Approach to Cutaneous Adverse Drug Reactions

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Every medication prescribed runs a risk of adverse reaction
Adverse Drug Reactions (ADRs)

WHO definition:

Any noxious, unintended, and undesired effect of a drug that occurs at doses used for prevention, diagnosis, or treatment.
Drug allergy ≠ “salah beri ubat”

Wanita Menderita Kerana Hospital Didakwa Salah Beri Ubat

Wanita dakwa sakit kulit angkara ubat hospital

NORMAH menunjukkan kulitnya yang mengelupas serta gatal selain mukanya yang bengkak selepas mendakwa memakan ubat diberi Hospital Raja Perempuan Zinab II, Kota Bharu. Kejadian berlaku selepas dapat rawatan buah pinggang.

KOTA BHARU: Seorang suri rumah terpaksa menanggung penderitaan penyakit kulit kronik, setelah memakan ubat yang didakwa tersalai diberikan Hospital Raja Perempuan Zinab II (HRPZ II) Kota Bharu.

Akibat kejadian itu, kulit wanita itu menggelupas serta gatal selain bengkak keseluruhan muka sehingga sukar untuk membuka mata, bercakap dan berjalan, menyebabkan suaminya bertindak membuat laporan polis, di Ibu Pejabat Polis Daerah Kota Bharu, dini semalam.
Classifications of ADRs

**Type A**
- 80% of all ADRs
- Predictable
- Dose dependent
- Related to the pharmacologic actions of the drugs
- Subdivided into
  1. Overdose
  2. Side effects
  3. Secondary effects
  4. Drug interactions

**Type B**
- 10-15% of all ADRs
- Unpredictable
- Dose independent
- Unrelated to the pharmacologic actions of the drugs
- Occur only in susceptible subjects
- Subdivided into
  1. Drug intolerance
  2. Drug idiosyncrasy
  3. Drug allergy
  4. Pseudoallergy

**Type C**
- Associated with long-term therapy
- Eg. Benzodiazepine dependence

**Type D**
- Carcinogenic and teratogenic effects
- Example:
  1. Colchicine induced diarrhoea
  2. Glicazide induced hypoglycaemia
  3. Chlorpheniramine induced somnolence
  4. Anticholinergic effect of tricyclic antidepressants
  Etc........

**Type F**
- Unexpected failure of therapy

---

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**Type C**
- Associated with long-term
- Example:
  1. Cutaneous adverse drug reactions (CADR)
  2. Drug induced liver injury (DILI)
  3. Drug induced kidney injury
  4. Drug induced bone marrow suppression

**Type D**
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- Example:
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*failure of therapy*
# Classifications of ADRs

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## Type C
- Dose related and time-related
- Associated with long-term therapy

## Type D
- Carcinogenic and teratogenic effects

## Type E
- Withdrawal
- Eg. Opioid withdrawal syndrome

## Type F
- Unexpected failure of therapy

**Example:**
Hypothalamus-pituitary-adrenal axis suppression by corticosteroids
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Type D
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Example: Thalidomide – sedative, antiemetic

Type E
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Type F
- Unexpected failure of therapy
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**Type F**
- Unexpected failure of therapy
DRUG ALLERGY

Type B ADR

Immunologically mediated

Not a pharmacological action
1. **Type I** – IgE mediated

2. **Type II** - Immunoglobulin mediated cytotoxic mechanisms eg blood dyscrasia

3. **Type III** - Immune complex-mediated eg vasculitis

4. **Type IV** – T cell mediated/delayed hypersensitivity
## Immunologically mediated ADRs

### The Gell & Coombs System of Hypersensitivity

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Drug-specific IgE antibodies → Mast cell activation</td>
<td>Urticaria, angioedema, anaphylaxis</td>
</tr>
<tr>
<td>II</td>
<td>Cytotoxic reactions mediated by drug-specific IgG or IgM antibodies → Phagocytes, NK cells</td>
<td>Haemolytic anemia, Thrombocytopenia</td>
</tr>
<tr>
<td>III</td>
<td>IgG-soluble antigen → complement immune complex</td>
<td>Vasculitis, serum sickness</td>
</tr>
<tr>
<td>IV</td>
<td>Delayed-type hypersensitivity reactions cellular immune mechanisms</td>
<td></td>
</tr>
<tr>
<td>IVa</td>
<td>IFN-γ, TNF-α (Th1) → activation of Monocytes</td>
<td>Contact dermatitis</td>
</tr>
<tr>
<td>IVb</td>
<td>IL5, IL4, IL13 (Th2) → activation of Eosinophils</td>
<td>MPE, DRESS</td>
</tr>
<tr>
<td>IVc</td>
<td>Perforin/Granzyme B (CTL) → activation of CD4+ or CD8+ T cells</td>
<td>SJS, TEN, MPE, DRESS</td>
</tr>
<tr>
<td>IVd</td>
<td>IL8, GM-CSF → activation of Neutrophils</td>
<td>AGEP</td>
</tr>
</tbody>
</table>

National Center for Adverse Drug Reactions Monitoring
Annual report 2016

Total ADR Report Received in Malaysia (2010-2017)

<table>
<thead>
<tr>
<th>Year</th>
<th>LAPORAN ADR TANPA AEIM</th>
<th>LAPORAN AEIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>5550</td>
<td>1529</td>
</tr>
<tr>
<td>2011</td>
<td>6202</td>
<td>3183</td>
</tr>
<tr>
<td>2012</td>
<td>8199</td>
<td>1903</td>
</tr>
<tr>
<td>2013</td>
<td>9678</td>
<td>1795</td>
</tr>
<tr>
<td>2014</td>
<td>11921</td>
<td>1080</td>
</tr>
<tr>
<td>2015</td>
<td>12489</td>
<td>1186</td>
</tr>
<tr>
<td>2016</td>
<td>12834</td>
<td>955</td>
</tr>
<tr>
<td>2017</td>
<td>14533</td>
<td>1403</td>
</tr>
</tbody>
</table>

National Pharmaceutical Regulatory Agency (NPRA), MOH Malaysia
Who is vulnerable?

1. The elderly
2. Underlying viral infections (Human Immunodeficiency Virus, Epstein Barr Virus etc)
3. Autoimmune connective tissue disease (Systemic Lupus Erythematosus, Rheumatoid Arthritis)
4. Malignancy (Lymphoma, Leukaemia)
5. Polypharmacy (drug-drug interaction)
6. On “high risk drugs” (allopurinol, carbamazepine, phenytoin, Non Steroidal Anti-inflammatory drugs)
7. Genetic predisposition
   - HLA B*1502 – Carbemazepine SJS/TEN in Han Chinese
   - HLA B*5801 – Allopurinol SJS/TEN in Han Chinese
   - HLA A30, B13, Cw6 – FDE due to Cotrimoxazole
   - HLA-B*5701 – Abacavir hypersensitivity
Whenever a patient treated with a drug develops an exacerbation OR a new medical problem

→ ADR is one of the possibilities
**ADR – the great mimicker!**

### Differential diagnosis of the most frequent cutaneous drug eruptions

| IgE-Mediated Urticaria | • Pseudoallergy and other nonimmune-mediated mast cell degranulations (eg, Aspirin, opiates)  
|                        | • Viral infections  
|                        | • Connective tissue disease |
| T-cell Meditated Maculopapular Exanthema | • Viral and bacterial infections (eg, syphilis)  
|                                         | • Generalized eczema  
|                                         | • Connective tissue disease  
|                                         | • Cutaneous lymphoma  
|                                         | • Graft-versus host disease  
|                                         | • Skin toxicity (eg, chemotherapy)  
|                                         | • Cytokine dysbalance (eg, tumor necrosis factor blockers)  
|                                         | • Superantigen stimulations (Kawasaki syndrome, staphylococcal scaled skin syndrome) |
## Classification of drug allergy: Immediate vs non immediate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Immediate Reaction</th>
<th>Nonimmediate Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time between exposure and onset</td>
<td>≤ 1 h (in special conditions such as intolerance to acetylsalicylic acid ≤ 3 h)</td>
<td>≥ 6 h (in the case of strong T-cell sensitization earlier)</td>
</tr>
<tr>
<td>of the reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of recovery</td>
<td>Few hours</td>
<td>Several days to weeks</td>
</tr>
<tr>
<td>Clinical nature of the reaction</td>
<td>Urticaria, angioedema, anaphylaxis</td>
<td>Maculopapular exanthema and other skin manifestations including late appearing urticarial rash and angioedema, disorder of blood cells, systemic reactions such as drug rash with eosinophilia, and systemic symptoms (DRESS)</td>
</tr>
</tbody>
</table>

Urticaria

**Wheal**
- Transient superficial dermal swelling due to plasma leakage
- Pruritic & pink/pale in the center
- Individual lesions come & go rapidly within 24 hours

**Angioedema**
- Deep swellings of the skin or mucosa
- Painful, less well defined, tend to be normal in color
- Last for 2-3 days
Angioedema
Anaphylaxis
more than just Angioedema

- Palmar ± plantar itch with/out urticaria and/or angioedema
- Nausea, abdominal pain, vomiting or diarrhoea
- Rhinoconjunctivitis
- Obstructive respiratory symptoms
- Cardiovascular events
- Altered mental state
- Fainting
## Table 2. Grade of Severity for Quantification of Immediate Hypersensitivity Reactions

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cutaneous signs: generalized erythema, urticaria, angioedema</td>
</tr>
</tbody>
</table>
| II    | Measurable but not life-threatening symptoms  
Cutaneous signs, hypotension, tachycardia  
Respiratory disturbances: cough, difficulty inflating |
| III   | Life-threatening symptoms: collapse,  
tachycardia or bradycardia, arrhythmias, bronchospasm |
| IV    | Cardiac and/or respiratory arrest |

Drug & vaccine related Anaphylaxis
Malaysian data 2009-2014

• Total cases reported = 315 (0.55% of 56,890 ADR reported)
• Median age = 41 years (4 months – 86 years)
  – 8.6% paediatric (≤ 17 years)
• Male:female = 1:1.18
  – Adult M:F = 1:1.19
  – Paediatric M:F = 1:1.07

Data: Centre for Adverse Drug Monitoring,
National Pharmaceutical Regulatory Agency (NPRA)
Drug & vaccine related Anaphylaxis
Malaysian data 2009-2014

• Rate of adrenaline used = 173 (54.9%)
• Time to onset

<table>
<thead>
<tr>
<th>Time to Onset</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate/≤5 minutes</td>
<td>44</td>
<td>13.9%</td>
</tr>
<tr>
<td>5 -30 minutes</td>
<td>98</td>
<td>31.1%</td>
</tr>
<tr>
<td>&gt;30-1 hour</td>
<td>34</td>
<td>10.8%</td>
</tr>
<tr>
<td>&gt;1 – 2 hour</td>
<td>22</td>
<td>7.0%</td>
</tr>
<tr>
<td>&gt;2 -4 hour</td>
<td>18</td>
<td>5.7%</td>
</tr>
<tr>
<td>&gt;4 hour</td>
<td>47</td>
<td>14.9%</td>
</tr>
<tr>
<td>Unknown</td>
<td>52</td>
<td>16.5%</td>
</tr>
</tbody>
</table>

55.8%

Data: Centre for Adverse Drug Monitoring, National Pharmaceutical Regulatory Agency (NPRA)
Drug & vaccine related Anaphylaxis
Malaysian data 2009-2014

• **Outcome (n=315)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>7 (2.2%)</td>
</tr>
<tr>
<td>Recovered without sequelae</td>
<td>269 (85.4%)</td>
</tr>
<tr>
<td>Unknown/Not yet recovered</td>
<td>39 (12.4%)</td>
</tr>
</tbody>
</table>

• **Suspected Causative agents (n=357)**

<table>
<thead>
<tr>
<th>Number</th>
<th>Agent</th>
<th>Percentage (Within Group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Antibiotic (33.1%) → β-lactam (75.4%) → penicillin group</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NSAIDs &amp; paracetamol (28.8%) → Diclofenac (52.4%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Neuromuscular blocking agents (4.8%) → Atracurium (52.9%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cytotoxic agents (3.6%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Modified fluid gelatin (2.5%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Radiocontrast media (2.2%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Snake antivenom (1.96%)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Acetylcystein; Morphine; Hydrocortisone (1.4% each)</td>
<td></td>
</tr>
</tbody>
</table>

Data: Centre for Adverse Drug Monitoring, National Pharmaceutical Regulatory Agency (NPRA)
Drug & vaccine related Anaphylaxis
Malaysian data 2009-2014

• Vaccine related anaphylaxis ➔ 4 (1.12%)
  – Human papilloma virus vaccine (2)
  – Inactivated influenza virus vaccine (1)
  – Pneumococcal vaccine (1)

Fatal drug induced anaphylaxis (n=7)
  – Antibiotic (1 Ceftriazone, 1 Ciprofloxacin, 1 Piperacillin/tazobactam)
  – Intraoperative agents (Rocuronium/midazolam/fentanyl)
  – Diclofenac acid
  – Iohexol (2 cases)

Drug reaction relationship - possible

Data: Centre for Adverse Drug Monitoring, National Pharmaceutical Regulatory Agency (NPRA)
Drug & vaccine related Anaphylaxis
Malaysian data 2009-2014

<table>
<thead>
<tr>
<th>Drug groups</th>
<th>Name of drug</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Penicillin/amoxicillin/Augmentin/Unasyn/Cloxacillin/Benzylpenicillin/Ampicillin/Bacampicillin</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Cephalosporin</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin/levofloxacin/moxifloxacin</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Streptomycin</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Azithromycin</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Metronidazole</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Bactrim</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Doxycycline</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Lincomycin</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Piperacillin/tazobactam</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rifampicin</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
<td>1</td>
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Drug & vaccine related Anaphylaxis
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<td>Diclofenac</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Ibuprofen</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Mefenamic acid</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Naproxen</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Aspirin</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Paracetamol</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Celecoxib/etericoxib/Parecoxib</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Piroxicam</td>
<td>1</td>
</tr>
<tr>
<td><strong>Neuromuscular blocking agents (n=17)</strong></td>
<td>Atracurium</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Suxamethonium</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Rocuronium</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Mivacurium</td>
<td>1</td>
</tr>
<tr>
<td><strong>Anti-neoplastic agents (n=13)</strong></td>
<td>Paclitaxel/Docetaxel</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>L Asparaginase</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>5- Fluorouracil</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>PEGfilgrastin</td>
<td>1</td>
</tr>
<tr>
<td><strong>Radiocontrast media (n=8)</strong></td>
<td>Iohexol</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Iopamidanol</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Iopromide</td>
<td>1</td>
</tr>
</tbody>
</table>

Data: Centre for Adverse Drug Monitoring, National Pharmaceutical Regulatory Agency (NPRA)
Erythema Multiforme
Erythema multiforme

• prodrome: fever, URTI symptoms
• annular erythematous patches and urticaria-like plaques with central dusky areas
  – Target lesions: 3 rings
  – Atypical target lesions: 2 rings
• erosions at mucous membranes
• other causes: infections (herpes simplex, mycoplasma), hematological malignancy
Maculopapular eruption:
Generalised small red macules and papules
Fixed Drug Eruption
burning patches occurring at same +/- additional sites
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)

Hausermann et al. Contact dermatitis 2004:51:297-310
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)
Vasculitis:
Purpuric macules or papules or plaques

- arthralgia, myalgia
- ± kidney, lung involvement
- + myeloperoxidase- antinuetrophil cytoplasmic Ab MPO-ANCAs, ANA, anti-histone, IgM anticardiolipin Ab, ↓C4

Photodermatitis
rash over sun exposed areas

The 5 “C”s
• Chlorothiazide
• Chlortetracycline
• Chlorpropamide
• Carbamazepine
• Chlorpromazine

The “Anti-”s
Antibiotics - tetracyclines
Anti-fungals - griseofulvin
Anti-arrhythmics - amiodarone
Anti-hypertensives - thiazides, β-blockers, ACE inhibitors
Anti-diabetics - sulphonylureas
Anti convulsants - carbamazepine
Anti-psychotics - phenothiazines
Drug induced lichenoid eruption

Lichen planus like