

Medication Allergies and Cross-Reactivity

Andrea Passarelli, PharmD, BCPS
Clinical Pharmacy Specialist,
Neurocritical Care
apassarelli@christianacare.org



CHRISTIANA CARE
HEALTH SYSTEM

Disclosures

I have no relevant financial relationships or commercial interests to disclose for this presentation.

Learning Objectives

At the conclusion of this presentation, the audience member should be able to:

- Explain the pathophysiology of medication allergies and sensitivities
- Describe the risk for allergic cross-reactivity for beta lactam antibiotics, sulfa drugs, opioids, and NSAIDs
- Given a patient case, identify appropriate medication therapy taking into consideration the allergy history

PATHOPHYSIOLOGY

Allergic Drug Reactions

- **Allergic drug reaction**- adverse medication effect that involves immunologic mechanisms
 - Ex. anaphylaxis from β -lactam antibiotics, dermatitis from sulfonamides, serum sickness from phenytoin
- **Allergic-like/pseudoallergic reaction**- not proven to be immune mediated but resembling an allergic reaction
 - Ex. shock after radiocontrast media, aspirin-induced asthma, opiate-related urticaria, flushing after vancomycin
- Account for up to 15% of adverse drug reactions

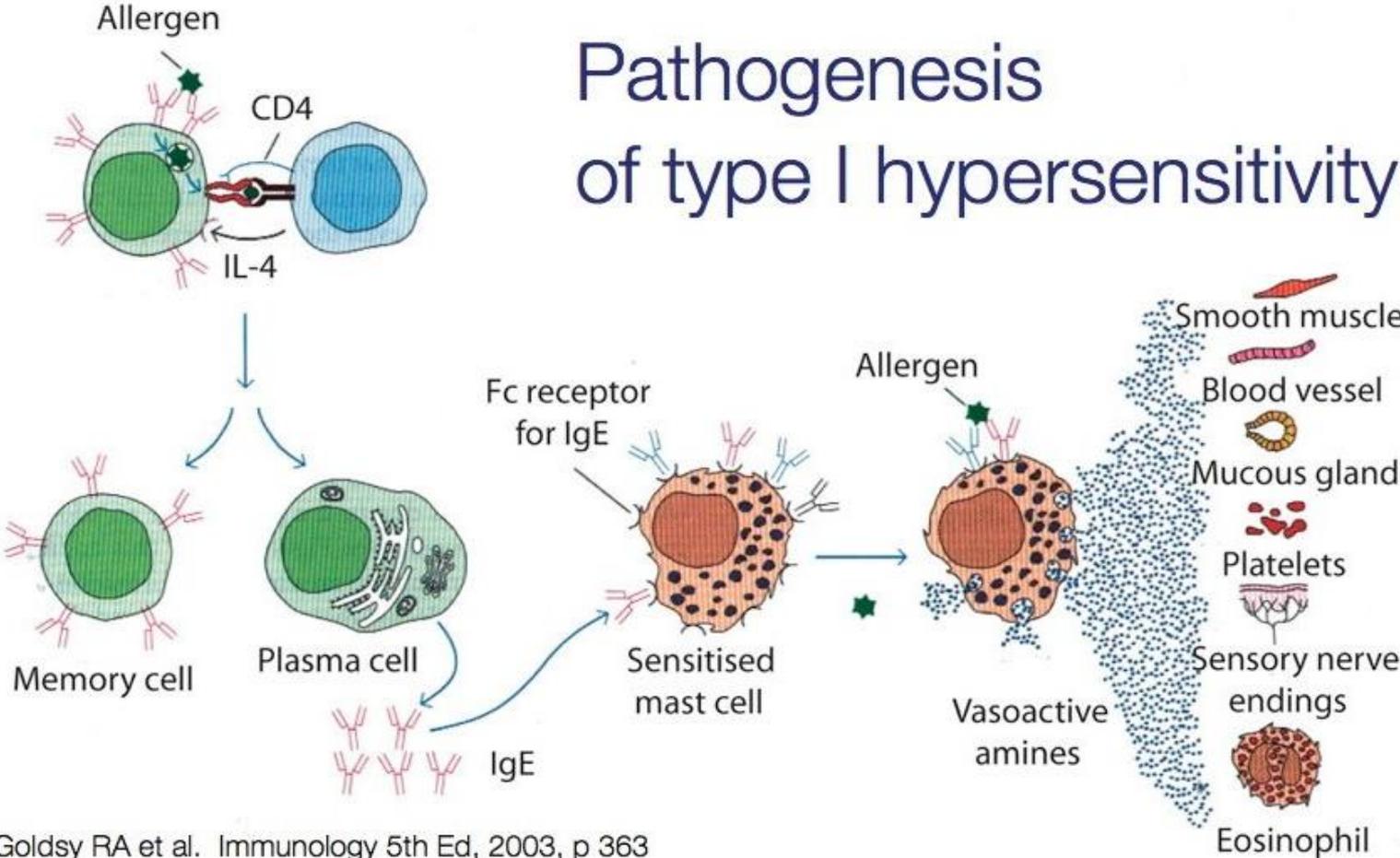
Factors Related to the Occurrence and Severity of Drug Allergies

- Dose
- Duration of exposure
- Metabolism
- Protein-binding
- Route of administration
- Sensitivity of patient
 - Age
 - Genetics
 - Environmental factors

Types of Immune Reactions

Type	Descriptor	Mediators	Onset	Clinical Manifestations
I	Anaphylactic (IgE mediated)	IgE, mast cells, basophils	Within 30 minutes	Anaphylaxis, urticaria, laryngeal edema, wheezing
II	Cytotoxic	Cell-bound Ag, IgM, IgG	5-12 hours	Hemolytic anemia, interstitial nephritis, cytopenias
III	Immune complex	Ag-Ab complexes, complement	3-8 hours	Serum sickness, glomerular nephritis
IV	Cell-mediated (delayed)	T cells	1-3 days	Contact dermatitis
Idiopathic	Precise mechanism unknown		Any time	Fever, hepatitis, interstitial pneumonitis, rash, Stevens-Johnson syndrome

Pathogenesis of type I hypersensitivity



Goldsy RA et al. Immunology 5th Ed, 2003, p 363

Anaphylaxis

- Acute, life-threatening allergic reactions involving multiple organ systems
 - Dermatologic
 - Respiratory
 - Gastrointestinal
 - Cardiovascular
- Accounts for 1500 deaths per year in the US
- Occurs within 30 minutes of exposure
- Monitor for late phase reaction for 12 hours

Treatment of Anaphylaxis

- **Discontinue offending agent!**
- Epinephrine 1:1,000 0.5 mg IM
 - Can be repeated in 15 minutes x 1
 - Counteracts bronchoconstriction and vasodilation
- Steroid (hydrocortisone 250mg IV)
 - Reduces risk of late-phase reaction
- Antihistamine (diphenhydramine 25-50mg IV)
- IV fluids
- Vasopressors for refractory hypotension

Anaphylactoid Reactions

- Similar to anaphylaxis in clinical signs/symptoms
- May produce direct release of inflammatory mediators rather than through IgE
- Ex. vancomycin-induced “red man syndrome”

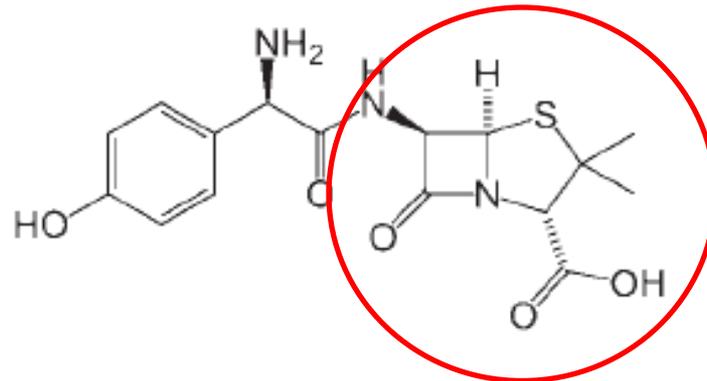
BETA LACTAM ANTIBIOTICS

Penicillin Allergy

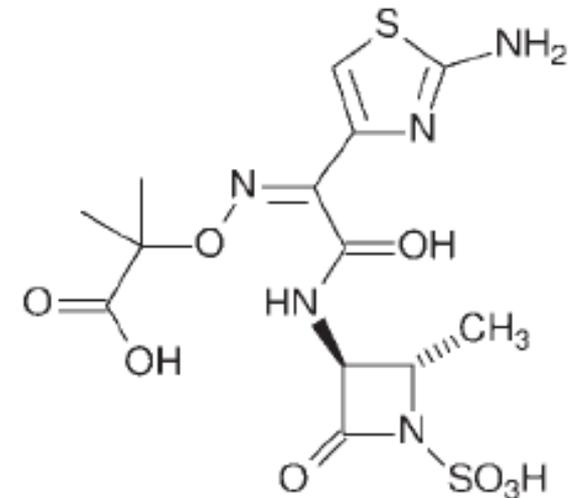
- Major determinant
 - Penicilloyl group, accounts for 85-90% of penicillin breakdown product
- Minor determinants
 - Other chemical byproducts of penicillin
- Risk factors for IgE reaction
 - Multiple short courses of penicillin, especially via parenteral and topical route
 - Allergic diseases
 - Age (most common between ages 20-49)

Beta Lactam Chemical Structure

Amoxicillin, a penicillin



Aztreonam, a monobactam



Imipenem, a carbapenem

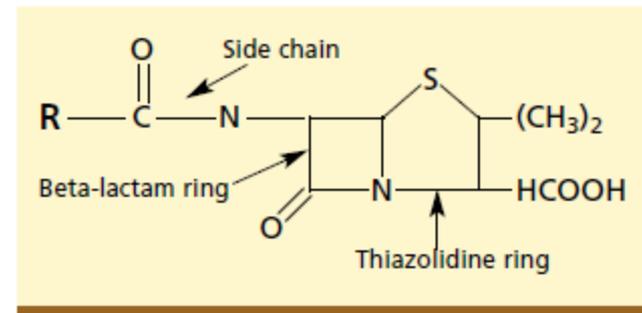
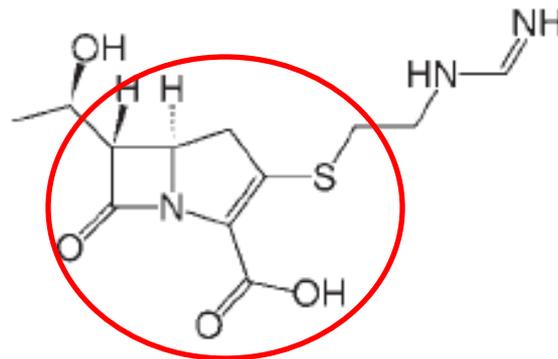


FIGURE 1. Chemical structure of penicillin

Journal of Antimicrobial Chemotherapy (2007) **60**, 107–111

doi:10.1093/jac/dkm146

Advance Access publication 16 May 2007

JAC

Aminopenicillin-induced exanthema allows treatment with certain cephalosporins or phenoxymethyl penicillin

Jiri Trcka^{1,2}, Cornelia S. Seitz¹, Eva-B. Bröcker¹, Gerd E. Gross² and Axel Trautmann^{1*}

¹*Department of Dermatology, Venerology and Allergology, University of Würzburg, Würzburg, Germany;*

²*Department of Dermatology and Venerology, University of Rostock,
Rostock, Germany*

Aminopenicillins

- Up to 100% of patients with viral infection have ampicillin-induced rash (not IgE-mediated)
- Cohort of 71 patients with non-IgE mediated hypersensitivity to aminopenicillins
 - All patients underwent skin testing and graded challenge
 - 97.2% tolerated cephalosporins (cefpodoxime or cefixime)
 - 71.8% tolerated penicillin
- May cross-react with cephalosporins with aminobenzyl side chain (i.e. cephalexin)

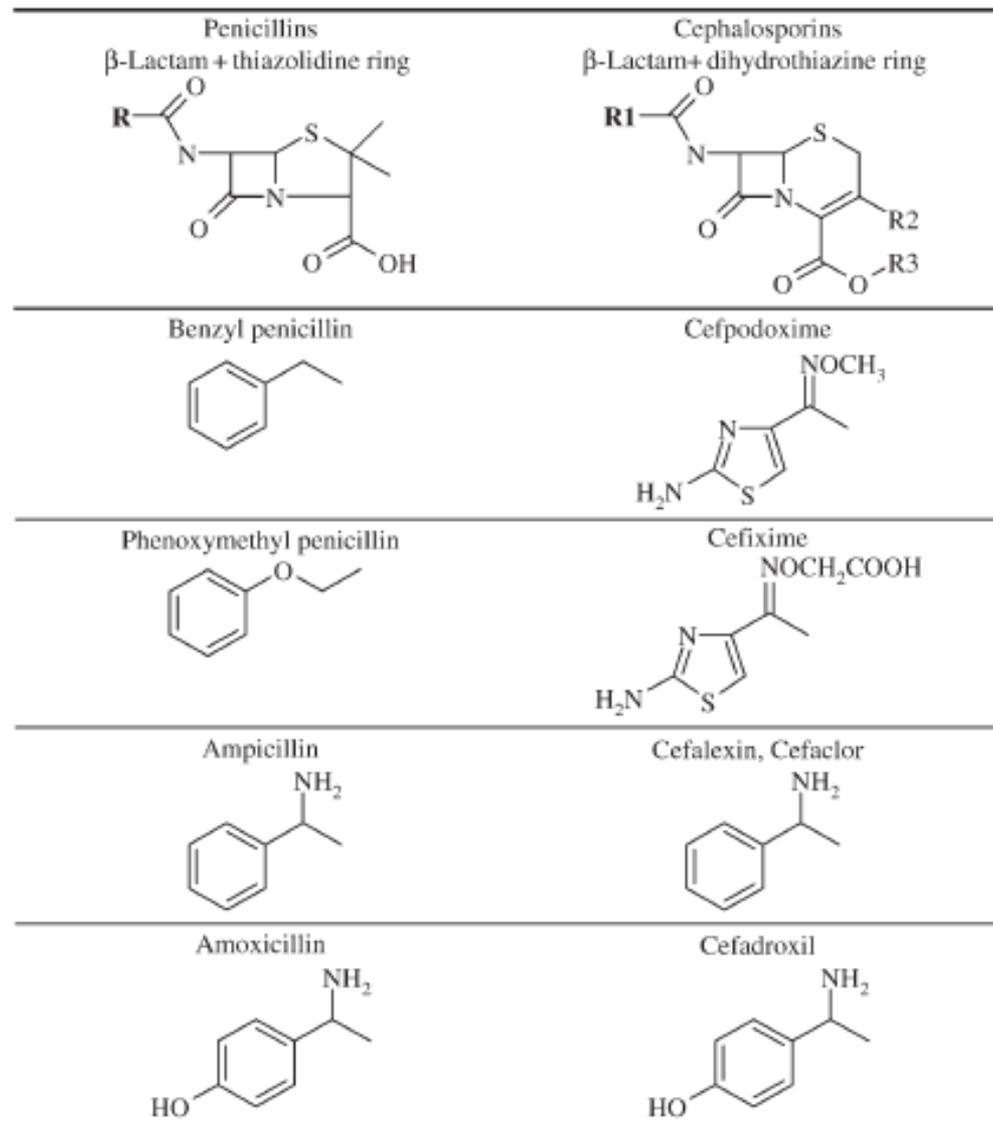


Figure 1. Side chains of β -lactams. Left-hand column, R side chains of different penicillins; right-hand column, R1 side chains of different cephalosporins.

Cephalosporins

- Cross-reactivity with penicillin allergy is up to 10%
 - Higher incidence with 1st generation cephalosporins
 - Patients with negative skin test are at no higher risk than general population
- Management
 - Positive skin test – avoidance or desensitization
 - Mild reaction to penicillin – proceed with caution

Carbapenems

- Incidence of hypersensitivity 0.3-2.3%
- Cross-reactivity
 - Proven, suspected, or possible IgE mediated reaction to β lactams: 1.6 to 5.9%
 - Proven IgE mediated reaction to β lactams: 0.5%
 - Positive PCN skin test: 0.06 to 1.9%
 - Negative PCN skin test: no reaction
- Management
 - In patients with proven IgE mediated reactions to β -lactams, consider graded challenge in ICU

Ann Pharmacother 2009;43:304-15.

Clin Infect Dis 2014;59:1113-22.

Monobactams (Aztreonam)

- No clinical cross-reactivity between β -lactam antibiotics and aztreonam
- Exceptions:
 - Cystic fibrosis patients can develop sensitization reactions
 - Ceftazidime shares similar structure, use in caution with ceftazidime allergy

Penicillin Skin Testing

- Pre-Pen® contains benzylpenicilloyl, the major determinant of penicillin allergies
- Puncture testing vs. intradermal testing
- Negative control required, positive control can be considered
- Negative test associated with risk of Type I allergic reaction < 5%
****in healthy patients****

Penicillin skin test reagents*

Benzylpenicilloyl-polylysine (Pre-Pen full strength)[†]

Penicillin G (10,000 U/mL)

Penicillin minor determinants (mixture, 10–2 M[‡])

Ampicillin (1–3 mg/mL)

Amoxicillin (1–3 mg/mL)

Cephalosporin (1–3 mg/mL)

Saline solution (negative control)

Histamine (positive control)

*One drop of each reagent is used for the prick tests;
0.02 mL is used for the intradermal tests.

[†]Penicillin G concentration of 10,000 U/mL needs to be prepared daily.

[‡]Penicillin minor determinant mixtures are available only at some research centers. Ideal concentration for skin test may vary.

Graded Challenge vs. Desensitization

Graded Challenge

- Test doses given to ensure no reaction
- Ex. 1%, 10%, 100% of total dose
- Use if low likelihood of true allergy

Desensitization

- Many small doses given to prevent anaphylactic reaction
- Many steps, labor intensive
- Use if true allergy is suspected

Intravenous protocol for penicillin desensitization

STEP*	SOLUTION (U/mL) [†]	DOSE (mL)	DOSE (U)
1	100	0.1	10
2	100	0.2	20
3	100	0.4	40
4	100	0.8	80
5	1,000	0.15	150
6	1,000	0.30	300
7	1,000	0.60	600
8	1,000	1.00	1,000
9	10,000	0.2	2,000
10	10,000	0.4	4,000
11	10,000	0.8	8,000
12	100,000	0.15	15,000
13	100,000	0.30	30,000
14	100,000	0.60	60,000
15	100,000	1.00	100,000
16	200,000	25	200,000
17	400,000	25	400,000
18	800,000	25	800,000
19	1,600,000	25	1,600,000
20	3,200,000	25	3,200,000
21	5,000,000	25	5,000,000

*Each step is administered at 15-minute intervals

[†]Use penicillin G for dilutions in 0.9% sodium chloride

Case #1

JT is a 56 yom with a history of DM, HTN, and HLD. He presents with MSSA bacteremia secondary to a diabetic foot infection. He has a history of penicillin allergy.

How would you manage his infection?

SULFONAMIDES

Sulfonamide-Associated Reactions

- Anaphylaxis
- Angioedema
- Erythema multiforme
- Flushing
- Photosensitivity
- Pustular eruption
- Urticaria
- Bullous eruption
- Erythroderma
- Fixed drug eruption
- Lupus erythematosus
- Psoriasis
- Vasculitis
- Exanthema
- Aphthous stomatitis
- Erythema nodosum
- Exfoliative dermatitis
- Sweet's syndrome
- Pruritus
- Stevens-Johnson syndrome
- Toxic epidermal necrolysis
- Serum sickness
- Hepatitis
- Hemolytic anemia

Sulfonamides and Loop Diuretics

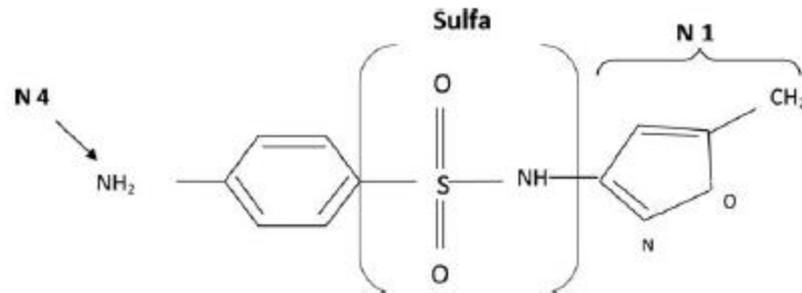


FIGURE 4. Sulfamethoxazole (SMX) molecule structure.

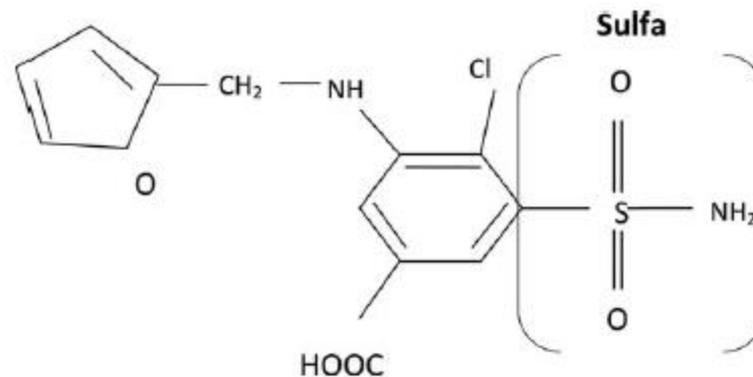


FIGURE 5. Furosemide molecule structure.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Absence of Cross-Reactivity between Sulfonamide Antibiotics and Sulfonamide Nonantibiotics

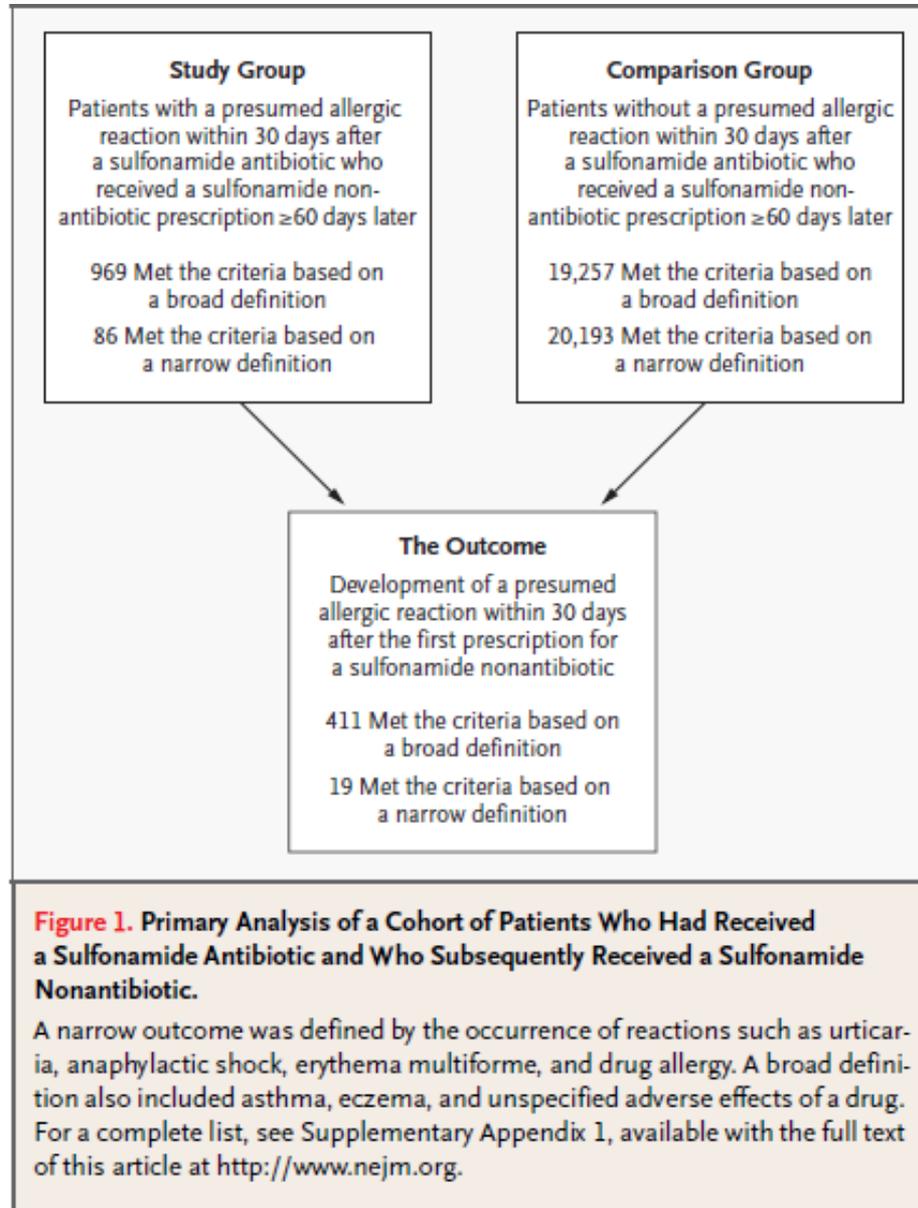
Brian L. Strom, M.D., M.P.H., Rita Schinnar, M.P.A., Andrea J. Apter, M.D.,
David J. Margolis, M.D., Ph.D., Ebbing Lautenbach, M.D., M.P.H., M.S.C.E.,
Sean Hennessy, Pharm.D., Ph.D., Warren B. Bilker, Ph.D., and Dan Pettitt, D.V.M.

Cross-Reactivity of Sulfonamide Antibiotics and Nonantibiotics

- Retrospective cohort study of 20,279 patients who received a sulfonamide antibiotic followed by a sulfonamide nonantibiotic within 60 days

Table 1. Sulfonamide Nonantibiotic Drugs.

Acetazolamide	Cyclopenthiiazide	Glyburide	Probenecid
Acetohexamide	Dapsone	Glymidine	Quinethazone
Bendroflumethiazide	Diazoxide	Hydrochlorothiazide	Sulfasalazine
Benzthiazide	Dichlorphenamide	Hydroflumethiazide	Sulthiame
Bumetanide	Furosemide	Indapamide	Tolazamide
Chlorothiazide	Glibornuride	Mefruside	Tolbutamide
Chlorpropamide	Gliclazide	Methyclothiazide	Torsemide
Chlorthalidone	Glimepiride	Metolazone	Xipamide
Clopamide	Glipizide	Piretanide	
Clorexolone	Gliquidone	Polythiazide	



Cross-Reactivity of Sulfonamide Antibiotics and Nonantibiotics

- Most common reactions observed
 - Asthma (70.1%)
 - Eczema (14.1%)
 - Adverse drug reaction (11.4%)
- 18 patients had symptoms consistent with type I hypersensitivity
- Previous reaction to a sulfonamide antibiotic was associated with a 2.8 times higher likelihood of having a reaction to the nonantibiotic
 - Similar risk was observed for patients with a sulfonamide allergy who received penicillin

Ethacrynic Acid

- Non-sulfa loop diuretic
- Approx. \$3000 per dose for IV
- 1:1 conversion from IV:PO
- Higher incidence of ototoxicity compared to other loop diuretics
- Reserve for patients with allergic reactions to loop diuretics

Case #2

AP is a 72 yof with a history of MI s/p CABG, CHF, HTN, and HLD. Her medication allergies include trimethoprim/sulfamethoxazole (Bactrim®). When asked she says it causes rash.

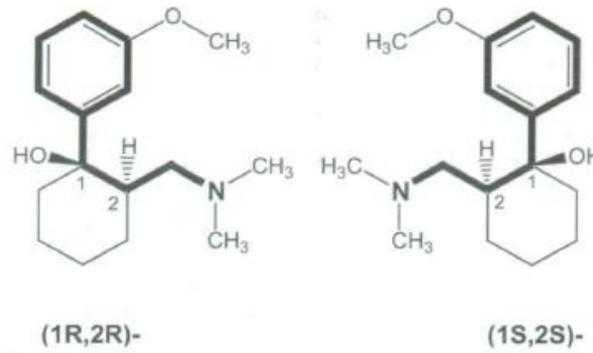
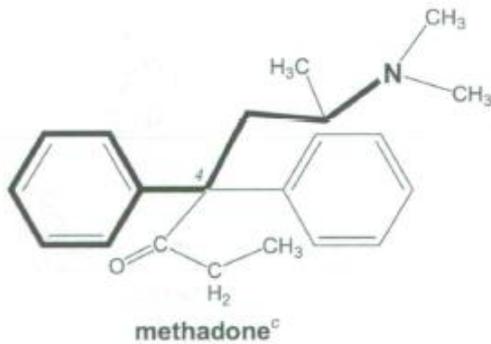
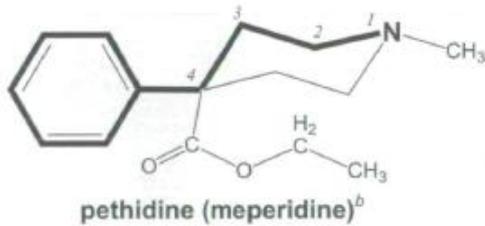
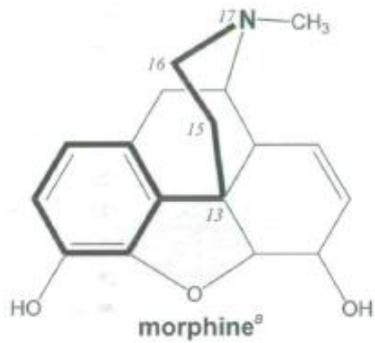
When you order furosemide 40 mg IV in PowerChart you get an alert saying she has a sulfa allergy. What do you do?

OPIOIDS

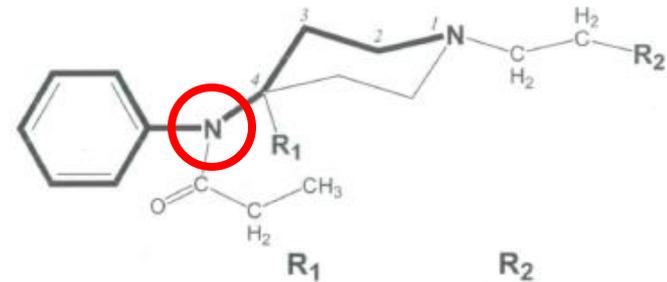
Terminology

- Opiate – drugs derived from opium poppy
 - Morphine, codeine, heroin
- Opioid – natural and synthetic drugs with morphine-like activity
 - Hydromorphone, oxycodone
- Many opiates and opioids are histamine releasers and can cause anaphylactoid reactions

Phenylpropylamine structure



Anilidopropylamine structure (Phenyl links to the propylamine sequence via a nitrogen)

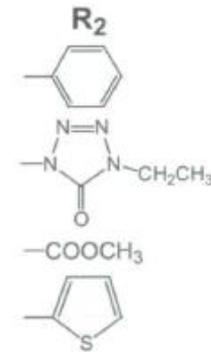


fentanyl^d —H

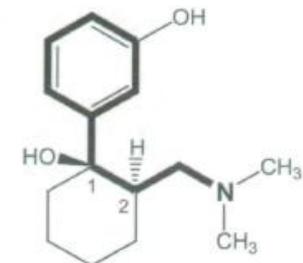
alfentanil^e —CH₂OCH₃

remifentanyl^f —COOCH₃

sufentanyl^g —CH₂OCH₃

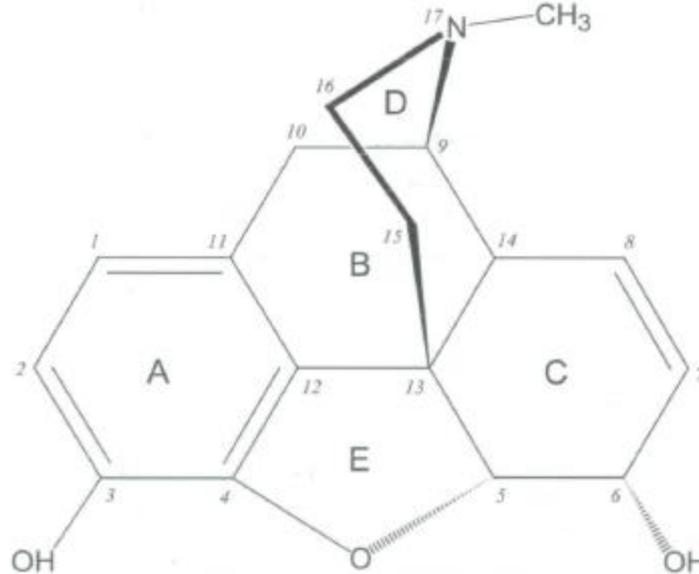


tramadol



O-desmethyltramadol

Structure of morphine and some chemically-related naturally occurring or semi-synthetic clinically-important opioid drugs



Drug	Substituent at position				Bond(s) at positions 7-8
	3	6	14	17	
Morphine	-OH	-OH	-H	-CH ₃	Double
Codeine	-OCH ₃	-OH	-H	-CH ₃	Double
Heroin	-OCOCH ₃	-OCOCH ₃	-H	-CH ₃	Double
Hydromorphone	-OH	=O	-H	-CH ₃	Single
Oxymorphone	-OH	=O	-OH	-CH ₃	Single
Hydrocodone	-OCH ₃	=O	-H	-CH ₃	Single
Oxycodone	-OCH ₃	=O	-OH	-CH ₃	Single
Buprenorphine*	-OH	-OCH ₃ **	**	-CH ₂ - 	Single
Naloxone	-OH	=O	-OH	-CH ₂ CH=CH ₂	Single

* Has a 1-hydroxy-1,2,2-trimethylpropyl substituent at C-7. ** Endo-ethano bridge between C-6 and C-14.

Anaphylactoid Reaction

- **NOT** IgE-mediated
- Mast cells release histamine
- Histamine release causes:
 - Increased heart rate
 - Increased force of myocardial contraction
 - Vasodilation → flushing & hypotension
 - Itching
- More common with morphine, codeine, and meperidine
- Premedicate with antihistamines

Opioid Allergy

- Type I reactions are very rare
 - Limited to case reports with morphine, heroin, meperidine, and fentanyl
 - Fentanyl is most commonly reported
 - <0.1% incidence with tramadol
 - Only 1 report confirmed IgE antibodies
- Opioids account for ~1% of drugs implicated in perioperative anaphylaxis
- Use caution with intradermal testing due to known histamine release with some opioids

Management of Reported Opioid Allergies

- Obtain thorough history
 - Cardiovascular collapse and bronchospasm more common in anaphylactic reactions
 - Cutaneous symptoms more common in anaphylactoid reactions
- Use appropriate skin tests and/or challenge tests
- Consider IgE antibody immunoassays or serum tryptase level
- Use non-opioid analgesics when possible
- Cross-reactivity with true Type I allergies is poorly understood

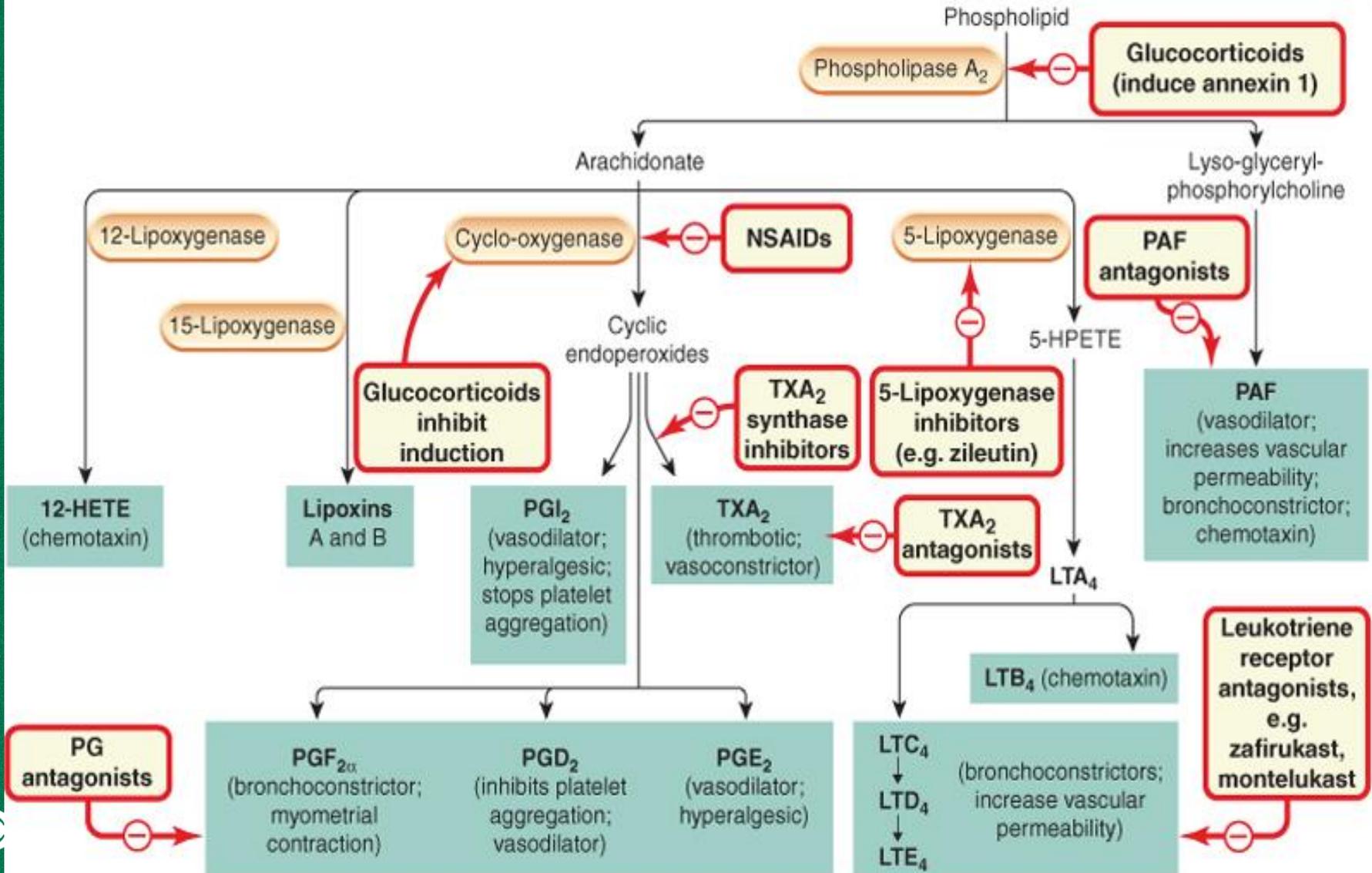
Case #3

LP is a 25 yof who presents to the ED with a tibia-fibula fracture after an ATV accident. When you offer her hydromorphone for pain, she says she can't take it because she is allergic to morphine.

What do you do?

ASPIRIN AND NSAIDS

NSAID Mechanism of Action



Aspirin: Respiratory Reactions

- Symptoms: bronchospasm, rhinorrhea, conjunctival injection, periorbital edema, generalized flushing
- Onset: 2-3 hours after ingestion
- Risk factors: asthma (4-21%), nasal polyps (35-52%), or both (65%)
- Mechanism: COX-1 inhibition depletes PGE2 and increases leukotriene production
- Cross-reactivity:
 - Will cross react with other nonselective NSAIDs that inhibit the COX-1 enzyme
 - COX-2 selective NSAIDs can be safely used
 - Limit APAP doses to < 1000 mg and salsalate to < 2 g

Aspirin: Skin Reactions

- Symptoms: urticaria, skin eruptions
- Onset: within 4 hours of ingestion.
Symptoms will diminish in 24-48 hours but can continue for up to 2 weeks
- Risk factors: atopy, female sex, intermittent NSAID use for pain relief
- Mechanism: COX-1 inhibition PGE2 and increases leukotriene production
- Cross-reactivity:
 - Will cross react with other nonselective NSAIDs that inhibit the COX-1 enzyme
 - Up to 4% of patients may cross react with COX-2 selective NSAIDs

Aspirin: Anaphylaxis

- Symptoms: urticaria, angioedema, bronchospasm, hypotension
- Onset: within 30 minutes
- Risk factors: previous exposure to the drug
- Mechanism: IgE antibody production
- Cross-reactivity: **will not cross-react** except for those with nearly identical structures

Management of Aspirin Sensitivity

- Skin testing not routinely done
- Manage underlying disease state (i.e. asthma)
- Desensitization
 - Can be considered for aspirin-induced asthma or IgE-mediated reaction
 - Decreases leukotriene production and extracellular histamine levels
 - Will return to sensitivity within 2-4 days
 - Confers “cross-desensitization” to other nonselective NSAIDs
- Leukotriene antagonists

Case #4

LF is a 63 yom with a h/o asthma, DM, HTN, HLD, and PVD who presents with unstable angina and is going to go for PCI with probable stent placement. He has been unable to tolerate aspirin in the past due to severe bronchospasm.

What do you do?

RADIOCONTRAST MEDIA

Radiocontrast Media

- Cause allergic-type reactions in up to 12% of patients
 - 1-3% have delayed skin reactions over 5-7 days
 - Anaphylactic reactions occur in up to 0.04% of patients
 - Can cause dose-dependent hypotension
- Mechanism: histamine release and mast cell triggering (IgE or direct activation)
- Higher risk in women, atopic patients, and with older agents
- Seafood allergy does **NOT** predispose to allergic reaction!
- May premedicate with steroids or antihistamines

Conclusions

- A thorough history is imperative to distinguish between IgE mediated and allergic-type reactions
- Patients with a history of drug allergy are more likely to be allergic to other medications, even those which are structurally unrelated
- Consider risks and benefits of exposure to medications in the same class in patients with IgE mediated allergic reactions

Medication Allergies and Cross-Reactivity

Andrea Passarelli, PharmD, BCPS
Clinical Pharmacy Specialist,
Neurocritical Care

apassarelli@christianacare.org



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HEALTH SYSTEM