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In the USA ADR 15.1% and serious ADR 6.7% (Lazarou et al. J Am Med Assoc 1998; 279: 1200-5)

- Responsible for 3.1 to 6.2% of hospitalizations
- Inpatient ADRs responsible for 106,000 deaths annually
- 4th to 6th leading cause of death
- In outpatients 17 to 25%, serious 13%
- Most common offenders: Antibiotics, NSAIDs, diuretics, anticonvulsivants

**CLASSIFICATION OF ADVERSE REACTIONS TO DRUGS**

<table>
<thead>
<tr>
<th>Type</th>
<th>Characteristics</th>
<th>Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYPE A: PREDICTABLE</strong> (80%)</td>
<td>Dose dependent, related to known pharmacologic action, in healthy individuals</td>
<td>TOXICITY (OVERDOSE) SIDE EFFECTS SECONDARY EFFECTS INTERACTIONS</td>
</tr>
<tr>
<td><strong>TYPE B: UNPREDICTABLE</strong> (20%)</td>
<td>Dose independent, unrelated to pharmacologic action, in susceptible individuals</td>
<td>INTOLERANCE IDIOSYNCRASY ALLERGY PSEUDOALLERGY</td>
</tr>
</tbody>
</table>

**CLASSIFICATION OF ADVERSE REACTIONS TO DRUGS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Structure, molecular weight, dose, route of administration, duration of Tx, repetitive exposure, concurrent illnesses.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host</td>
<td>Age, sex, atopy, specific genetic polymorphisms, inherent predisposition to react to multiple unrelated drugs (multiple drug allergy syndrome), underlying diseases, and specific genetic polymorphisms</td>
</tr>
</tbody>
</table>
**Drug Reactions**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Example</th>
<th>Reaction</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdose</td>
<td>Acetaminophen-induced liver necrosis</td>
<td>Intolerance</td>
<td>Tininitus from ASA</td>
</tr>
<tr>
<td>Side effect</td>
<td>Albuterol-induced tremor</td>
<td>Idiosyncracy</td>
<td>Dapsone-induced HA in def of G6PD</td>
</tr>
<tr>
<td>Secondary effect</td>
<td>C. difficile (clindamycin)</td>
<td>Allergy (6-10%)</td>
<td>Anaphylaxis due to PCN</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>Cardiac arrhythmia from terfenadine/erythromycin</td>
<td>Pseudoallergy</td>
<td>Anaphylactoid reaction from RCM</td>
</tr>
</tbody>
</table>

**UNPREDICTABLE REACTIONS**

- **ALLERGY**: Immunologically mediated response resulting in the production of drug-specific antibodies, T cells, or both.
- **PSEUDOALLERGY**: Mimic IgE-mediated allergic reactions but are due to direct release of mediators from mast cells and basophils. Do not require previous sensitization (opiates, colloid volume expanders, polymyxin B, ACTH, RCM, excipients, vancomycin).

**Hypersensitivity Reactions Mediated by Antibodies (I-III) and Delayed Hypersensitivity Reactions (IV a-d)**

- Type I: IgE-mediated
- Type II: Cytotoxic
- Type III: Immune complex
- Type IV: Delayed hypersensitivity

**Clinical picture**

- Drugs

**Drugs**

- Type I: IgE-mediated: Urticaria, angioedema, bronchospaam, anaphylaxis
- β-lactam antibiotics, platinum, perioperative agents
- Type II: Cytotoxic: Hemolytic anemia, thrombocytopenia, granulocytopenia
- Penicillin, quinidine, α-methylidopa, sulfonamides
- Type III: Immune complex: Serum sickness
- Penicillin, infliximab, thymoglobulin, procainamide, phenylpropanolamine
- Type IV: Delayed hypersensitivity: Contact dermatitis, exanthema
- Neomycin, bacitracin, glucocorticoids, penicillin, sulfonamides, local anesthetics, antihistamines

**According to temporal relationship**

- IMMEDIATE (<1 hour)
- ACCELERATED (1 hour to 3 days)
- DELAYED (>3 days)

**pi concept**

- A drug binds noncovalently to a T-cell receptor, leading to an immune response via interaction with a major histocompatibility complex receptor.
- No sensitization required.
- Direct stimulation of memory and effector T cells.
**DIAGNOSIS**

- **History and physical examination:** previous and current use, previous reactions, temporal sequence
- Most frequent in the skin.
- **Complementary tests:** chest X-ray, EKG, CBC with differential, ESR, CRP, ANA, ANCAs, tryptase.
- IgE-mediated: skin testing, sIgE *in vitro.*
- Basophil activation test.
- Patch testing.
- Skin biopsy.

**DRUG ALLERGY: DIAGNOSTIC METHODS**

<table>
<thead>
<tr>
<th>Type I: IgE-mediated</th>
<th>Diagnostic methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin tests, in vitro IgE, tryptase, 24-hour urine histamine or N-methylhistamine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type II: Cytotoxic</th>
<th>Diagnostic methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct and indirect Coombs test</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type III: Immune complex</th>
<th>Diagnostic methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoglobulins, Clq binding, Raji cell assay, complement</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type IV: Delayed hypersensitivity</th>
<th>Diagnostic methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patch testing, lymphocyte proliferation assays, skin biopsy</td>
<td></td>
</tr>
</tbody>
</table>

**DIAGNOSIS CLINICAL CRITERIA**

1. Symptoms compatible with unpredictable drug reaction
2. Temporal relationship
3. Class and structure of the drug have been associated with reactions
4. Previous exposure
5. There is no other clear cause
6. STs, laboratory tests compatible

**CUTANEOUS MANIFESTATIONS**

<table>
<thead>
<tr>
<th>Clinical picture</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maculopapular eruption</td>
<td>Allopurinol, aminopenicillins, cephalosporins, antiepileptic, sulfonamides</td>
</tr>
<tr>
<td>Fixed drug eruptions</td>
<td>Tetracyclines, NSAIDs, carbamazepine</td>
</tr>
<tr>
<td>Urticaria and angioedema</td>
<td>Penicillins, NSAIDs, ACE inhibitors</td>
</tr>
<tr>
<td>Photosensitivity reactions</td>
<td>Oxirans</td>
</tr>
<tr>
<td>Lichenoid eruptions</td>
<td>ACE inhibitors, furosemide, NSAIDs, proton pump inhibitors, imatinib</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>Doxorubicin</td>
</tr>
<tr>
<td>Acne, AGEP</td>
<td>Glucocorticoids, androgens, lithium, phosphen, isoniazid, sirolimus, antibiotics, calcium channel blockers</td>
</tr>
<tr>
<td>Sweet syndrome</td>
<td>GM-CSF, sulfonamides, minocycline</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>Captopril, penicillamine</td>
</tr>
<tr>
<td>Pemphigoid</td>
<td>ACE inhibitors, furosemide, penicillin, sulfasalazine</td>
</tr>
<tr>
<td>Purpura and petechiae</td>
<td>Antibiotics, NSAIDs, diuretics</td>
</tr>
<tr>
<td>Erythema multiforme</td>
<td></td>
</tr>
<tr>
<td>Exfoliative dermatitis</td>
<td></td>
</tr>
</tbody>
</table>
FIXED DRUG ERUPTION (MEFENAMIC ACID)


Exanthematous Pustulosis induced by Nimesulide

Pustuloderma induced by Amoxicillin/clavulanic acid

Male, 14 years old. DICLOFENAC

Contact dermatitis induced by etofenamate 10% gel in a 37 year-old female patient.
Self-reported allergy 10%, up to 90% tolerate PCNs
- Anaphylaxis 1-2 per 10,000 treated patients
- ST with major and minor determinants (NPV 100%, PPV 40-100%)
- In vitro testing has uncertain predictive value (specificity 97-100%, sensitivity 29-68%)
- Ampicillin and amoxicillin induce IgE to R-group side chain
- Aztreonam does not cross react with other β-lactams except for ceftazidime
- Patients with positive PCN STs: administer carbapenems via graded challenge
**Structure of β-lactamic Antibiotics**

<table>
<thead>
<tr>
<th>Penicillin</th>
<th>Cephalosporins</th>
</tr>
</thead>
<tbody>
<tr>
<td>1- β-lactamic ring</td>
<td>1- β-lactamic ring</td>
</tr>
<tr>
<td>2- thiazolidine ring</td>
<td>3- dihydrothiazide ring</td>
</tr>
</tbody>
</table>

**CEPHALOSPORINS**

- Reaction rate ~ 10-fold lower than PCN.
- Most HRs directed at the R-group side chains.
- Avoid cephalosporins with similar R-group side chains.
- 2% of PCN skin test-positive patients react to cephalosporins.
- Most patients with history of PCN reaction and negative skin tests for PCN may receive cephalosporins.
- If PCN STs are positive: 1. Use alternate non-β-lactam ATB, 2. Graded challenge with cephalosporin, or 3. Rapid tolerance induction.

**CEPHALOSPORINS**

- Allergic to amoxicillin avoid Cephalosporins with identical R-group side chains (cefadroxil, cefprozil, cefatrizine).
- Allergic to ampicillin avoid Cephalosporins and carbacephems with identical R-group side chains (cephalexin, cefaclor, cephadine, cephaloglycin, loracarbef).
**β-LACTAM ANTIBIOTICS THAT SHARE IDENTICAL R1 GROUP SIDE CHAINS**

- Amoxicillin
- Cefadroxil
- Cefprozil
- Cefatrizine
- Ampicillin
- Cefaclor
- Cephalexin
- Cephradine
- Cefazolin
- Cefpodoxime
- Cefditoren
- Cefditoren
- Cefuroxime
- Cefoxitin
- Cefoxitin
- Cephaloridine
- Cephalothin
- Cefamandole
- Cefonicid
- Ceftriaxone
- Cefotaxime
- Cephaloglycin
- Loracarbef
- Cephapirin
- Cefuroxime
- Cefotetan
- Cefamandole
- Cefonicid
- Ceftazidime
- Aztreonam

**PENICILLIN ADMINISTRATION TO A PATIENT WITH A HISTORY OF PCN ALLERGY**

Option 1
Consider skin testing with cephalosporin
Give cephalosporin directly (only in absence of severe and/or recent PCN allergy reaction history. Although less than 1% will have a reaction within 24 hours, this is controversial as their reactions may be anaphylactic

Option 2
Give cephalosporin via graded challenge
Options:
1. Alternate drug
2. Desensitize to cephalosporin

Option 3
Penicillin skin testing
Give penicillin
Options:
1. Alternate drug
2. Desensitize to penicillin

**CEPHALOSPORIN ADMINISTRATION TO A PATIENT WITH A PAST HISTORY OF ALLERGY TO ANOTHER CEPHALOSPORIN**

Via graded challenge, give cephalosporin that does not share identical side chain with previous cephalosporin
Skin test with new cephalosporin using non-irritating concentration This testing is not standardized

Options:
1. Alternate drug
2. Desensitize to the cephalosporin

**NONIRRITATING CONCENTRATIONS OF 15 ANTIBIOTICS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Full-strength concentration</th>
<th>Dilution</th>
<th>Nonirritating concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>100 mg/mL</td>
<td>$10^4$</td>
<td>10 μg/mL</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>100 mg/mL</td>
<td>$10^1$</td>
<td>10 mg/mL</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>100 mg/mL</td>
<td>$10^1$</td>
<td>10 mg/mL</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>330 mg/mL</td>
<td>$10^1$</td>
<td>33 mg/mL</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>100 mg/mL</td>
<td>$10^1$</td>
<td>10 mg/mL</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>100 mg/mL</td>
<td>$10^1$</td>
<td>10 mg/mL</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>150 mg/mL</td>
<td>$10^1$</td>
<td>35 mg/mL</td>
</tr>
<tr>
<td>Cotrimoxazole</td>
<td>80 mg/mL</td>
<td>$10^2$</td>
<td>800 μg/mL</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>50 mg/mL</td>
<td>$10^3$</td>
<td>50 μg/mL</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>40 mg/mL</td>
<td>$10^1$</td>
<td>4 mg/mL</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>100 mg/mL</td>
<td>$10^3$</td>
<td>10 μg/mL</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>200 mg/mL</td>
<td>$10^4$</td>
<td>5 μg/mL</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>200 mg/mL</td>
<td>$10^1$</td>
<td>20 mg/mL</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>80 mg/2ml.</td>
<td>$10^1$</td>
<td>4 mg/mL</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>50 mg/mL</td>
<td>$10^4$</td>
<td>5 μg/mL</td>
</tr>
</tbody>
</table>
### Classification of Hypersensitivity reactions to ASA and NSAIDs

<table>
<thead>
<tr>
<th>Reaction time</th>
<th>Clinical picture</th>
<th>Type of reaction</th>
<th>Underlying disease</th>
<th>Putative mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (immediate to several hours)</td>
<td>Rhinitis/asthma (AERD)</td>
<td>CR</td>
<td>Asthma/RS/NP</td>
<td>Inhib. COX-1</td>
</tr>
<tr>
<td></td>
<td>Urticaria/AE (AECD)</td>
<td>CR</td>
<td>CSU</td>
<td>Inhib. COX-1</td>
</tr>
<tr>
<td></td>
<td>Urticaria/AE/ anaphylaxis</td>
<td>Induced by multiple NSAIDs</td>
<td>None</td>
<td>Unknown - Inhib. COX-2?</td>
</tr>
<tr>
<td></td>
<td>Urticaria/AE/ anaphylaxis</td>
<td>Induced by a single drug</td>
<td>Asthma, Food allergy, Drug allergy</td>
<td>Specific IgE</td>
</tr>
<tr>
<td>Delayed (&gt;24h)</td>
<td>FDE</td>
<td>Induced by one or multiple drugs</td>
<td>Generally no T Cells</td>
<td>Cytotoxic T cells, NK cells, Other</td>
</tr>
<tr>
<td></td>
<td>Severe bullous reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maculopapular eruption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pneumonitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aseptic meningitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nephritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Contact and photocontact dermatitis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kowalski ML et al. Allergy 2011

**ASPIRIN EXACERBATED CUTANEOUS DISEASE**

ASPIRIN EXACERBATED CUTANEOUS DISEASE

Lip angioedema induced by diclofenac in a 30 years old female patient with chronic spontaneous urticaria and angioedema.
Chronic urticaria exacerbated by sodium diclofenac

15 years old, ibuprofen

Tolerance to NSAIDs in patients with acute cross-reactive hypersensitivity to ASA

- Ibuprofen
- Indomethacin
- Sulindac
- Naproxen
- Fenoprofen
- Meclofenamate
- Ketorolac
- Flurbiprofen
- Nabumetone
- Mefenamic acid

Group A: NSAIDs cross-reactive in most patients (60-100%) - Ibuprofen

Group B: NSAIDs cross-reactive in a minority of patients (2-10%)

- Acetaminophen (<1000 mg)
- Meloxicam
- Nimesulide

Group C: NSAIDs well tolerated by all patients

- Selective COX-2 inhibitors
- Trisalicylate
- New selective COX-2 inhibitors (etoricoxib, parecoxib)

Algorithm for the management of patients with urticaria, angioedema and anaphylaxis induced by NSAIDs

1. Careful history to determine host risk factors
2. Avoidance of cross-reactive drugs
3. Use of predictive tests, when available
4. Proper and prudent prescribing of drugs
5. Use oral route when possible
6. Documentation of ADR in the medical record
7. Medic Alert tags and bracelets
8. Induction of drug tolerance: where an alternate non-cross reacting drug cannot be used
9. Graded challenge: cautious introduction in patients who are unlikely to be allergic

DRUG ALLERGY: PREVENTION AND MANAGEMENT