ALLERGIES TO ANTIMICROBIALS
IMPACT UPON CLINICAL PRACTICE

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Needs Statement

- Antimicrobial agents often cause allergic reactions in patients. Understanding the immune mechanisms that cause these reactions, and how to extrapolate the impact of these reactions to their impact on therapy is difficult. This activity will discriminate between the various immune mechanisms associated with antimicrobial allergy, and practitioners will learn how to manage these issues in patients.
Objectives

- Discuss the etiology and pathogenesis of drug allergies
- Discern the likely immunopathology of specific drug reactions, and determine how each type impacts therapeutic decisions as they apply to patients being treated with antimicrobial agents
- Develop a plan for antimicrobial utilization in patients with proven or reported drug hypersensitivities
Overview

- ADRs and drug allergy
- Epidemiology and risk factors
- Pathogenesis and immunological mechanisms
- Clinical manifestations
- Testing
- Desensitization
- Cross-sensitivity
Nomenclature

- **Immune mediated drug hypersensitivity (drug allergy)**
  - Clinical symptoms due to different types of specific immune reactions (T-cell & B-cell/Ig mediated)

- **Non immune mediated drug hypersensitivity (non-allergic drug hypersensitivity)**
  - Symptoms and signs similar to immune mediated hypersensitivity, but failure to demonstrate a specific immune process to the drug
  - Older term: “pseudoallergy”

- **Idiosyncrasy**
  - Symptoms and signs due to some genetic alterations, e.g. an enzyme deficiency: e.g. hemolytic anaemia due to certain drugs in patients with G-6-P-deficiency

Nomenclature

Drug hypersensitivity

Drug allergy

IgE-mediated drug allergy

Non-IgE mediated drug allergy

Non-allergic hypersensitivity

eg: Non-specific histamine release, Arachidonic acid pathway activation, Bradykinin pathway alteration, Complement activation

Epidemiology

- ADRs account for 3 to 6% of admissions
  - Occur in 10 to 15% of hospitalized patients
- Drug allergy estimated to account for a third of all ADRs
- Few epidemiologic studies performed focusing on drug allergy alone
- In hospitalized patients, incidence of cutaneous allergic reactions
  - 2.2 per 100 patients
  - 3 per 1,000 courses of drug therapy
- True incidence of drug-induced anaphylaxis unknown

Risk Factors

- Nature of drug
  - Interaction with immune system, dose, duration, route
  - Cross-sensitization

- Patient
  - Age: studies among children and adults not comparable
  - Genetic factors (HLA type, Acetylator status)
  - Concurrent medical illness (e.g. Ebstein-Barr Virus (EBV), human immunodeficiency virus (HIV), asthma)
  - Previous drug reaction
  - Multiple allergy syndrome
## Reaction Types

<table>
<thead>
<tr>
<th>Type of Reaction</th>
<th>Mechanisms</th>
<th>Clinical Symptoms</th>
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</thead>
<tbody>
<tr>
<td>Type I (immediate)</td>
<td>IgE mediated Mast cells</td>
<td>Urticaria Angioedema Anaphylaxis/shock Bronchial asthma Rhinitis, conjunctivitis</td>
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<tr>
<td>Type II (cytotoxic)</td>
<td>Antibody mediated (IgG) FcR+ cells (phagocytes, NK)</td>
<td>Immune hemolytic anemia Thrombocytopenia Blood cell dyscrasias Organ-specific reactions</td>
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<td>Type III (immunocomplex)</td>
<td>Immunocomplex mediated (IgG) FcR+ cells, complement</td>
<td>Serum sickness–like syndrome Vasculitis Organ-specific reactions</td>
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<td>Type IV (delayed)</td>
<td>T cell mediated Antigen presented in MHC, T cells produced cytokines that recruit Monocytes Eosinophils Neutrophils</td>
<td>Maculopapular exanthema SJS TEN Organ-specific reactions AGEP Fixed drug eruption Contact eczema Delayed urticaria</td>
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</table>

**Abbreviations:** AGEP, acute generalized exanthematous pustulosis; DRESS/DHIS, drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis
Stimulation of the Immune System

- **Hapten**
  - Chemically reactive drug
  - Able to bind covalently to proteins
  - Recognized by immune system (Ig, T cells, B cells, innate cells)

- **Prohapten**
  - Chemically non reactive drug
  - Becomes reactive upon *metabolism* (transformation of prohapten $\rightarrow$ hapten)

- **p-i concept**
  - Parent, chemically non reactive drug
  - Unable to bind covalently to proteins
  - Can nevertheless interact with “immune receptors” like T-cell receptors for antigen and elicit an immune response
PenG is a hapten like drug, as it can rapidly form covalent bonds to other proteins.

1. via the β-lactam ring (1), which opens and forms bridge to lysine
   *major determinant*

2. via the thiazolidin moiety (2) of the penicillin
   *minor determinant*
Hapten Concept

Binding of a chemically reactive structure to

1) Soluble proteins (IgE, IgG) or

2) Membrane bound proteins (→ IgG + T-cell reactions) or

3/4) MHC-peptide complexes directly (→ only T-cells)

Distinct clinical consequences of hapten carrier formation depending on binding to soluble or cell bound proteins
Many drugs are potentially highly immunogenic as they are transformed to chemically active intermediates.

Potent and rapid intracellular detoxification mechanism (i.e. GSH) may prevent immunogenicity of the generated reactive metabolites.

Can restrict clinical manifestations to the organ where metabolism (generation of hapten) takes place.

- Liver (hepatitis)
- Kidney (interstitial nephritis)
Prohapten: Metabolism required

GSH

sulfamethoxazole

sulfamethoxazole hydroxylamine

GSH

nitroso sulfamethoxazole

sulfamethoxazole protein conjugate

R = N\_O\_C\_H\_3

Cribb & Spielberg, 1992
Gill et al., 1997

HYPERSENSITIVITY

ANTIGEN PROCESSING

IMMUNE RESPONSE
P-I Concept

- Pharmacological interaction with immune receptors
  *p-i concept*
  - Direct stimulation of T-cells by drugs binding to the TCR
  - No involvement of the innate immune system
  - Leads to different types of T cell responses
Clinical Manifestations

- Urticaria, anaphylaxis
- Blood cell dyscrasia
- Vasculitis
- Maculopapular exanthem
- Bullous or pustular exanthems (AGEP)
- Stevens-Johnson Syndrome (SJS), toxic-epidermal necrolysis (TEN)
- Hepatitis, interstitial nephritis
- Drug induced autoimmunity
- Drug induced hypersensitivity syndrome (DiHS/DRESS)
  - Drug rash w/ eosinophilia and systemic symptoms
Clinical Features

- Maculopapular exanthem (MPE)
- Bullous exanthem
- Stevens-Johnson Syndrome (SJS), toxic-epidermal necrolysis (TEN)
- Acute generalized exanthematous pustulosis (AGEP)
- Drug induced hypersensitivity syndrome (DiHS), or drug reaction with eosinophilia and systemic symptoms (DRESS)
- (Interstitial) nephritis, pancreatitis, colitis, pneumonitis, hepatitis
- Urticaria, angioedema, anaphylaxis, bronchospasm
- Blood cell dyscrasia, hemolytic anaemia, thrombocytopenia, agranulocytosis
- Vasculitis
- Drug induced autoimmunity (SLE)

IgE

IgG & Compl.
Anaphylaxis and Shock

Anaphylaxis and anaphylactic shock

IgE mediated drug allergies: the faster, the more dangerous
Urticaria

- A wheal and flare reaction
  - Small venules of the skin in response to substances that cause vasodilatation, increase vascular permeability
  - Dermal mast cells, basophils release histamine, eicosanoids
  - Stimulate cutaneous neurons to release neuropeptides (axon reflex)

- Transient skin swelling and itching
- No desquamation, no mucus membrane involvement
Angioedema

- Well-demarcated non-pitting edema
- Same pathological factors that cause urticaria
- Reaction occurs deeper in dermis and subcutaneous tissues
- Face, tongue, lips, eyelids most commonly affected
- May cause life-threatening respiratory distress
T-cells recognize the drug and exert, depending on their function, a specific pathology.
MPE vs. Bullous Exanthem

- Higher activation of circulating T-cells (CD4 and CD8) in bullous exanthem
- Higher activation of CD8+ T-cells in the skin of patients with bullous exanthem

CD8 T cells can kill all cells, not only activated MHC II+ cells
Appearance of Symptoms

Immediate type: 1-2hrs
Mainly IgE-mediated “silent” sensitization, well tolerated; at re-exposure quick development of symptoms (urticaria, anaphylaxis)

Delayed type: 2 hrs-10 days
Mostly T cell mediated (exanthems)

*Timing doesn’t always go by the book
Delayed Reactions: Danger Signs

- Extensive, confluent infiltrated exanthema
- Bullae, pustules
- Nikolsky sign (slight rubbing = exfoliation)
- Painful skin
- Mucosal affection
- Facial edema
- Lymphadenopathy
- Constitutional symptoms (higher fever, malaise, fatigue)

- Stop all ongoing drugs. Do liver, renal and blood tests.
Mortality in Delayed Reactions

- Stevens-Johnson Syndrome (SJS) & toxic epidermal necrolysis (TEN): bullous exanthema and mucosal affection
- DRESS (DHiS): Drug reaction with eosinophilia and systemic symptoms (often hepatitis, sometimes pancreatitis, interstitial lung disease, colitis, myocarditis, pleuritis, pericarditis, nephritis)
- AGEP (acute generalized exanthematous pustulosis)
- Isolated hepatitis, interstitial nephritis, interstitial lung disease, pancreatitis

Mortality

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Viral Infections and Drug Allergy

Generalized immune stimulation in the frame of

- Acute EBV infections
  - Maculopapular exanthem with aminopenicillins
- HIV infection
  - Sulfonamides: MPE, SJS/TEN
  - SJS/TEN to various drugs is 500-fold more frequent
Diagnosis of Drug Allergy

1. Can it be a drug hypersensitivity? If so, allergic or non-allergic?

2. Documentation of acute stage
   - Case specifics (semiology, chronology, all drugs taken)
   - Severity of symptoms, including laboratory analysis if any
   - Establish temporal relationship of drug intake to appearance of symptoms
   - Risk factors (underlying disease)
   - Rule out possible differential diagnosis

3. Identifying the responsible drug
Identifying the Responsible Drug

1. History
2. Drug properties/common reactions
3. Determine presumed pathomechanism (IgE, T-cell, IgG)
4. Skin tests with non toxic preparations of the drug
   - Skin prick test (SPT); Intradermal test (IDT)
   - Late reading IDT and patch tests
5. Serology/specific IgE
   - Drug specific IgE (available for few drugs only)
   - Basophil activation tests (in theory, available for many drugs but not in routine use)
6. Drug provocation tests (where 4-6 not available/not validated)
Lab Tests for Serious Reactions

Immediate reactions

- Serum tryptase
- Serum hisamine

Delayed reactions

- Complete blood count: eosinophilia and lymphocytosis, leukocytosis
- Liver function tests: ↑ ALT, AST, ALP
- ↑ Serum creatinine
- Urine microscopy and dipstick: nephritis, proteinuria
- CRP (can ↑ or ↓)
An elevated level supports a diagnosis of anaphylaxis.
Skin Prick and Intradermal Tests

- For IgE-mediated reactions
- Skin prick test (SPT), Intradermal test (IDT)

Penicillin example: sensitivity/specificity

- Sensitivity 70% if test ALL:
  - Major determinant (penicilloyl polylysine (PPL))
  - Minor determinant mix (MDM)
  - Amoxicillin
  - Ampicillin
- Specificity for most β-lactams 97-99%
Skin Prick Test (SPT)

- Specific
- Fairly sensitive
- Simple to perform
- Rapid (result in 15-20 min)
- Educational for patient
Intradermal Skin Test (IDT)

- More sensitive than skin prick test
- May induce false positive reactions
- May induce systemic reactions
- Should be done only if skin prick test is negative and allergen is highly suspect
Drug specific IgE Tests

- Commercially available
  - Phadia CAP®/ ImmunoCAP (fluorescent enzyme immunoassay)
  - Penicilloyl G, penicilloyl V

- Less sensitive and more expensive
  - Sensitivity for penicillins/amoxicillin from 38-54%
  - Specificity for penicillins/amoxicillin from 87-100%
Drug Provocation Tests (DPT)

- **Indications**
  - Exclude hypersensitivity in non-suggestive history
  - Utilize structurally similar drugs in proven hypersensitivity e.g. beta-lactams
  - Definitive diagnosis in suggestive history with negative, non-conclusive or non-available tests

- **Contraindications**
  - Pregnancy
  - Co-morbidity where DPT may provoke situation beyond medical control
    - Acute infection, uncontrolled asthma, underlying cardiac disease
  - Immunobullous drug eruptions
  - Severe systemic initial reaction

Aberer W, et al. ENDA, the EAACI interest group on drug hypersensitivity. Allergy 2003; 58:854-63
Drug Provocation Tests (DPT)

- Risks/benefits explained to patient
- Informed consent
- Cessation of antihistamine
  - short-acting 3 days
  - long-acting 7 days
- Fasted overnight
- Careful observation with resuscitation equipment

Aberer W, et al. ENDA, the EAACI interest group on drug hypersensitivity. Allergy 2003; 58:854-63
Desensitization

- Making a patient tolerant to a drug he/she is allergic to
- When there are no reasonable alternatives
- Contraindicated: SJS/TEN
- Not contraindicated: anaphylaxis
- Patient still considered allergic to the drug
- Rapid desensitization (PCN), slow desensitization (sulfa)
- Possible mechanisms (IgE-mediated reactions)
  - Consumption of IgE in immune complexes
  - Mediator depletion from mast cells and basophils
  - Antigen specific mast cell desensitization
Desensitization

- Possible mechanisms (IgE-mediated reactions)
  - Consumption of IgE in immune complexes
  - Mediator depletion from mast cells and basophils
  - Antigen specific mast cell desensitization

- Recent research models
  - Cross-linking of inhibitory receptors on mast cells
  - In-vitro desensitization of human mast cells depletes syk, an upstream signal transducing molecule necessary for IgE signaling

- Mechanism in delayed reactions unknown
Desensitization

- **Recommendations**
  - MUST be performed by a physician, ICU recommended
  - D/C all beta-adrenergic antagonists (even ophthalmics)
  - IV line, ECG monitoring
  - Do not premedicate (PCNs) with corticosteroids/antihistamines
    - For some drugs, premedication recommended (FQ, vanco)
  - 30% patients will have transient allergic reaction either during desensitization or treatment
Desensitization

- Can be done orally or parenterally
- Start low
  - Ampicillin oral 0.03mg
  - Benzylpenicillin 10 units intradermal
- Double the dose every 20-30 minutes until reach target
- Must not be a lapse in treatment
Cross-Reactivity

- **Beta-lactams**
  - Especially with Type I reactions
  - Non-immediate hypersensitivity cross-reactivity is uncommon (even within classes)
  - If IgE-mediated reaction to PCNs, 10% cross-reactivity to cephalosporins
    - Greater incidence with 1st generation cephs
    - Special case: amoxicillin and cefadroxyl share same side chain, cross-sensitivity is 30%

Torres MJ et al. Med Clin N Am 2010; 94: 805-20
Cephalosporin Cross-Reactivity

- Patient group: rxn to ceph but NOT PCN
  - Higher incidence of ceph cross-reactivity among drugs with similar R1 side-chains
    - Ceftriaxone = cefotaxime = cefepime
    - Cefuroxime ≈ ceftazidime

- Cephalosporin study, IgE-mediated
  - 63.2% reaction to only 1 ceph
  - 36.8% reacted to multiple, based on similar side chains
  - Only 2 reacted to PCN determinants

Cross-Reactivity

- Cross-reactivity between other groups very low
  - PCNs and carbapenems: 0.9% for IgE-mediated
    - However, recent study of cell-mediated allergy showed a 5.5% cross-sensitivity
  - Aztreonam and beta-lactams: almost 0%

Schiavino D et al. Allergy 2009; 64: 1644-8
Sulfonamides

- 2-4% of hospitalized patients develop allergies, but up to 50% of HIV infected patients (MPE > urticaria > anaphylaxis > SJS)
- SMX can become a hapten (SMX-NO), able to cause all forms of drug allergies (type I - IVd)
- T-cell reactions (exanthema IVa-IVd) mainly due to p-i concept, namely a direct stimulation of TCR by SMX
- Cross reactivity with non-antimicrobial drugs with sulfa moiety very low, poorly studied (10% in NEJM study)

Strom BL et al. MEJM 2003: 349: 1628-35
Flouroquinolones

- Immediate and delayed hypersensitivities
  - Immediate
    - Cross-reactive potential, avoid all FQ
  - Delayed
    - Conflicting data
    - Can challenge, desensitize
    - Generally 10% cross-sensitivity

Sherer K et al. Curr Allergy Asthma Rep 2005; 5: 15-21
Treatment

- **Inpatient:** observation, i/v, skin care, allergist referral
  - Angioedema (oropharyngeal/laryngeal), anaphylaxis
  - Severe skin: bullous drug eruption, EM/SJS/TEN
  - Systemic symptoms: fever, lymphadenopathy, organomegaly
  - Possibly > 1 implicated drug

- **Outpatient**
  - Urticaria/maculopapular rash
  - Fixed drug eruption
  - Drug allergy without systemic symptoms

- **When to refer to allergist**
  - Uncertain whether the reaction was drug allergy
  - Uncertain which drug: need for re-evaluation and specific testing
  - Desensitization
Treatment

- Stop the suspected drug/drugs
- Resuscitation in serious reactions
  - ABC (airway, breathing, circulation) in anaphylaxis
- Drugs:
  - Antihistamine: i/v, oral.
  - i/m epinephrine: anaphylaxis
  - Systemic corticosteroids: for DiHS, SJS
  - High dose IVIG 1g/kg/d x 2 days: for early TEN/SJS overlap, TEN
- Emollients & Skin care
- Hydration and prevention of skin superinfection (TEN)