Rash Decisions: Approaches for Antibiotic-associated Hypersensitivity Reactions

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Disclosure Statement

The presenters have no vested interest in or affiliation with any corporate organization offering financial support or grant monies for this continuing education activity, or any affiliation with an organization whose philosophy could potentially bias our presentation.
Objectives

Upon conclusion of the program, the participant should be able to:

1. Differentiate between medication-associated hypersensitivity reactions, considering the underlying pathophysiologic mechanisms and clinical presentations specific to particular antimicrobial agents
2. Identify and understand patterns of cross-reactivity between antimicrobial agents
3. Apply an appropriate management strategy for the patient presenting with suspected antibiotic-associated hypersensitivity

Antibiotic Associated Allergy

- Approximately 10-15% of patients report a history of penicillin allergy
- 80-90% of PCN allergic patients have negative PCN skin tests
- Erroneous labeling of patients as PCN-allergic → higher costs, antimicrobial use, risk of acute care admission, mortality

AAAAI. Ann Allergy Asthma Immnol. (2010)
Introduction

- Assessment of antibiotic allergy knowledge amongst immunologists, allergists, PCPs, ID physicians have demonstrated deficiencies in drug allergy knowledge
- 40% of physicians do not verify the documented antibiotic allergy labels during a hospital admission
- Only 38% of hospital doctors aware of their patient’s PCN allergy
- PCN allergy often recorded in >8% of inpatients; 36% missing description of the reaction in the EHR

Adverse Drug Reactions

- **Definition**: all unintended pharmacological effects of a drug except therapeutic failure, intentional overdose/abuse, or administration errors; occurs despite appropriate prescribing and dosing

<table>
<thead>
<tr>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacologically predictable</td>
<td>Pharmacologically unpredictable</td>
</tr>
<tr>
<td>Dose-dependent</td>
<td>Non dose-dependents</td>
</tr>
<tr>
<td>Non-immune mediated</td>
<td>Often immune mediated</td>
</tr>
<tr>
<td>~ 80% of ADRs</td>
<td>~ 20% of ADRs</td>
</tr>
<tr>
<td>Example: orthostatic hypotension with antihypertensives</td>
<td>Example: Hypersensitivity reactions</td>
</tr>
</tbody>
</table>

Adverse Drug Reactions

- **Drug intolerance**: undesirable pharmacologic effect; may occur at low/usual doses without alterations in ADME parameters; scientific explanation for response not established

- **Drug idiosyncrasy**: abnormal and unexpected effect unrelated to intended pharmacologic action; reproducible; potentially due to underlying alterations in ADME

- **Drug allergy**: immunologically mediated response in a sensitized person
  - Anaphylaxis: rapid IgE-mediated response in a sensitized individual
  - Pseudoallergic (anaphylactoid) reaction: immediate systemic reaction; mimics anaphylaxis, but non-IgE mediated

Gell and Coombs Classification

<table>
<thead>
<tr>
<th>IMMUNE REACTION</th>
<th>MECHANISM</th>
<th>CLINICAL MANIFESTATIONS</th>
<th>TIMING OF REACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (IgE-mediated)</td>
<td>Drug-IgE complex binding to mast cells with release of histamine, inflammatory mediators</td>
<td>Urticaria, angioedema, bronchospasm, pruritus, vomiting, diarrhea, anaphylaxis</td>
<td>Minutes to hours after drug exposure</td>
</tr>
<tr>
<td>Type II (cytotoxic)</td>
<td>Specific IgG or IgM antibodies directed at drug-hapten coated cells</td>
<td>Hemolytic anemia, neutropenia, thrombocytopenia</td>
<td>Variable</td>
</tr>
<tr>
<td>Type III (immune complex)</td>
<td>Tissue deposition of drug-antibody complexes with complement activation and inflammation</td>
<td>Serum sickness, fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis</td>
<td>1 to 3 weeks after drug exposure</td>
</tr>
<tr>
<td>Type IV (delayed, cell-mediated)</td>
<td>MHC presentation of drug molecules to T cells with cytokine and inflammatory mediator release</td>
<td>Allergic contact dermatitis, maculopapular drug rash*</td>
<td>2 to 7 days after cutaneous drug exposure</td>
</tr>
</tbody>
</table>

Gell and Coombs’s classification: is it still valid?

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Abstract

The Gell and Coombs’s classification divides drug allergies into four pathophysiological types, namely anaphylaxis (type I), antibody-mediated cytotoxic reactions (type II), immune complex-mediated reactions (type III), and delayed type hypersensitivity (type IV). Although this classification was proposed more than 30 years ago, it is still widely used. As only a limited number of drug allergies fit into this classification which does not include our current understanding of the immune response, its use is not recommended, particularly in the context of the preclinical safety evaluation of new therapeutic agents. In fact, three different situations can be identified, namely pseudo-allergic reactions, primarily antibody-mediated reactions and cell-mediated reactions, which could serve as a basis for modern and more adequate classifications © 2001 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Drug allergy; Gell and Coombs; Pathophysiology; Pseudo-allergy

Figure 1. Re-classification of Adverse Drug Reactions
Adapted from Pete164, White et al. 201524 and Phillips et al. 201523
Type I Reactions (Immediate)

- Common Antibiotics: Penicillin, Cephalosporins
- Typical Onset: within 1 hour
  - Should not occur several days into a course of therapy
- Presentation
  - Urticarial rash (wheel and flare)
  - Pruritus
  - Flushing
  - Angioedema, Wheezing, Hypotension, AMS, Anxiety
  - No fever; no increased CRP

Timing – “Delayed” Reactions

Table 2. Approximate Timing of Onset of Symptoms Due to Hypersensitivity Reactions in Previously Sensitized and Nonsensitized Patients

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Previously Sensitized Patients</th>
<th>Patients Not Previously Sensitized</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0–1 h</td>
<td>0–1 h</td>
</tr>
<tr>
<td>II</td>
<td>24–36 h</td>
<td>7–14 d</td>
</tr>
<tr>
<td>III</td>
<td>24–36 h</td>
<td>7–14 d</td>
</tr>
<tr>
<td>IV</td>
<td>48–96 h</td>
<td>14 d</td>
</tr>
</tbody>
</table>

Legendre et al. CID. (2014).
Type II Reactions (Delayed)

- Presentation
  - Hemolytic anemia – penicillin, cephalosporins
  - Thrombocytopenia – beta-lactams, vancomycin, linezolid, sulfonamides
  - Variable in severity: asymptomatic to fulminant (hepatitis, nephritis)

Legendre et al. CID. (2014).

Type III Reactions (Delayed)

Presentations
- **Vasculitis** – penicillins, cephalosporins, sulfonamides
  - Palpable purpura and/or petechiae (will not blanch on pressure)
  - Lymphadenopathy
  - Labs: elevated ESR, low complement
- **Drug Fever** – SMX/TMZ, minocycline
- **“Serum sickness” (SSLRs)** – amoxicillin, cefaclor (possibly SMX/TMZ)
  - Fever
  - Urticarial or purpuric rash
  - Arthralgias
  - Lymphadenopathy
  - Acute glomerulonephritis

Legendre et al. CID. (2014).
Harrison’s Principles of Internal Medicine, 20e. (2018)
Type IV (Delayed)

- Cluster of various presentations – various subcategories of type IV classifications

- Presentations:
  - Contact Dermatitis
  - Morbilliform Eruptions
  - Stevens-Johnson Syndrome (SJS)
  - Toxic Epidermal Necrosis (TEN)
  - Drug-induced Hypersensitivity Syndrome (DiHS/DRESS)

Contact Dermatitis

- Associated abx: topical antibiotics (various other topicals and adhesive)
- Presentation
  - Erythema
  - Edema
  - Vesicles/bullae - rupture to leave a crust

Legendre et al. CID. (2014).
Harrison’s Principles of Internal Medicine, 20e. (2018)

Morbilliform eruptions

- Associated abx: penicillins, sulfonamides
  - Often exaggerated by co-morbid viral infections (e.g. Epstein-Barr)
- Presentation
  - Diffuse, pink plaques
  - Generalize within 2 days

Legendre et al. CID. (2014).
Harrison’s Principles of Internal Medicine, 20e. (2018)
SJS/TEN

Serious cutaneous reactions

- Initial flu-like illness, "target-like lesions"
- Erythroderma
- Extensive erosions and/or bullae
- Sloughing of skin and mucosal surfaces

- Causal Antibiotics: sulfonamides, tetracyclines, dapsone
  - SMX/TMZ in HIV patients

Incidence

- SJS: 1 to 7 cases per million person-years
- TEN: 0.4 to 1.5 cases per million person-years

Associated mortality

- SJS: 1-3%
- TEN: 30-50%

Legendre et al. CID. (2014).
Harrison’s Principles of Internal Medicine, 20e. (2018)

Drug-induced Hypersensitivity Syndrome (DiHS, DRESS)

- Associated Abx: sulfonamides, minocycline, dapsone (HLA-B*13:02)
- Timing: Typically 2-8 weeks after therapy initiation
- Presentation
  - Fever, flu-like Sx for several days
  - Diffuse, morbilliform eruptions (usually involving face)
  - Facial/hand/foot swelling
  - Multiorgan failure – liver, kidneys, heart, and/or lungs most common
  - Minocycline – typically heart, lung involvement
- Mortality: 2-14%

Cross-Reactivity of Beta-Lactams

- Medications with similar structures could prompt similar adverse reactions
- Cross-reactivity of penicillins and cephalosporins is 2-5%
- Up to 40% cross-reactivity with similar/identical side chains
- Over estimation of cross-reactivity due to manufacturing process
- Carbapenems share structural properties with little cross-reactivity, 1%
- Monobactam negligible cross-reactivity, except ceftazidime
Penicillins and Cephalosporins

Penicillins and cephalosporins share a beta-lactam ring.
Cross-reactivity likely due to similar side chains, not the beta-lactam ring.

R - unique to each antibiotic

Thiazolidine ring

Beta-lactam ring
Management - Why be concerned with drug allergy?

![Table 2. Differences in outcome and in antibiotics (Ab) administration, and cost between the allergic and the non-allergic patients during hospitalization](image)

<table>
<thead>
<tr>
<th></th>
<th>Allergic</th>
<th>Non-allergic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>118</td>
<td>118</td>
<td></td>
</tr>
<tr>
<td>Hospitalization mortality</td>
<td>2</td>
<td>3</td>
<td>NS</td>
</tr>
<tr>
<td>Transportation to other departments</td>
<td>3</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of hospitalization (days)</td>
<td>5.2</td>
<td>5.5</td>
<td>0.41</td>
</tr>
<tr>
<td>Number of Ab per hospitalization</td>
<td>1.67</td>
<td>1.43</td>
<td>0.49</td>
</tr>
<tr>
<td>Parental Ab (%)</td>
<td>65</td>
<td>71</td>
<td>0.09</td>
</tr>
<tr>
<td>Doses per day (n)</td>
<td>2.5</td>
<td>2.6</td>
<td>0.075</td>
</tr>
<tr>
<td>Duration of Ab treatment (days)</td>
<td>3.99</td>
<td>4.44</td>
<td>0.057</td>
</tr>
<tr>
<td>Price of each Ab dose (US$)</td>
<td>33.9</td>
<td>19.9</td>
<td>0.0061</td>
</tr>
<tr>
<td>Price of each Ab treatment (US$)</td>
<td>328.1</td>
<td>232.5</td>
<td>0.0065</td>
</tr>
<tr>
<td>Total costs of Ab during hospitalization (US$)</td>
<td>548.8</td>
<td>394.7</td>
<td>0.0015</td>
</tr>
<tr>
<td>Total cost per Ab treatment per day (US$)</td>
<td>136.7</td>
<td>78.4</td>
<td>0.0015</td>
</tr>
</tbody>
</table>

SD, standard deviation.

Call for Drug Allergy Pathways (2018 AAAAI/WAO Symposium)

Controversies in Drug Allergy: Drug Allergy Pathways

Special Article

Key design considerations for beta-lactam pathways

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient Clinical Data</td>
<td>High-quality data required for standardization of recommendations</td>
</tr>
<tr>
<td>Patient eligibility for pathway</td>
<td>• Clinically unstable patients – may consider such patients an exclusion or include as high risk</td>
</tr>
<tr>
<td></td>
<td>• Acute care location: may be inclusive of all acute care or restrict to certain populations (i.e. inpatient, ED, ICU, peri-op, etc.)</td>
</tr>
<tr>
<td></td>
<td>• Consider patient characteristics: pediatric, geriatric, pregnancy</td>
</tr>
<tr>
<td>Risk stratification by allergy history</td>
<td>• Most important tool in pathway design</td>
</tr>
<tr>
<td></td>
<td>• No standardized history tool – some pathways may exclude all high risk patients (e.g. anaphylaxis) or stratify recommendations by reaction type</td>
</tr>
<tr>
<td>PCN allergy epidemiology</td>
<td>Epidemiology differs geographically</td>
</tr>
<tr>
<td>Cross-reactivity</td>
<td>Local variations in beta-lactam cross-reactivity exist</td>
</tr>
<tr>
<td>Allergy specialist/procedure access</td>
<td>Intervention will vary based on facility access/availability</td>
</tr>
</tbody>
</table>

Adapted from Fig 1 in Demoly and Castells. World Allergy Organization Journal. (2018)
Example Pathways

Partners HealthCare System (Boston, MA)
- Developed by Massachusetts General Hospital
- Electronic form created; originally used in large northeastern U.S. health system
- Experiences at multiple U.S. centers demonstrate pathway as safe & effective

Australian Therapeutic Guidelines
- National drug allergy pathway
- Provides framework for institutional prescribing throughout Australia


C. Therapeutic Guidelines

Suggested management of patients reporting hypersensitivity to penicillins in whom a beta-lactam antibiotic is definitely required

- **Report of hypersensitivity to penicillins in a patient in whom a beta-lactam antibiotic is definitely required**
  - History of an IgE-mediated (allergic) immediate reaction to penicillins (NIH1)
  - History of a delayed-type (nonimmmediate) reaction to penicillins

- **Avoid penicillins, cephalosporins, and carbapenems (NIH2)**
- Administer a non-beta-lactam antibiotic or aminoac (NIH3)
  - If a penicillin is definitely preferred, perform desensitisation.

- In a non-urgent situation consider specific allergy testing and/or a drug provocation test under specialist supervision.

- **DRESS syndrome with eosinophilia and systemic symptoms**: SJS/TEN = Stevens-Johnson syndrome/ toxic epidermal necrolysis.

NIH1: An IgE-mediated (allergic) immediate reaction is characterised by the development of urticaria, angioedema, bronchospasm or anaphylaxis within 1 to 2 hours of drug administration.

NIH2: A cephalosporin or carbapenem may be considered in some circumstances.

NIH3: Immunology and some clinical data suggest that there is an increased risk of immediate hypersensitivity reactions to aztreonam in patients hypersensitive to cephalosporins, due to the similarity of their side chains.

Obstacles to Beta-Lactam Allergy Pathway Implementation

- Variability in provider drug allergy education/knowledge
- Provider concern of inducing a severe allergic reaction
- Professional liability concerns of providing a beta-lactam to patients with a history of PCN allergy, especially if alternative antibiotics available
- Providers may feel poorly equipped to explain drug allergy and cross-reactivity to patients


Antibiotic allergy labels—the impact of taking a clinical history

Adrienne Torda1,2 | Victor Chan1

Results: Three thousand eight hundred and fifty five patients were screened, 553 (14.35%) had an AAL, and 352 were interviewed. There were 426 AALs; 276 (64.8%) towards a penicillin. After taking a detailed clinical history of the type of reaction, approximately 20% could be immediately de-labelled and educated (non-allergic, non-severe reactions) and another 38% with either a definite or vague history of mild cutaneous reaction would be suitable for an attempt at clinical de-labelling DPT.

Conclusions: These simple measures to 'de-label' patients appropriately, would increase the quality of care of this group known to have higher costs, infection with more resistant bacteria and worse health outcomes that 'non-labelled' patients.
Questions to Ask – History-Taking

- When did the antibiotic-associated reaction occur?
  - The more distant the reaction event was, the less likely he/she will be allergic
- What kind of reaction occurred, if known?
  - Skin testing not helpful for non-IgE reactions
  - Generally, history of SJS, exfoliative dermatitis, hepatitis, nephritis associated reaction is a good reason NOT to test/treat with a beta-lactam
- Has the patient had any experience with beta-lactam antibiotics subsequent to the reaction?
- If decision to move forward with treatment, always be prepared to manage acute anaphylactic reaction


Other Medication Classes Causing Hypersensitivity Reactions

- Antiepileptics
- Antihypertensives
- Antiretrovirals
- Muscle Relaxants
- NSAIDs
- Allopurinol
- Platinum-based Chemotherapy
- Opiates

Legendre et al. CID. (2014).
After de-labeling, up to 1/3 of patients erroneously report a PCN allergy
Communication and education is key at any change in allergy status
Establishing appropriate criteria for outpatient referral for allergy workup is key
References (1)

7) Harrison’s Principles of Internal Medicine

References (2)

12) Sade et al. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital.
13) Ponvert et al. Allergy to beta-lactam antibiotics in children: results of a 20-year study based on clinical history, skin and challenge tests.
17) Torda A & Chan V. Antibiotic allergy labels – the impact of taking a clinical history.