Learning Objectives

1. Differentiate among adverse drug reactions (ADR’s) and develop understanding of those for which recent research has produced greater understanding of mechanisms
2. Discriminate between various ADRs and develop care plans with the interdisciplinary team
3. Explain the difference between immune-related reactions, cross-reactivity, multi-drug sensitivity, and infusion reaction
4. Match the most appropriate treatments to the specific type of allergy and outline desensitization protocols that have been developed for reactions to some of these agents.
5. Incorporate these new principles into patient monitoring and counseling

Background

• Until recently, adverse drug reaction management has been limited to:
  – Discontinuing the drug
  – Treating symptoms
  – Avoiding cross-reacting drugs

The Changing World of ADRs

New concepts:
- Therapeutic agents can treat certain severe reactions
- Cross-reactivity among similar medications better understood
- Desensitization to biological agents is possible

What are we talking about here?

- Stevens-Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Sulfonamide allergy
- NSAID allergy
- IgE-mediated reactions to specific drugs
SJS and TEN
A continuum of bullous reaction

SJS and TEN
• Start with fever, stinging eyes, painful swallowing
• Skin tenderness, erythema, epidermal necrosis and desquamation follow
  — Dusky (blue to black) erythematous macules progress to flaccid blisters
  — Two or more mucous membranes usually involved
  — Buccal, genital, ocular mucosa erythema and erosions
• Epidermal detachment
• Massive fluid loss and electrolyte imbalance

SJS and TEN
• Life-threatening because of multisystem involvement and skin-barrier breakdown
• Increased vulnerability to bacterial and fungal infections may lead to septicemia and severe fluid loss
• Mortality ranges from 5% in SJS to 30% in TEN.
• Survivors may suffer from mucous membrane strictures
• Severe ophthalmic involvement may lead to permanent scarring and blindness

SJS and TEN
• Most cases have no identified cause, but infections and medications have been associated with SJS
• Two probable factors:
  — impaired ability to detoxify intermediate drug metabolites
  — genetic susceptibility
  • When drugs are implicated, patients generally started therapy 1–3 weeks before the rash appears
  • Most common: antibacterial sulfonamides, anticonvulsants, NSAIDs, allopurinol

SJS and TEN: What’s New?
• Epidermal cell death and sloughing seen in TEN result from apoptosis.
• Fas is a cellular death receptor
• Keratinocyte apoptosis may be principally mediated through
  — increased expression of Fas ligand (FasL) on the keratinocyte surface
  — its binding to the Fas (CD95) receptor
SJS and TEN: What’s New?

- IVIG preparations at high dose (2-3 g/kg) have large amounts of Fas-blocking antibodies
- IVIG is expected to abrogate Fas-mediated apoptosis in TEN
- In addition, IVIG’s high content of a wide variety of autoantibodies, anti-idiotype antibodies, and complement components may help
- However, in vitro studies have shown conflicting results

Quick Review

**Type 1 hypersensitivity (IgE mediated)**
- Manifests various allergic diseases, such as allergic asthma, most types of sinusitis, allergic rhinitis, food allergies, and specific types of chronic urticaria and atopic dermatitis.
- IgE also pivotal in responses to allergens and anaphylaxis after exposure to drugs, bee stings, and antigen preparations used in desensitization immunotherapy.

**Type 2 hypersensitivity (Cell mediated)**
- Cytotoxic hypersensitivity
- Antibodies produced by the immune response bind to antigens on the patient’s own cell surfaces
- These cells are recognized by macrophages or dendritic cells, which act as antigen-presenting cells.
- Causes a B cell response, wherein antibodies are produced against the foreign antigen.

Quick Review

**Type 3 hypersensitivity (immune-complex-mediated)**
- Post-streptococcal glomerulonephritis
- Patient develops a strep infection
  - Makes an antibody that reacts against the strep and cross-reacts with some antigen in the glomerulus
  - Antigen-antibody complexes lodge there and cause nephritis

**Type 4 hypersensitivity (T-cell-mediated)**
- Delayed sensitivity
- Poison ivy
  1. Poison ivy exposure
  2. Helper T cells respond and some become memory cells
  3. Upon repeat exposure the memory T cells rush to the site, activating macrophages and causing inflammation

Allergy in General

- The best predictor of a future event is a past event
  - particularly for ADRs to drugs with similar structures
- The underlying mechanism of “multiple drug allergies” is unclear
  - probably involves, at least partly, genetic factors (gene polymorphisms)
- Recent data suggests that immunologic cross-reactivity is not universal among drugs of similar structures
Sulfonamides

Two basic groups contain a sulfa moiety

- Antibacterial sulfonamides
  - Have an N1 nitrogen-containing heterocyclic ring and an N4 arylamine group
- Non-antibacterial sulfonamides
  - No N1 heterocyclic ring or arylamine group

For many years, clinicians have worried that the sulfa moiety in antibacterial sulfonamides could cross-react with non-antibacterial sulfonamide derivatives.

Sulfonamide Allergy

- Antibacterial sulfonamides
  - Sulfacetamide
  - Sulfadiazine
  - Sulfamerazine
  - Sulfamethazine
  - Sulfamethizole
  - Sulfamethoxazole
  - Sulfanoxole
  - Sulfapyridine
  - Sulfinpyrazone

- Non-antibacterial sulfonamides
  - Acetazolamide
  - Bumetanide
  - Chlorpropamide
  - Chlorthalidone
  - Dapsone
  - Diazoxide
  - Diisopropylamine
  - Glyburide
  - HCTZ
  - Metolazone
  - Mefloquine
  - Probenecid
  - Sulfasalazine
  - Sumatriptan
  - Tolbutamide
  - Torsemide
  - Valdecoxib

For many years, clinicians have worried that the sulfa moiety in antibacterial sulfonamides could cross-react with non-antibacterial sulfonamide derivatives.

NSAID Allergy

- NSAIDs are so diverse that an IgE antibody to one does not recognize one from another
  - Reactions can be IgE-mediated (sometimes)
- NSAIDs (including aspirin) are COX inhibitors
- Pseudoallergic cross-reactivity between several NSAIDs is more likely to be mediated through COX-1 inhibition
- No tests available to confirm the diagnosis

More than 20 million American use an NSAID regularly
NSAID Allergy

1. COX-1 inhibition
2. Decreased prostaglandin E2 synthesis
3. Decreased 5-lipoxygenase inhibition
4. Proinflammatory moiety and bronchoconstrictor overproduction and release

NSAID Allergy

• Agents that inhibit COX-2 but not COX-1 may be safe in patients with
  – aspirin-exacerbated respiratory disease (AERD)
  – NSAID-induced cutaneous reactions
• Acetaminophen and certain salicylate derivatives such as sodium salicylate do not inhibit COX enzymes at usual doses, but may inhibit COX-1 at high doses

Desensitization

• Why desensitize?
• Usually, we can simply select another antibiotic, but in rare situations (e.g. syphilis), penicillin is needed
• Successive, rapid progressive penicillin re-administration (usually over 4 to 8 hours) can provide temporary tolerance
  – Developed 50 years ago
  – Used in 15 pregnant woman who had syphilis

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose</th>
<th>Source: Stark et al.39</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>100 U oral (penicillin V)</td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>200 U oral</td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>400 U oral</td>
<td></td>
</tr>
<tr>
<td>45 min</td>
<td>800 U oral</td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>1,600 U oral</td>
<td></td>
</tr>
<tr>
<td>1 h: 15</td>
<td>3,200 U oral</td>
<td></td>
</tr>
<tr>
<td>1 h: 30</td>
<td>6,400 U oral</td>
<td></td>
</tr>
<tr>
<td>1 h: 45</td>
<td>12,800 U oral</td>
<td></td>
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<tr>
<td>2 h</td>
<td>25,000 U oral</td>
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<tr>
<td>2 h: 15</td>
<td>50,000 U oral</td>
<td></td>
</tr>
<tr>
<td>2 h: 30</td>
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<tr>
<td>3 h</td>
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<tr>
<td>3 h: 15</td>
<td>200,000 U subcutaneous (penicillin G)</td>
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</tr>
<tr>
<td>3 h: 30</td>
<td>400,000 U subcutaneous</td>
<td></td>
</tr>
<tr>
<td>3 h: 45</td>
<td>800,000 U subcutaneous</td>
<td></td>
</tr>
<tr>
<td>4 h</td>
<td>1,600,000 U intramuscular</td>
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Desensitization

• Only immediate type 1 reactions to penicillin and b-lactams respond to rapid desensitization
  – Most human antibodies are IgG and protect against infection.
  – Type 1 reactions are IgE mediated; recognize agents that are not usually infectious
  – Reactions range from mild (sneezing and runny nose, or a few rashes) to severe (anaphylaxis or cardiopulmonary arrest)
• No desensitization for
  – maculopapular rashes
  – erythema multiforme
  – SJS or TENs
  – bullous erythema
  – erythroderma
  – serum sickness
  – hemolytic anemia
  – neutropenia
  – thrombocytopenia
  – acute interstitial nephropathy
Desensitization

- Reintroduces the drug slowly
- Divides the total dose into dilutions
- Delivers the dose very slowly over 12 to 16 steps
- Doubles the dose each time
- Tricks the immune system

Desensitization

- If a reaction occurs, stop the drug and treat the reaction, then continue
  - Diphenhydramine for hives
  - Albuterol for breathing
  - Steroids for throat tightness or oral swelling

Desensitization

- If it works with penicillin, can it work with other essential drugs?
  - aspirin for cardiac disease control and prevention
  - insulin in diabetes
  - chemotherapy drugs during cancer recurrence
  - chimeric humanized MABs in chronic inflammatory diseases
  - cystic fibrosis patients

Insulin

- Insulin allergy rare since human recombinant insulin and insulin analogs now available
- Human insulin and insulin analogs can also act as potential allergens, causing local, systemic, immediate or delayed reactions
- Insulin-associated allergy can be divided into
  - type I (IgE-mediated),
  - type III (IgG-mediated immune complex)
  - type IV (T-cell-mediated delayed-type) hypersensitivity.

Insulin

- Type I hypersensitivity, with its local edema, itching, wheals, and flares, is most common
  - May employ symptom relief using antihistamines or insulin desensitization
  - Systemic corticosteroids can be used but aggravate hyperglycemia
- Check injection technique!!!

Desensitization

- For drugs given daily, desensitization only needs to be performed once
- If the medication is taken daily, the desensitization state persists
- Studies have not been performed to test exactly how long desensitization lasts
- Generally, if more than 2 days have passed since the last dose, perform the desensitization again
- Patients being desensitized for chemotherapy and MABs, need extended infusions at every dose
What’s the Care Plan with the Interdisciplinary Team?

- Interdisciplinary care = organized, proactive, coordinated and multidisciplinary approach
- In ADR management
  - Confirm the diagnosis
  - Consider or r/o drug challenge
  - Find an appropriate algorithm or protocol
  - Document

What’s the Care Plan with the Interdisciplinary Team?

<table>
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| Physician and Specialist   | • Assess the nature of the ADR  
  • Document the ADR with laboratory confirmation if possible  
  • Propose and initiate discussion of approach |
| Pharmacist                 | • Recommend interventions  
  • Educate about possibilities and limitations  
  • Discuss administration and processes  
  • Elicitate specifics (e.g. FAS ligand antibody content)  
  • Look for possible alternatives |
| Nurse                      | • Administer medication  
  • Monitor for adverse events (i.e. blood pressure, cardiac parameters, O2 saturation monitor) |
| Respiratory therapist      | • Maintain a constant state of readiness |

Redundant Tasks

- Everyone on the team needs to
  - Obtain a detailed history of the ADR, including the timing and symptom pattern
  - Agree on WHO will handle WHICH TASKS
  - Deliver the same information to the patient
  - Counsel and educate the patient and caregivers

What Do Patients Want to Know?

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<thead>
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<th>Common Question</th>
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  • For desensitization for antineoplastics and MABs  
  • The first treatment will be in the hospital  
  • Subsequent care may be in the clinic |
| What if I react to the treatment? | • Discuss supportive care, stressing the antihistamine-corticosteroid-albuterol triad |
| Can I ever take this drug again? | • For severe allergy, no  
  • After desensitization, it’s a risk/benefit issue |

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| Do I need to get my affairs in order? | • At admission, hospital staff will work with the patient  
  • To develop advance directives and similar paperwork  
  • Discussing prognosis is a difficult call |
| Who’s in charge of what?        | • The physician will decide if treatment or desensitization is warranted  
  • The pharmacist is the best source for drug information  
  • The nursing staff will monitor, coordinate care, and educate |
| What are the side effects of the supportive care or premedication regimen?  | • During desensitization, antihistamines are given liberally. Advise patients not to drive for the remainder of the day. |
| What will my OOP costs be?      | • Unlikely. |

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