

# Update in Drug Hypersensitivity

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# Adverse Drug Reactions (ADR)

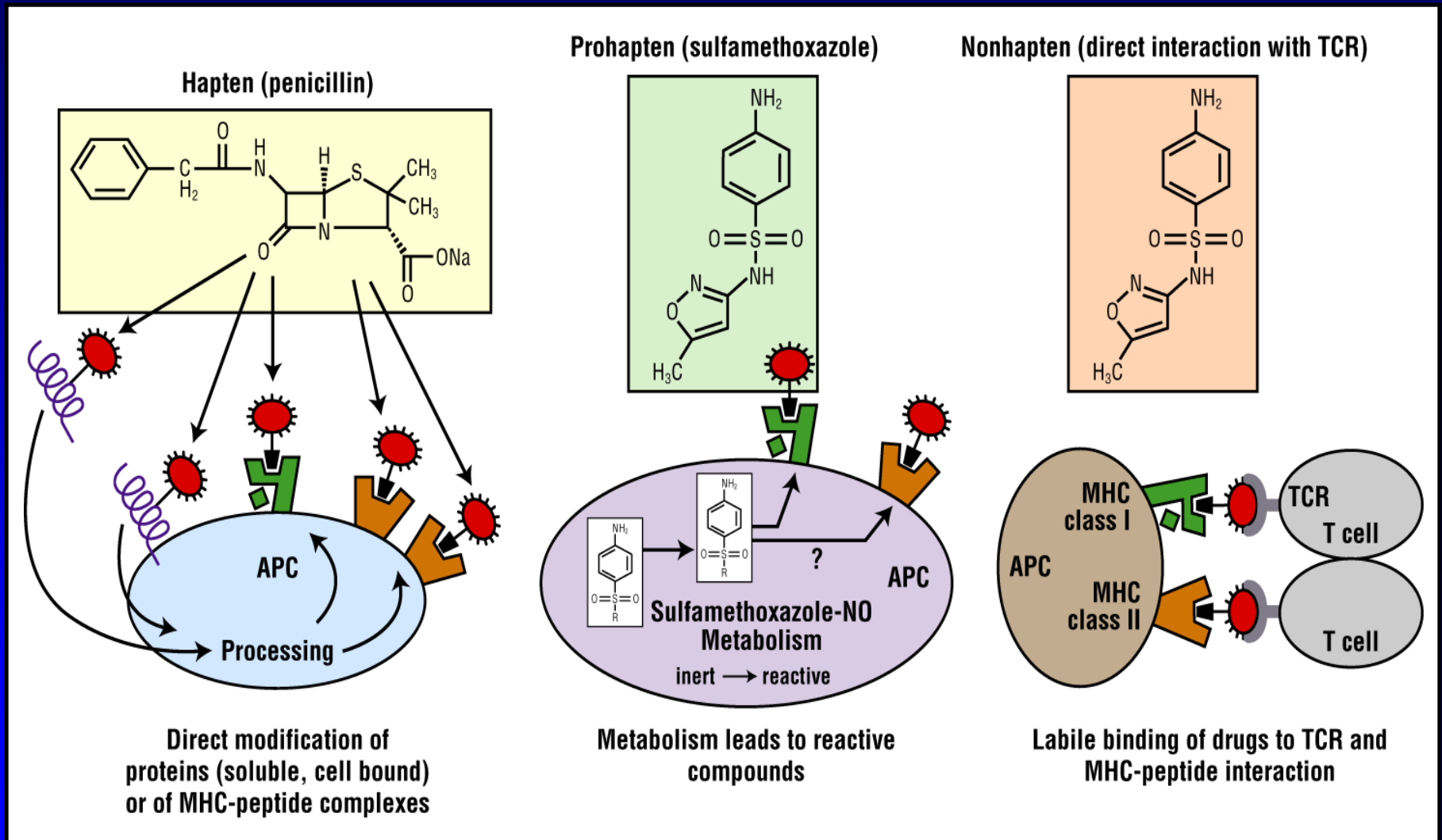
Any untoward reaction to a medication

- **Type A**: predictable, dose dependent, related to pharmacological action of the drug e.g. gastritis with NSAIDs (80-85% of all ADRs)
- **Type B**: unpredictable, dose-independent, unrelated to pharmacologic activity of the drug, only occur in susceptible individuals (10-15% of ADRs)
  - Drug intolerance (e.g. tinnitus with 1 dose ASA)
  - Drug Allergy
  - Pseudoallergic reactions

# Risk Factors for Drug Hypersensitivity

- Drug administration
  - Dose, route of administration, duration of treatment, repetitive exposure to drug
- Drug-specific
  - Molecular weight
  - Complexity
  - Chemical properties of drug

# Immune Recognition of Drug Antigens



Pichler WJ. Delayed drug hypersensitivity reactions. Ann Int Med 2003;139:683-

Courtesy M. Dykewicz MD

# Mechanisms (Gell and Coombs)

## Type I - Immediate Hypersensitivity

IgE mediated (e.g. anaphylaxis)

## Type II - Cytotoxic Reactions

IgG/IgM antibody and complement mediated hemolytic anemia, thrombocytopenia, granulocytopenia.

Heparin induced thrombocytopenia from antibody responses to heparin-platelet factor 4 complex, associated with thrombosis



# Type III - Immune Complex

## Serum-sickness reactions

- Immune response: IgG/IgM, complement
- 1-4 weeks after anti-sera (classic) or drugs

- Presentation variable

- Fever: nearly 100%
- Skin lesions: 95%
- Arthritis/ arthralgias (10-50%)
- Lymphadenopathy (10-20%)



Lawley. NEJM  
1984;311:1407

- Treatment: antihistamines, corticosteroids

# Type IV : Delayed Type Lymphocytic Reactivity: Extended Classification

Type IVa	Th1 (IFN- $\gamma$ )	Monocyte activation	Eczema
Type IVb	Th2 (IL-5, IL-4)	Eosinophilic inflammation	Maculopapular, bullous exanthema
Type IVc	CTL (perforin & granzyme B)	CD4+ and CD8+ mediated killing of cells (e.g. keratinocytes)	Eczema, maculopapular, bullous, pustular exanthema
Type IVd	T cells (IL-8)	Neutrophil recruitment and activation	Pustular exanthema

# Bullous Exanthema

- Combination of Type IVb and Type IVc mechanisms
- Erythema multiforme minor
- Erythema multiforme major
- Stevens-Johnson syndrome  
    < 10% body surface
- Toxic epidermal necrolysis  
    > 30% body surface



**Erythema multiforme minor**

Courtesy of Michael Redman, PA-C



**Stevens Johnson Syndrome**

Courtesy of Alan B. Storrow, MD

# Case History: Exantham

- 7 yo girl seen by pediatrician with CC: burning during urination, no other complaints, no significant PMH or FH
- No fevers/chills, hematuria, no prior medication allergies and not currently on any medications
- PE: afebrile, no rashes, unremarkable
- Labs: Urinalysis: WBC and microscopic hematuria
- Started on 10 d course of amoxicillin
- 8 days after starting medication an itchy rash developed which progressed over next 24h
- Presented back to pediatrician with symmetrical eruption, no blisters, fevers, arthralgias, or purpura.

## Morbilliform drug eruption



Drug-induced exanthems, such as this morbilliform eruption, often begin in dependent areas and generalize.

*Courtesy of Andrew Samel, MD.*



**Morbilliform drug eruption is a non-immediate type IV allergic reaction involving drug-specific T cells (CD4+) with direct cytotoxic effects and release of pro-inflammatory factors.**

# Penicillin: Beta Lactam Antibiotics

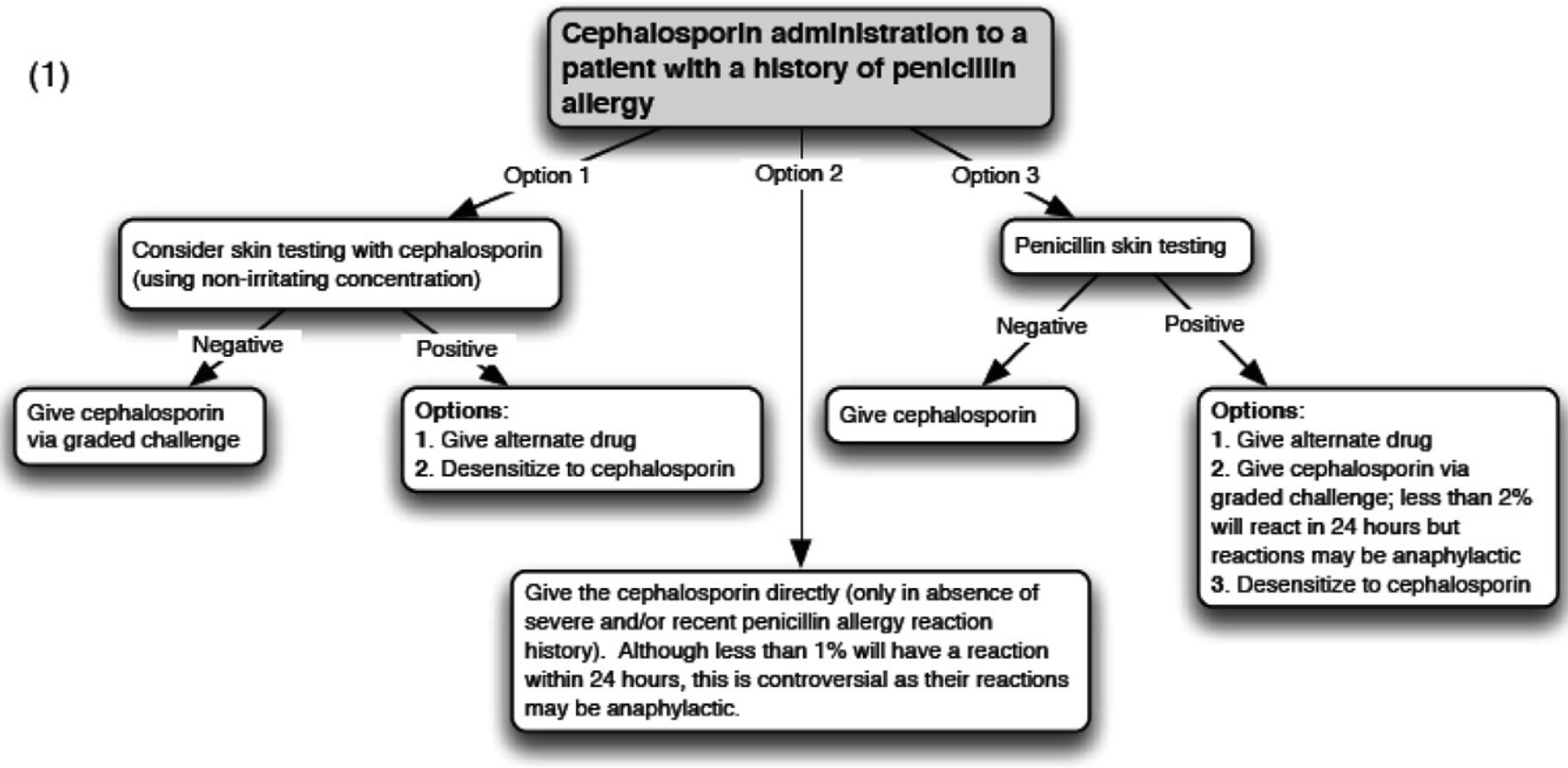
- Skin testing most reliable to make diagnosis.
- RAST testing not recommended
- Must haptenate to become active, majority is penicilloyl (95%) = major determinant (pre-pen) minor determinants: penicilloate and penilloate (not cross-reactive)
- “aged” PCN does not spontaneously form minor determinants
- PCN Skin test negative to PRE-PEN and PCN G (10,000 u/mL) similar reaction rates to PCN challenge as those tested with the full panel
- Risk of sensitization with skin testing very low (<3%)<sup>1</sup>
- Resensitization is very rare, if PCN allergic, tolerated an oral course, do not need to repeat each subsequent course of PCN (consider repeat testing if high dose parenteral PCN)<sup>2</sup>.

1. Nugent FS et al. Determination of the incidence of sensitization after penicillin skin testing. *Ann Allergy Asthma Immunol.* 2003; 90: 398-403.

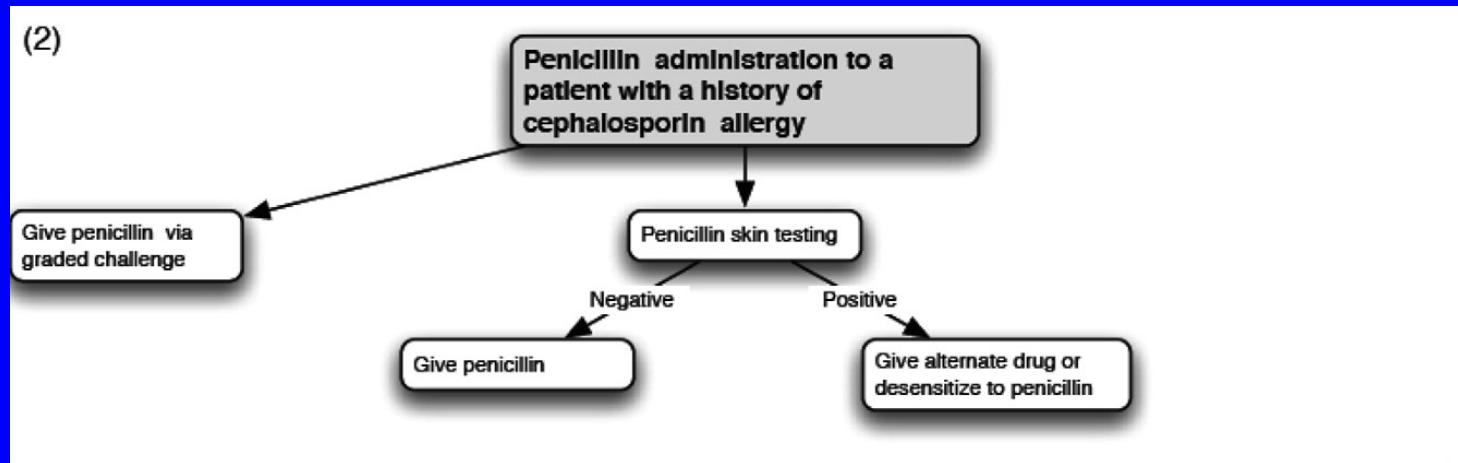
2. Macy E. Elective penicillin skin testing and amoxicillin challenge effect on outpatient use, cost and clinical outcomes. *JACI.* 1998; 102: 281-85.

# Cephalosporins

(1)

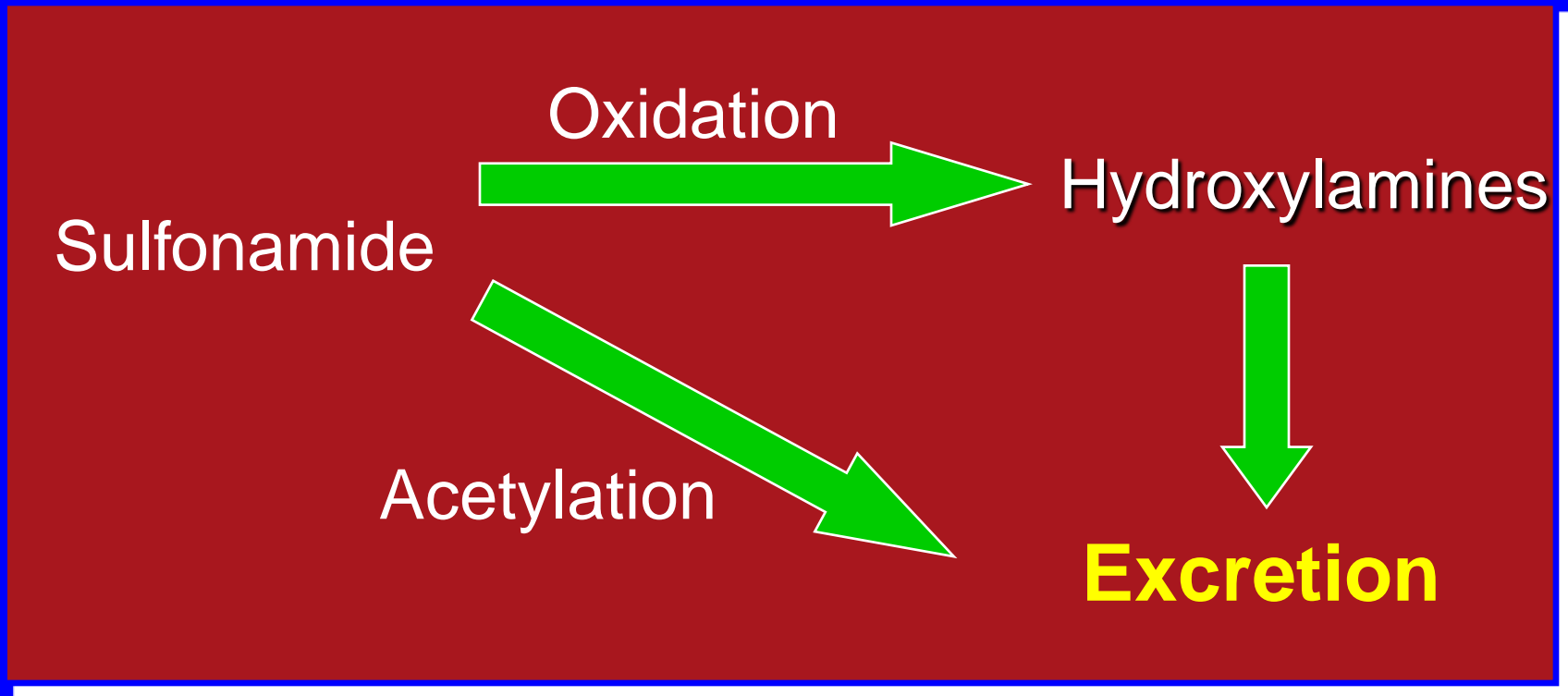


# HX of Cephalosporin Allergy: PCN Administration



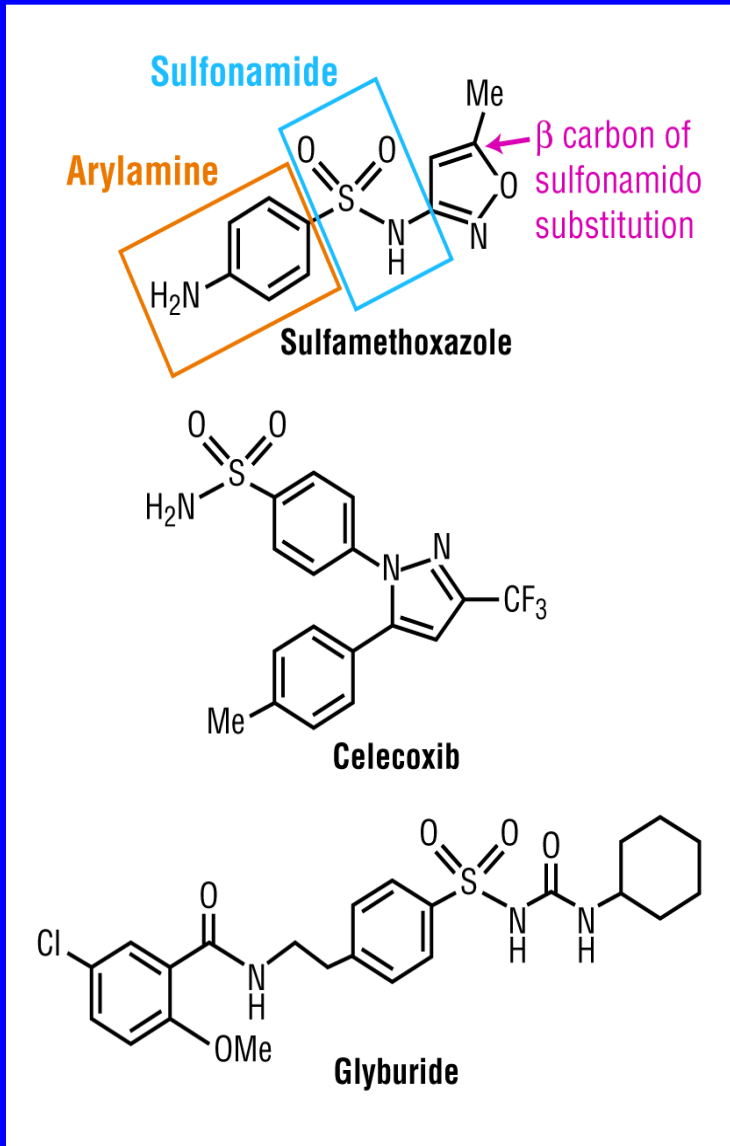
- Patients allergic to amoxicillin should avoid cephalosporins with identical R-group side chains (cephalexin, cefaclor, loracarbef)
- Monobactam (Aztreonam) only x-reacts with ceftazidime
- Carbapenems: low level of cross-reactivity with PCN
  - PCN skin test positive or history + : give via graded challenge

# Acetylator Phenotypes and Sulfonamide Sensitivity



- Slow acetylators almost twice as likely to develop sulfa allergy

# Cross reactivity between antibiotic and non-antibiotic sulfonamides?



## Sulfonamide antimicrobials

- aromatic arylamine group
- metabolized to hydroxylamines
- partial cross-reactivity among sulfa antibiotics

## Sulfonamide derivatives

- e.g., celecoxib, diuretics, sulfonylureas, sumatriptan
- (SO<sub>2</sub>-NH<sub>2</sub>), “nonaromatic amines” (no arylamine)
- not immune cross reactive with sulfa antibiotics

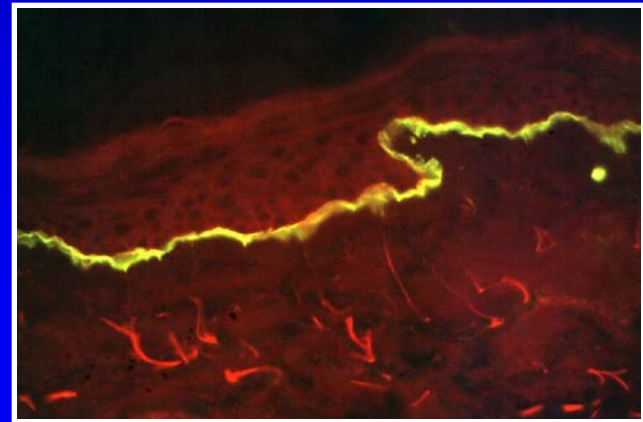
Figure adapted from MEDSCAPE

# Vancomycin Reactions

- Red man syndrome
  - Rate related histamine release
  - Reduce rate ( $< 10$  mg/min)
  - Use H1 (not H2 blockers)
- IgE mediated anaphylaxis
- Linear IgA bullous dermatosis

# Linear IgA Bullous Dermatositis (LABD)

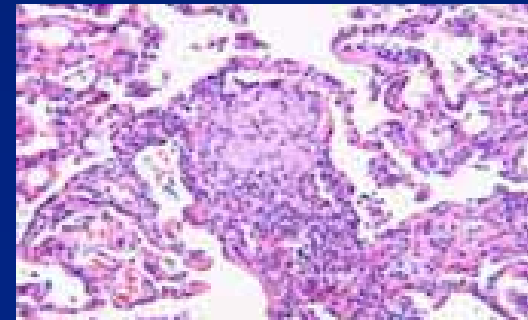
- Vancomycin most frequent cause
- Bullous disease, annular, may confuse with TEN, skin sloughing may result
- IgA deposited in basement membrane zone



# Reactions TO NSAIDS

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1. Allergic: single drug anaphylaxis
2. Pseudoallergic: result of inhibition of COX-1 enzyme
3. Idiosyncratic: aseptic meningitis, hypersensitivity pneumonitis, thrombocytopenia, interstitial nephritis, erythema multiforme, fixed drug eruptions, toxic epidermal necrolysis, Stevens Johnson syndrome, erythema nodosum, maculopapular eruptions, and bullous leukocytoclastic vasculitis



# Pseudoallergic Reactions to NSAIDs

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- Type 1: **NSAID-induced asthma and rhinosinusitis** — Aspirin exacerbated respiratory disease (chronic rhinosinusitis, polyps, asthma)
- Type 2: **NSAID-induced urticaria/angioedema (CIU)** in pts with chronic urticaria
- Type 3: **NSAID-induced urticaria/angioedema** in otherwise asymptomatic individuals
- Type 4: **Blended reactions**: otherwise asymptomatic, involve skin and respiratory tract triggered by COX-1 inhibition

Modified from: Stevenson, DD, Szczeklik, A, Ann Allergy Asthma Immunol. 2002;87:177-179.

# Allergic Reactions to NSAIDs

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- Elicited by single NSAID or rarely, by more than one if share similar molecular structures
- Need prior exposure to get sensitized
- Seen most often with ibuprofen
- Types of reactions
  - Urticaria and angioedema
  - Anaphylaxis (no confirmed cases to ASA)

# Approach to Cutaneous Reactors to COX-1 Inhibitors

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- NSAID-Induced urticaria/angioedema
  - Urticaria triggered by any Cox-1 inhibiting NSAID
  - Normals (no CIU): can be desensitized
  - Patients with Chronic Idiopathic Urticaria/angioedema:  
cannot be desensitized

Stevenson, DD, Szczeklik, A, Ann Allergy Asthma Immunol. 2002;87:177-179.

# Approach to Cutaneous Reactors to COX-1 Inhibitors

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- Single drug-induced urticaria/angioedema/anaphylaxis
  - If able to tolerate ASA :
    - Give a different NSAID (full dose challenge)
    - If unknown: ASA challenge (81mg or 325 mg)
    - anaphylaxis: 10mg ASA doubling every 30 minutes in ICU.
- Other/ “blended” reactions:
  - Celecoxib (& other highly selective Cox2 inh) typically OK

# Classification of Non-steroidal Anti-inflammatory

## Drugs by Structural Classes

### ENOLIC ACIDS

#### OXICAMS

Feldene (Piroxicam)

#### PYRAZOLES

Butazolidin (phenylbutazone)

Tandearil (oxyphenbutazone)

### CARBOXYLIC ACIDS

#### SALICYLATES

Aspirin  
(acetylsalicylic acid)  
Disalcid (salsalate)  
Dolobid (diffunisal)  
Trilisate (choline magnesium tri salicylate)

#### ACETIC ACIDS

Indocin (indomethacin)  
Lodine (etodolac)  
Clinoril (sulindac)  
Tolectin (tometin)  
Zomax (zomepirac)  
Voltaren (diclofenac)

#### PYRROLO-PYRROLE

Toradol (ketorolac tromethamine)

#### FENAMATES

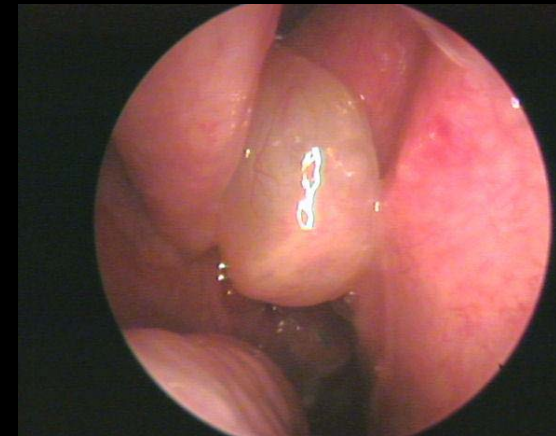
Meclomen  
(meclofenamate)  
Ponstel (mefenamic acid)

#### PROPIONIC

Motrin, Rufen  
(ibuprofen)  
Naprosyn (naproxen)  
Anaprox (naproxen sodium)  
Oraflex  
(benoxaprofen)  
Nalfon (fenoprofen)  
Orudis (ketoprofen)

# Aspirin-Exacerbated Respiratory Disease (AERD)

- Chronic eosinophilic rhinosinusitis, nasal polyposis, asthma
- ASA/NSAIDs induce rhinitis/asthma attacks
- Progressive disease despite careful avoidance of NSAIDs and ASA



## Selection of Patients for ASA desensitization

- All AERD patients except those controlled by topical steroids, long-acting beta agonists and LTMDs alone
- Patients with recurrent or chronic sinusitis and nasal polyps
- Individuals who require anti-platelet therapy with ASA or other COX-1 inhibiting NSAIDs

## Dosages of ASA for the Treatment of AERD

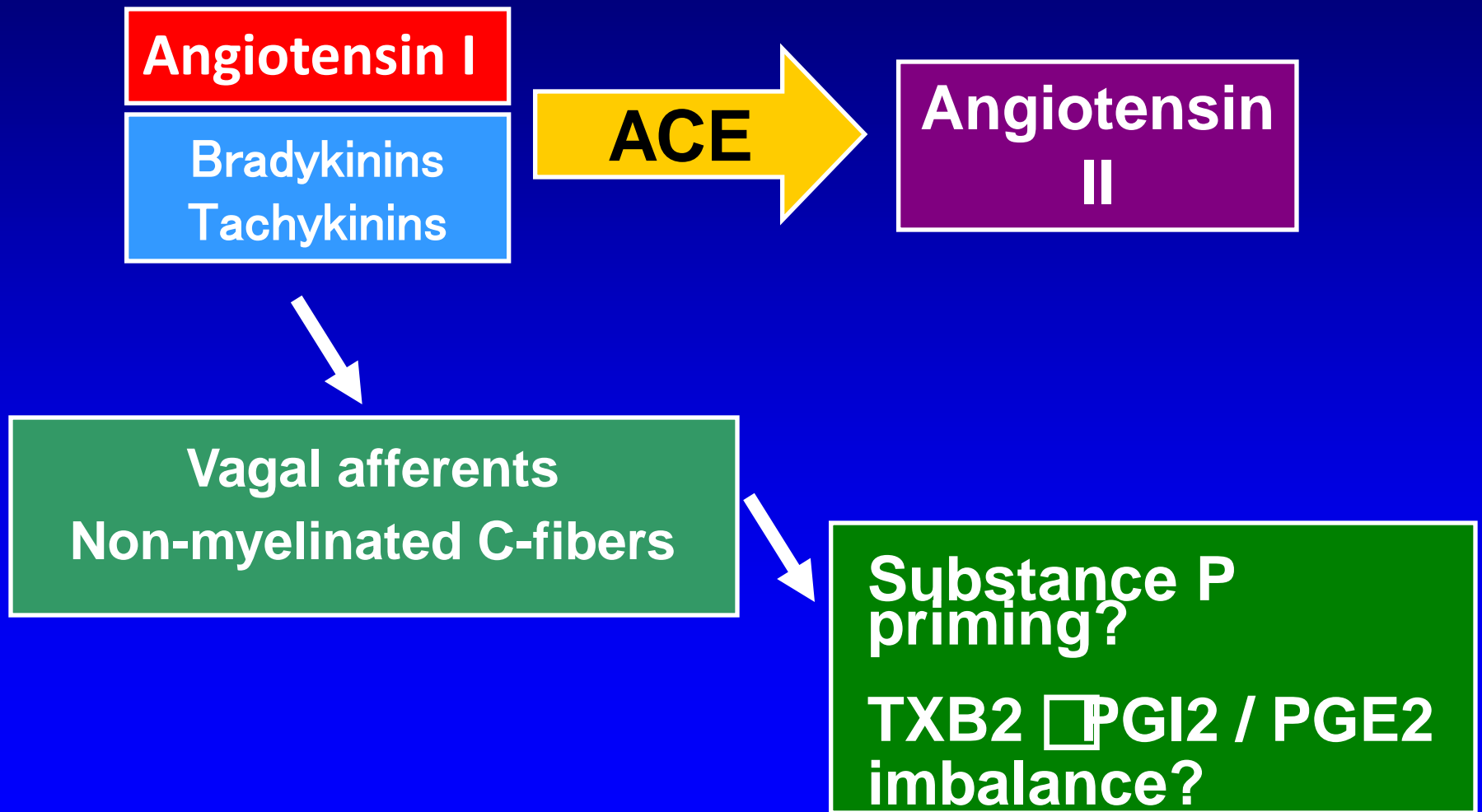
- 81 mg q.d. OK to remain desensitized for cardiovascular disease prevention
- 325 mg q.d. OK to be cross-desensitized to any doses of all NSAID's
- 650 mg BID initial starting dose for treatment of AERD; about 50% can decrease to 325 mg BID after 6-12 months

# ASA Treatment of AERD

- Aspirin desensitization as add on therapy:
  - (1) Decrease nasal congestion
  - (2) Decreases need for additional sinus/polyp surgery
  - (3) Decreases infectious sinusitis ( from 5 to 2/year)
  - (4) Improves sense of smell
  - (5) Improves asthma control: Direct or indirect
  - (6) Reduces need for nasal corticosteroids
  - (7) Reduces need for bursts of systemic steroids
  - (8) Reduces daily systemic steroids (10.7 to 3.8 mg.)

# ACE Inhibitors

Inhibit angiotensin converting enzyme (ACE)



# Angiotensin-Converting Enzyme Inhibitor: Cough and Angioedema

- Cough: within hrs of first dose to weeks of starting tx. Women, nonsmokers, and Chinese patients higher incidence
  - Resolves 1-3 wks post stopping
- Angioedema: 1 to 7/1,000 pts, African Americans at higher risk. Can occur even after being on drug for years. (mean onset 1.8 y)
  - 1/3 of all cases presenting to ER for angioedema
  - Head and neck, less common: GI tract
  - Mediated by bradykinin<sup>1</sup>
  - Angiotensin II receptor blockers ok, < 10% of patients experience persistent angioedema when switched<sup>2</sup>
  - Management: stop medication, management of airway (antihistamines not helpful) severe cases:

Banerji A. et al. Multicenter Study of patients with ACE-Inhibitor-induced angioedema who present to the Emergency department. Ann Allergy Asthma Immunol. 2008; 100: 327-32.

Haymore BR et al. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema to ACE-Is Ann Allergy Asthma Immunol. 2008; 101: 495-9.

# Radiocontrast Media (RCM)

- Anaphylactoid reaction (non-IgE mediated anaphylaxis)
  - 1%-3% ionic RCM studies <0.5% non-ionic RCM studies
  - Fatality rate 1 to 2 per 100,000 procedures
- Risk Factors: female, asthma, hx of prior anaphylactoid reaction (6-10x), beta blocker use, & cardiovascular conditions.
- Not associated with shellfish allergy
- European study: suggested skin testing helpful in some patients not yet confirmed in larger trials<sup>1</sup>

# RCM continued...

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- Pretreatment: prednisone 50mg 18, 12 and 6 h before (13, 7 and 1 h)
- Diphenhydramine 50mg IM 1 hour before
- No use of H2-blockers ( assoc with ↑ rate of RCM reactions)
- Delayed Reactions: >1h to 1 week 2% of patients pretreatment typically does not work.
- Occ case reports of SJS and TEN
- **Gadolinium**: much less common cause of reactions  
Nephrogenic systemic fibrosis if with renal insufficiency<sup>2</sup>

1. Greenberger PA et al. Prophylaxis against repeated radiocontrast media reactions in 857 cases. Adverse experiences With cimetidine and safety of beta-adrenergic antagonists. Arch Intern Med 1985; 145: 2197-2000.

2. Todd DJ, Kay J. Nephrogenic systemic fibrosis: an epidemic of gadolinium toxicity. Curr Rheumatol Rep 2008; 10:195-204

# Case #2: 45 yo woman with a pustular rash

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- 2 d h/o acute-onset, mildly pruritic rash.
- Started in axillae and groin now more generalized
- New onset fever this AM
- Dxd with PNA 4 days prior on azithromycin
- PMH: unremarkable, no personal or FH of psoriasis or drug allergy.
- Non-smoker with 2 young children at home and is a school teacher.
- PE: 102.0° F (38.9° C) p 88 bpm BP 124/76 RR 16
- Fine crackles base of left lung
- Skin Exam: hundreds of nonfollicular pustules on erythematous bases, all over body including face no crust or scale. No lesions on palms, soles, mucous membranes



This 46-year-old woman developed generalized erythema, most severe on the proximal extremities and trunk, several hours after receiving parenteral normal saline with iron, amino acids, and cobalamin at a medical clinic. Numerous confluent pustules superimposed on the erythematous edematous confluent plaques followed one day later. Although she was afebrile, leukocytosis (18,000/cubic mm) and elevated CRP were noted. A bacterial culture from the pustules was negative. A skin biopsy showed intracorneal pustules with numerous neutrophils and neutrophilic infiltration of the epidermis and upper dermis.

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## Case 2. Acute Generalized Exanthematous Pustulosis

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- Elevated WBC with increased PMNs, can see slight elevation of eos.
- Elevated CRP and ESR
- Culture and Gram Stain of lesions: negative
- Punch Biopsy: spongiform subcorneal pustules, edema of papillary dermis, marked perivascular infiltration of neutrophils, rare eosinophil

# AGEP

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- Most commonly assoc. with drugs: beta lactams and macrolides (not sulfonamides), mercury, NSAIDs, carbamazepine, acetaminophen
- Infectious assoc: enteroviruses and parvovirus B19
- Acute onset of reaction (can be within hours to days) first edematous erythema followed quickly by appearance of pustules
- Benign disease with self-limited course, pustules resolve spontaneously 4-10 d, usually just need mild supportive care, emollients and topical CCS.

# **DRESS (Drug-Related Eosinophilia with Systemic Symptoms)**

- Synonym: drug (or anticonvulsant) hypersensitivity syndrome
- Causes: anticonvulsants, dapsone, minocycline, sulfamethoxazole, sulfasalazine, allopurinol
- Severe systemic disease: lymphadenopathy, fever, skin eruptions, eosinophilia in >90%, fatal in 10%
- Activated T cells in circulation
- Inherited deficiency of epoxide hydrolase



# Clinical Evaluation and Diagnosis of Drug Hypersensitivity

- History
  - Current and past drug use
  - Known toxicity/allergenicity of drugs used
  - Interval between drug therapy and reaction
- General physical exam
- General lab studies: e.g. CBC, liver, renal studies
- Drug specific immunologic testing
  - Immediate-type skin testing
  - Patch testing
  - Lymphocyte proliferation assays

# Management and Prevention of Drug Hypersensitivity Reactions

- Anaphylaxis: epinephrine, adjunctive agents
- Stop suspect drugs
- Antihistamines
- Glucocorticosteroids
- Induction of tolerance (desensitization) when drug essential
- Slower graded challenge regimens
- Prevention of allergic reactions:
  - Take drug allergy history, avoid cross-reactive drugs
  - Use predictive skin tests when appropriate
  - Proper and prudent drug prescribing
  - Use oral in preference to parenteral drugs