Th1 (IFN-γ)</td>
<td>Monocytic inflammation, Eosinophilic inflammation</td>
<td>1–21 days after the start of the eliciting drug for MPE</td>
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<td></td>
<td>2–6 weeks after the start of the eliciting drug for DRESS</td>
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<tr>
<td>IVb</td>
<td>Th2 (IL-4 and IL-5)</td>
<td></td>
<td>1–2 days after the start of the eliciting drug for fixed drug eruption</td>
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<td></td>
<td>4–28 days after the start of the eliciting drug for SJS/TEN</td>
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<tr>
<td>IVc</td>
<td>Cytotoxic T cells (perforin, granzyme B, FasL)</td>
<td>Keratinocyte death mediated by CD4 or CD8</td>
<td>1–2 days after the start of the eliciting drug (but could be longer)</td>
</tr>
<tr>
<td>IVd</td>
<td>T cells (IL-8/CXCL8)</td>
<td>Neutrophilic inflammation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Maculopapular exanthema, SJS/TEN, pustular exanthema</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Acute generalized exanthematous pustulosis</td>
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</tbody>
</table>

Classification of DHRs

**Immediate** – possibly induced by an IgE-mediated mechanism
- Occur within first hour
- Urticaria, angioedema, conjunctivitis, rhinitis, bronchospasm, GI symptoms or anaphylaxis

**Non-immediate**: from 1 hour after initial drug administration
- Commonly occur after many days of treatment
- Often a/w delayed T-cell dependent mechanism
- Maculopapular exanthem, delayed urticaria
Risk Factors for Drug Allergy

- Female – some drugs eg. Intra-operative NMBA
- Prior history of allergic drug reactions
- Recurrent drug exposure (repeated courses eg. CF)
- Genetics – HLA types, drug metabolism
- **Not** risk factors: Age, atopy
Clinical History

- Indication for use
- Dose and route of medication taken
- What was the reaction? (Timeline)
- Timing of onset of reaction (precipitating dose & initiation of course)
- Concurrent medications
- Treatments required and response
- How long ago was the reaction?
- Prior or subsequent exposure to the medication
- Prior or subsequent history of exposure to other agents in the same class
Limitations of history

- History often not reliable as different drugs often taken simultaneously
- Often imprecise history
- Clinical picture of DHRs heterogenous, can mirror pathophysiological events
Investigation

- When to evaluate?
  - History of prior DHR & the drug is required without an equally effective, structurally unrelated alternative
    - Eg. B-lactams, NSAIDs, anaesthetics or disease-specific medications
  - History of prior severe DHR for other drugs (find the culprit agent for safety of the patient)
Investigation

- When not to evaluate?
  - No drug allergy causality:
    - Noncompatible symptomatology
    - Noncompatible chronology
    - Drug taken since with no reaction
    - Reaction without having taken the drug
    - Alternative diagnosis
Antibiotics: Penicillins

- Approximately 10% of patients report penicillin allergy
  - Following evaluation, >90% are able to tolerate drug
  - Rate of penicillin-induced anaphylaxis 1-2/10,000 patients

- Majority allergic to degradation products rather than intact molecule

- Cross-reactivity between penicillins & cephalosporins
  - Approximately 2% of penicillin skin test-positive patients react to treatment with cephalosporins
  - If penicillin allergy history only, there is < 1% chance of reaction with cephalosporin

- Before 1980, penicillin allergy history-positive patients had 10-20% reaction rate
  - Contamination of 1st generation cephalosporins: use of cephalothin or cephaloridine – similar sidechain to benzylpenicillin
| Table 1. Antibiotic options, allergy cross reactivity, activity and considerations for selected pathogens. 10-11 |
|-----------------|-------------------------|-------------------|-----------------------------|-------------------------------|
| % Cross reactivity with patients reporting penicillin allergy (range) | Activity | No activity | Notes |
| **1st generation cephalosporin** | MGH formulary examples | | | |
| | cefazolin, cephalaxin† | Selected Enterobacteriaceae, MSSA, Strep spp, Some anaerobes | MRSA, Enterococcus, Pseudomonas | |
| **2nd generation cephalosporins** | cefuroxime, cefoxitin | Unlikely (-0.8 to 0.2) | Selected Enterobacteriaceae, MSSA, Strep spp, Some anaerobes | MRSA, Enterococcus, Pseudomonas |
| **3rd generation cephalosporins** | ceftriaxone, ceftazidime‡ | Unlikely (-0.8 to 0.2) | Selected Enterobacteriaceae, MSSA, Strep spp, Some anaerobes, Pseudomonas (see "Notes") | MRSA, Enterococcus, Ceftazidime has activity against Pseudomonas, Ceftriaxone has no activity against Pseudomonas |
| **4th generation cephalosporins** | cefepime | Unlikely (-0.8 to 0.2) | Selected Enterobacteriaceae, MSSA, Strep spp, Pseudomonas | MRSA, Enterococcus, Anaerobes, Some Pseudomonas isolates have reduced susceptibility to aztreonam compared to cefepime, ceftazidime, piperacillin/tazobactam or carbapenems |
| **Monobactam** | aztreonam‡§ | 0 | Selected Enterobacteriaceae, Pseudomonas | MRSA, Strep spp, Enterococcus, Anaerobes, Reserved primarily for ESBL organisms or when no other reasonable options exist. Ertapenem is not clinically indicated for treatment of Pseudomonas |
| **Carbapenems** | imipenem, meropenem, ertapenem | 0.9 | Selected Enterobacteriaceae, Pseudomonas (see "Notes"), MSSA, Strep spp, Some anaerobes | MRSA |

† Note that cefalaxin and ampicillin have similar side chains so a reaction with one precludes use of the other.
‡ Note that ceftazidime and aztreonam have similar side chains so a reaction with one precludes use of the other.
§ Aztreonam should be reserved for the patient with a type 1 (IgE-mediated) allergy.
MSSA: Methicillin-sensitive Staphylococcus aureus; Strep: streptococcus; MRSA: methicillin-resistant Staphylococcus aureus
Cephalosporins

- Most hypersensitivity reactions to cephalosporins directed at the R-group side chain rather than the core B-lactam portion.

- Cephalosporin skin testing not as well validated as for penicillins.

| Table 16. Groups of β-Lactam Antibiotics That Share Identical R₁-Group Side Chains¹ |
|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|
| Amoxicillin                            | Ampicillin                              | Ceftriaxone                             | Cefoxitin                               | Cefamandole                             | Ceftazidime                             | Aztreonam                               |
| Cefadroxil                             | Cefaclor                                | Cefotaxime                              | Cephaloridine                           | Cefonicid                               |                                         |                                         |
| Cefprozil                              | Cephalexin                              | Cepodoxime                              | Cephalothin                             |                                         |                                         |                                         |
| Cefatrizine                            | Cephradine                              | Ceftizoxime                             |                                         |                                         |                                         |                                         |
|                                        | Cephaloglycin                           | Cefmenoxime                             |                                         |                                         |                                         |                                         |
|                                        | Loracarbef                              |                                         |                                         |                                         |                                         |                                         |

¹ Each column represents a group with identical R₁ side chains.

| Table 17. Groups of β-Lactam Antibiotics That Share Identical R₂-Group Side Chains¹ |
|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------------------|
| Cephalexin                             | Cefotaxime                              | Cefuroxime                             | Cefotetan                               | Cefaclor                                | Loracarbef                              | Ceftibuten                             | Ceftizoxime                             |
| Cefadroxil                             | Cephalothin                             | Cefoxitin                              | Cefamandole                             |                                         |                                         |                                         |                                         |
| Cephradine                             | Cephaloglycin                           | Cephapirin                             | Cefmetazole                             |                                         |                                         |                                         |                                         |
|                                        |                                         |                                         | Cepiramide                              |                                         |                                         |                                         |                                         |

¹ Each column represents a group with identical R₂ side chains.
Peri-operative anaphylaxis

- Greater morbidity & mortality than other forms of anaphylaxis
  - Mortality 1.4-1.6%, 2% morbidity of brain damage

- Incidence 1/10,000 - 20,000

- Most common causes: antibiotics, NMBAs

- May also include induction agents, latex, chlohexidine/betadine
  - Opiates – IV administration can cause flushing & urticaria
    - Dermal mast cells express opioid receptors that stimulate mediator release without sIgE. Reduced rate of administration can lessen severity of ADE.
    - Fentanyl does not interact with mast cell opioid receptor

- Challenges to recognising peri-operative anaphylaxis:
  - Decreased occurrence of skin manifestations
  - Multiple physiologic changes during surgery can mask or emulate anaphylaxis
  - Surgical draping limits recognition of urticaria or flushing
  - Inability of patients to verbalise symptoms

- Measure serum tryptase (post reaction AND baseline)
Skin testing

- SPT & IDT for IgE-dependent mechanism
- Diagnostic value not fully evaluated for all drugs
- Should be performed 4-6 weeks after reaction (may be falsely negative)
- Immediate DHRs:
  - SPT – initial screening. Simple, quick, low cost, high specificity but low sensitivity
  - IDT – enhanced sensitivity
Intradermal Testing

- Available for:
  - Antibiotics + penicillin metabolites
  - Neuromuscular blocking agents
  - Local anaesthetics
  - Insect venom

- A positive result indicative of allergy, provided nonirritating concentrations used

- May induce systemic reactions
  - Reported 8.8% of patients with systemic reactions to B-lactam skin tests

- Is a painful procedure. Difficult in young children

- Negative results do NOT exclude allergy
  - Patient may be allergic to metabolites of the medication or metabolite/protein complexes
In vitro testing

- Only available for a few antibiotics
- Absence of drug-specific circulating IgE does not exclude a diagnosis of immediate drug allergy

Future:
- Genetic markers
- Basophil activation tests
- Lymphocyte transformation/activation tests
Drug patch testing

- Patches placed on upper back. Read at 20 minutes with delayed readings at 48, 96 hours and 7 days

- May be useful for presumed non-IgE delayed cutaneous drug reactions
Drug Challenge

- Gold standard to establish/exclude the diagnosis of DHRs
  - Exclude cross-reactivity of related drugs in proven allergy

- Contraindications:
  - Severe cutaneous reactions eg. SJS, TEN, DRESS, vasculitis, AGEP
  - Systemic reactions eg. DRESS, organ involvement, haematological reactions
  - Severe anaphylaxis (may be tested after risk/benefit analysis)
  - Severe concurrent illness or pregnancy (unless drug essential for illness or during pregnancy)
Drug Challenge Protocol

- **1st dose:** 1/100th of top dose
- **2nd dose:** 1/10th of top dose - 45 minutes post
- **3rd dose:** Full top dose – 45 minutes post

- To complete 7 days or finish full course at home
Outcomes of drug challenges

- A negative test does not prove tolerance for the drug in the future
- IgE sensitivity may decrease over time
- Co-factors may influence outcome: food, exercise, viral infections
- Extension of challenge protocol to one week leads to higher sensitivity
  - Also hypothesised that finishing DPT with high dose (as close to ‘cumulative daily dose’ as possible)
Drug desensitisation is the induction of a temporary state of clinical unresponsiveness/tolerance to a compound responsible for a drug hypersensitivity reaction.
- If drug is discontinued, tolerance state is lost!
- Still considered allergic
- Used for both IgE and non-IgE mediated allergies

Used if drug is either irreplaceable or more effective than alternatives.

Administer increasing doses of medication over a short period of time until total cumulative therapeutic dose tolerated.

CI: other significant co-morbidity, beta-blocker use
- Absolute CI: severe, life-threatening immuno-cytotoxic reactions or bullous skin diseases

<table>
<thead>
<tr>
<th>Step</th>
<th>Penicillin (mg/ml)</th>
<th>Flow rate (ml/h)</th>
<th>Dose (mg)</th>
<th>Cumulative dose (mg)</th>
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<td>0.015</td>
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<td>10.0</td>
<td>200</td>
<td>500.0</td>
<td>1000.0</td>
</tr>
</tbody>
</table>

Observe patient for 30 min, then give full therapeutic dose by the desired route.
*The interval between doses is 15 min (ref. 22).
Little known about mechanism of desensitisation

Consecutive administration of suboptimal doses of antigen prior to the optimal dose renders the tissue mast cells unresponsive to drug compound but not other stimuli

Increasing sub-therapeutic doses can provide sufficient amounts of antigenic determinants to bind to IgE anchored to surface FcεRI receptors, but not to cross link such IgE
Desensitisation – practical aspects

- Can be done oral and IV routes.
  - Can be equally effective, oral route safer & easier

- Starting dose determined by severity of reaction, usually double dose at each step

- Success of desensitisation dependent on both dose and time
  - If doses too high & given too fast, state of unresponsiveness may be delayed (Breakthrough reactions)

- Pre-treatment with systemic steroids & antihistamines may mask early signs of reaction & interfere with rapid desensitisation. (controversial)

- Breakthrough reactions: Protocols vary – can treat through reactions or can modify with inserting intermediate dosing steps (reduces reactions)

- Mild reactions reported 30-80% in penicillin desensitisations

Chemotherapy Desensitisation
Castells Immunol Allergy Clin N Am 29 (2009)
Prevention

- Patient Education
  - Potentially cross-reacting drugs
  - Medic Alert cards/bracelets
- System: update medical records
Summary

- Different mechanisms of drug allergy/DHR
- History is key to diagnosis
- Methods of testing
- SCARS
Latex Allergy
Latex Allergy

- Latex: milky sap of the tree Hevea brasiliensis from which natural rubber is manufactured

- Approx. 250 natural latex polypeptides
  - 60 able to bind human IgE antibody

- Exposure: contact through skin, MM, parenteral, IV & inhalation

- Prevalence of latex sensitisation/allergy increased mid- to late-1990’s due to significant increase in use of latex gloves.
  - Subsequent avoidance of powdered latex gloves resulted in marked decrease of new cases

- General population: < 1% IgE mediated latex allergy

- Healthcare community: 4-7% (? Even lower). Peak at 12%
Risk Factors

- Occupational exposure (healthcare/rubber industry)
- Children with spina bifida (5% sensitisation, 0.8% allergy) & other congenital urogenital abnormalities
- Number of prior operations
- Atopy
- Patients sensitised to other allergens & those with eczema or fruit & vegetable allergy
- Route of exposure
- Amount of allergen in natural rubber product
Irritant dermatitis

- Most common
- Non-allergic skin rash
  - Erythema, dryness, scaling, vesiculation & cracking
- Caused by sweating or irritation of glove with its powder residue or frequent washing, soaps & detergents
Type 4 mediated immune response (T-cell mediated)
- Sensitised lymphocytes react to chemical additives in gloves

1-4 days after direct skin contact - Eczematous lesion, often associated with vesicles
- Then becomes dry, crusted & thickened

Chemical additives commonly implicated

Diagnosis – patch testing

Change to gloves without chemical or cotton lining gloves usually improves dermatitis

Breaches in skin barrier may increase risk of IgE-mediated latex sensitisation (increased absorption of allergens)
IgE mediated

- Allergic rhinoconjunctivitis
- Urticaria/angioedema
- Asthma
- Anaphylaxis
Cross-sensitisation

- 30-50% show associate hypersensitivity to certain plant-derived foods
  - Most patients react to only a small number
  - Up to 50% food reactions can be anaphylactic

- Major panallergen is defense-related protein – similar structure to Hev b 6.01

- Hev b 8 contributes to cross-reactivity with tree, grass and weed pollens (birch, Timothy)
Patterns of allergic cross-reactivity between latex and food

The numeric risks cited here are based upon findings in limited series of patients and may not be generalizable to all populations. Foods that uncommonly cause reactions in latex-allergic patients include carrot, coconut, apricot, strawberry, loquat, spinach, pineapple, cherimoya, passion fruit, papaya, mango, and celery.

References:

Diagnosis

- **Clinical history**
  - Temporal association with exposure
  - Hand dermatitis
  - Fruit/vegetable allergy
  - Atopy

- **Testing**
  - SPT (latex extract)
    - Sn 65-96%, sp 88-94% in paediatric patients
  - Serology: sn 70%, sp > 95%
**LATEX CHALLENGE**

**Equipment**
1. Latex glove
2. Non-latex glove (vinyl)
3. Latex balloon

**Preparation Instructions**
1. Instruct child to wash hands thoroughly, shaking off excess water, but leaving both hands damp.
2. Carefully apply a non-latex glove to the child’s right hand.
3. Carefully apply a latex glove to the child’s left hand and be careful not to touch any other areas of the child’s skin during application.
4. Wash your own hands thoroughly after applying both gloves.
5. Instruct the child to keep both hands still (resting on a pillow is good) and not to touch/scratch any areas of their skin.

**Challenge Protocol**

Perform 10 minutely observations of chest and skin, carefully peeling back both gloves to observe the skin of the hand under the gloves. Always perform observations on the non-latex gloved hand first to avoid cross contamination and carefully wash your own hands after each set of observations.

Leave both gloves on for 30 minutes, if no reactions noted. Any changes to skin (including erythema, urticaria, angioedema, pruritis) or chest should be immediately reported to the challenge supervisor. Gloves should be removed if the child is reacting.

If a reaction occurs, the challenge is then **POSITIVE** and the child observed and managed according to the challenge supervisor.

If there is **NO reaction** to the glove application, a latex balloon should be applied to the child’s lip, ensuring good contact with the mucosa of both lips (approx 1-2 minutes of repeatedly blowing up and letting down the balloon works well).

The child’s lips should then be observed for any changes, along with chest observations, every 10 minutes for 30 minutes.

If there are no reactions noted post the glove and balloon exposure, the child can be discharged 1 hour after the contact with the balloon. This is then a **NEGATIVE** challenge.

**PLEASE NOTE:** The balloon portion of the challenge does not proceed if the glove exposure is **POSITIVE**.
Management

- **Prevention**
  - Work practices to reduce sensitisation
    - Barrier cream when wearing latex gloves
    - After removing gloves, wash & dry hands thoroughly
    - Care with removing gloves to reduce risk of exposure to latex allergens to self/colleagues
    - Powder-free non-Hevea glove alternatives
    - ‘Hypoallergenic’ gloves refers to chemical additives, not latex
  - Frequently clean areas & equipment contaminated with latex-containing dust
Latex Allergic

- Avoid all latex products
- HCW: Avoid areas where they may inhale the powder from latex gloves worn by other workers
- MedicAlert Bracelet
- Advise doctors/dentist & anyone else who may perform procedure (hairdresser)
  - Need careful planning of surgical procedure
- Carry own supply of non-latex gloves
- Epipen if history of systemic reaction to latex
Summary

- Risk factors for latex allergy
- Mechanisms of latex allergy
- Cross-sensitisation with plant derivatives
- If diagnosed with latex allergy, AVOID
Severe Cutaneous Adverse Reactions
SJS/TEN

- Severe mucocutaneous reactions
  - Extensive necrosis & detachment of the epidermis

- 1-3 days of fever and flu-like symptoms
  - Photophobia & conjunctival itch/burning, pain on swallowing
  - Malaise, myalgia & arthralgia

- Cutaneous lesions: begin as erythematous macules with purpuric centres with prominent skin pain
  - Vesicles & bullae form & skin begins to slough

- Mucosa: oral, ocular, urogenital, pharyngeal. Intestinal involvement rare

- SJS: skin detachment <10% BSA; ~ 10% mortality

- TEN: skin detachment > 30%; > 30% mortality
## SJS associated drugs

### Strongly associated*

- Allopurinol
- Carbamazepine
- Lamotrigine
- Meloxicam
- Nevirapine
- Phenobarbital, primidone
- Phenytoin, fosphenytoin
- Piroxicam, tenoxicam
- Sulfadiazine, sulfadoxine, sulfamethoxazole, sulfasalazine

### Associated

- Amifostine
- Amoxicillin, ampicillin
- Azithromycin, clarithromycin, erythromycin
- Cefadroxil, cefixim, ceftriaxone, cefuroxim
- Ciprofloxacin, levofloxacin, pefloxacín
- Diclofenac
- Doxycyclin
- Etoricoxib
- Metamizole
- Oxcarbazepine
- Pipemidic acid
- Rifampicin
DRESS
(Drug reaction with eosinophilia and systemic symptoms)

- Skin eruption (morbilliform to diffuse, confluent erythema, facial oedema)
- Haematologic abnormalities: eosinophilia, atypical lymphocytosis
- Lymphadenopathy, fever
- Internal organ involvement (liver, kidney, lung + others)

- Long latency (2-8 weeks) between drug exposure & disease
  - Prolonged course with frequent relapses despite discontinuation
  - Relapses reported with HHV6 reactivation
  - Most recover within weeks-months. May develop autoimmune disease
  - Mortality rate 5-10%
Drug causality in ~80% of cases

- Antiepileptic agents (eg. Carbamazepine, lamotrigine, phenytoin, phenobarbital)
- Allopurinol
- Sulfonamides
- Minocycline
- Vancomycin
AGEP
(Acute generalised exanthematous pustulosis)

- ~90% caused by drugs
  - Aminopenicillins, macrolides, cephalosporins, quinolones, tetracyclines, bactrim
  - Antifungals
  - Diltiazem

- Rapid development of non-follicular, sterile, pinhead-sized pustules on background of oedematous erythema with flexural accentuation

- Usually occurs few hours to days after administration

- a/w fever, leukocytosis, neutrophilia & eosinophilia

- Organ involvement uncommon

- Usually resolve without treatment in 1-2 weeks. Followed by desquamation. Complications rare – usually elderly or co-morbid