A Review of Adverse Drug Reactions: with a Focus on the overdiagnosis of "Penicillin Allergy"

Dr. Neil Gershman
Allergy/Immunology

Relevant Disclosures

- None

Learning Objectives

1) Gain an understanding of the spectrum of adverse drug reactions
2) Be able to identify characteristics not consistent with drug allergy
3) Realize that most patients labeled as "drug allergic" are not!
4) Understand when diagnostic testing or desensitization procedures are indicated

Drug Allergy: An Updated Practice Parameter

These parameters were developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology.

Chief Editors

Roland Solensky, MD, and David A. Khan, MD

Workgroup Contributors

I. Leonard Bernstein, MD; Gordon R. Bloomberg, MD; Mariana C. Castells, MD, PhD; Louis M. Mendelson, MD; and Michael E. Weiss, MD

Task Force Reviewers

David I. Bernstein, MD; Joann Blessing-Moore, MD; Linda Cox, MD; David M. Lang, MD; Richard A. Nicklas, MD; John Oppenheimer, MD; Jay M. Portnoy, MD; Christopher Randolph, MD; Diane E. Schuller, MD; Sheldon L. Spector, MD; Stephen Tilles, MD; and Dana Wallace, MD

Ann Allergy Asthma Immunol 2010;105:273e1-e78.

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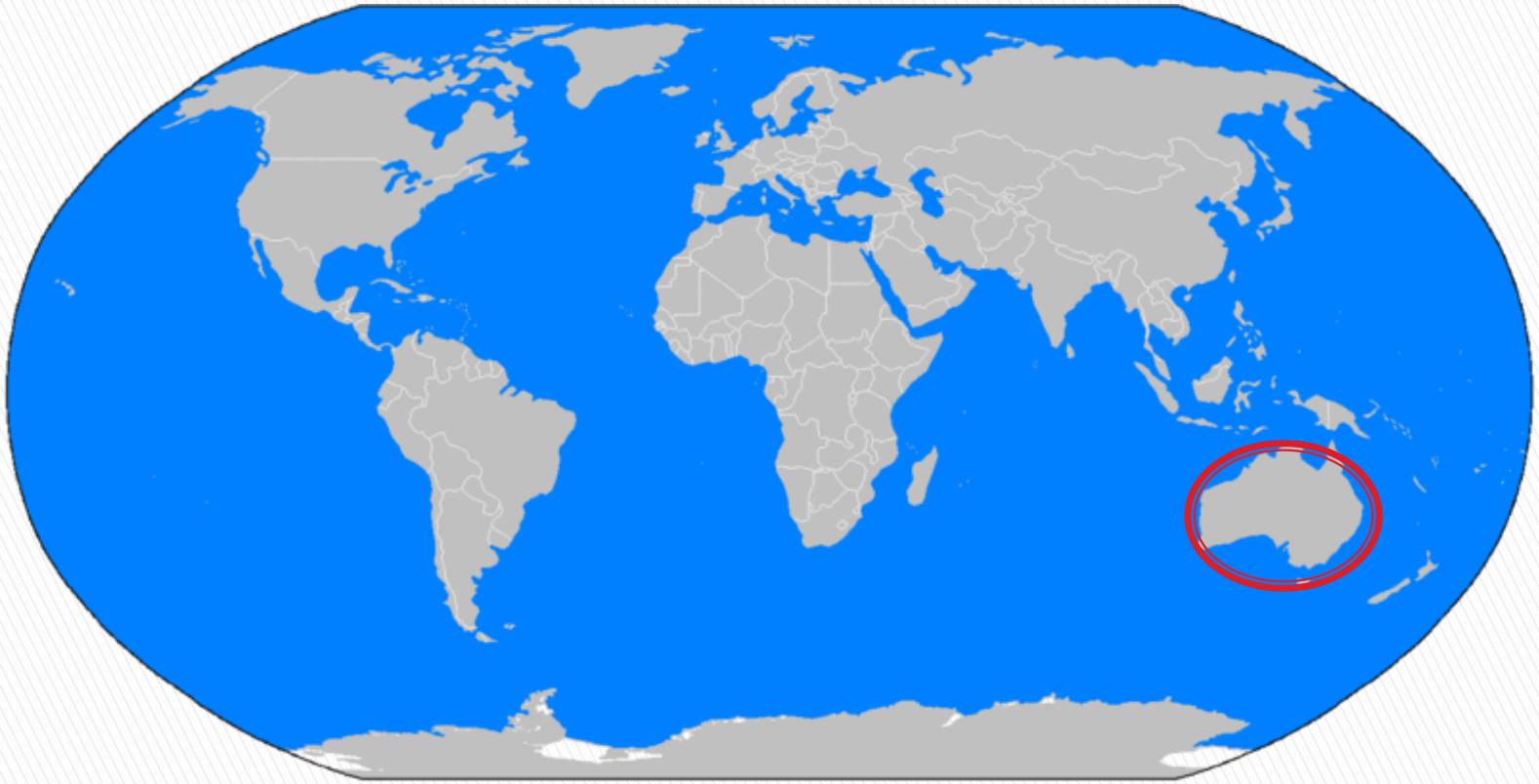
Take Home Message: Misdiagnosis of penicillin allergy

- 10% of all patients report pcn allergy
- 90% are not truly pcn allergic
- Elective PCN testing may decrease the inappropriate use of broad-spectrum antibiotics, leading to less drug-resistant organisms, lower costs and less toxicity

Adverse Drug Reactions ≠ Drug Allergy

Key Point 1



"The World of Adverse Drug Reactions"

Drug Allergy is Australia

Analogous to food allergy

Problem: Adverse Drug Reactions are confused with Drug Allergy

- Who or What is to blame?
- Our Limited Time and the EHR
  - Detailed history of drug reactions often not done
  - Often done by our MAs
  - EHRs make it difficult to *descriptively* document reactions
  - More on this later……..

Adverse Drug Reactions

Definitions
Mechanisms

Adverse Drug reactions are like personalities – Type "A" or Type "B"

- Type A – common, no specific host factors, all drugs cause them

- Type B – uncommon, specific host factors, relatively few drug cause them

Type A Reactions

- Most common – "intolerance, side effects"
  - Features
    - Related to pharmacologic actions of the drug
    - Typically dose related
    - Examples:
      - Side effects (sedation – antihistamines)
      - Toxicity (renal failure – aminoglycosides)
      - Secondary effects (diarrhea – antibiotics)
      - Drug interactions (Theo toxicity with macrolides)

    Do you think it's amusing that this talk will contain this one slide for 80% of the problem??

Type B Reactions

- **Unpredictable**
- Much less Common
- Can occur at tiny doses
- Specific host factors
- Includes allergy and "allergy-ish" reactions
- For all intents and purposes, tell patients it's "allergy"

Examples of Type B Reactions

- Type B Reactions
  - Allergy or Hypersensitivity(specific immunologic)
    - Urticaria from Bactrim, hemolytic anemia from high dose penicillin
  - Allergy-ish (non -immunologic)
    - Idiosyncratic - Hemolysis with dapsone in G6PD deficiency
    - Pseudoallergic - Anaphylactoid reaction to radiocontrast media
    - Abnormal metabolism - Aspirin-induced urticaria and ACE inhibitor angioedema

The definition of "Drug Allergy"

- "an immunologically-mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person"
- There are multiple mechanisms of true allergy
- IgE-mediated reactions are the most understood

Immunopathology of Drug Reactions

- Gell & Coombs Classification
  - Type I
    - Immediate hypersensitivity (IgE-mediated)
  - Type II
    - Cytotoxic reactions (e.g. hemolytic anemia PCN)
  - Type III
    - Immune complex (e.g. serum sickness, drug fever)
  - Type IV
    - Delayed hypersensitivity (e.g nickel, amox exanthems)

Unknown?? but thought to be allergic - EM/SJS/TEN

Mechanisms of "Allergy-ish" Reactions

- Pseudoallergic reactions
  - Resemble type I reactions
  - Due to non-IgE-mediated mast cell activation
  - Examples
    - Opiates, vancomycin, radiocontrast media

- Innate metabolic abnormalities
  - Bradykinin release (ACE-I induced angioedema)
  - Atypical response to cox-inhibition (ASA/NSAIDS)

13 year old allergist's son develops this rash 2 hours after a dose of minocycline. His first exposure to the drug began 2 weeks ago for acne

Lessons from this case

- Urticarial rash, likely IgE-mediated (type I)
- Time course of 2 weeks consistent with the production of IgE to the drug
- Next exposure could result in an severe, immediate reaction
- Documentation of the type of rash, time course important for the future
- Educate the patient/parent
- Testing for non-penicillin antibiotic unreliable, so must presume allergy here

Skin is the window to the allergic drug reaction's mechanism

Drug allergies can affect multiple organs, but the skin is the most commonly affected organ and can help in determining the mechanism

Different Types of Drug Rashes Mean Different Things

Key Point #2

Cutaneous Drug Eruptions

TABLE E1. Spectrum of cutaneous drug reactions

Common cutaneous drug reactions
Exanthems
Urticaria
Angioedema
Fixed drug eruption
Pruritus
Acneform
SCARs
DRESS
SJS/TEN
AGEP
Less common cutaneous drug reactions
Acanthosis nigricans
Alopecia
Aphthous stomatitis
Black hairy tongue
Bullous eruptions
Erythema nodosum
Exfoliative dermatitis
Gingival hyperplasia
Lichenoid eruptions
Lupus erythematosus
Phototoxic/photoallergic
Pigmentation
Pityriasis rosea–like eruptions
Psoriasis
Purpura
Vasculitis

Khan DA. J Allergy Clin Immunol 2012;130:1225-e6.

Case A

- This patient developed the rash 30 minutes after taking amoxicillin
  - Caveat: in a perfect world you'd have pictures of a previous reaction!

Case B

- This patient developed the rash below 5 days after taking amoxicillin

Question 1

- Which patient is at risk for anaphylaxis if amoxicillin is administered again?
  A. Patient A
  B. Patient B
  C. Both A & B
  D. Neither

A

B

Question 2

- Which patient might you consider doing an oral challenge, without any testing, in your office? (presuming an accurate history)
  A. Patient A
  B. Patient B
  C. Both A & B
  D. Neither

A

B

Drug-Induced Urticaria and Angioedema

- IgE-Mediated
- Pseudoallergic Reactions
- Serum Sickness
- ASA/NSAIDS
- Bradykinin-mediated
  - Angioedema w/o urticaria

IgE-Mediated Reactions

- Onset
  - Usually minutes to hour after drug exposure
  - Requires prior exposure to drug or cross-reacting drug (sensitization)
- Symptoms
  - Urticaria, flushing, pruritus, angioedema, anaphylaxis
- Rash resolves without peeling, blistering or changes in pigmentation
- Most common with beta-lactam antibiotics

Pseudoallergic Reactions

- Resemble true IgE allergic reactions but IgE not involved
- Pathophysiology
  - Non-specific mast cell degranulation
- Onset usually minutes to hours after exposure (like IgE)
  - May occur with 1st exposure
- Urticaria, flushing, pruritus, but rarely hypotension
- Examples
  - Opiates, vancomycin, contrast, ASA/NSAIDs

Drug Exanthem

Drug Exanthems (Maculopapular Eruptions)

- Most common drug allergic reaction
- Pathophysiology mixed
  - Often T-cell mediated
- Onset variable often within days or longer
- Pruritic, usually starts on trunk and spreads to extremities in a symmetric fashion
- Often resolves with scaling/peeling
- **Does not evolve into anaphylaxis**
- **Extremely common in children given amoxicillin**

Drug Allergy Cases

Case 1– a quickie

- 42 year old man presents with fever, sinus headache and cough for several days
- Drug allergy history: He was told by his mother never to take penicillin because he had a “rash” after taking it as a 2 year old
- “Drug tolerance history”
  - A few months ago he went to an urgent care and was prescribed augmentin – you’re done!
  - Tricky part – removing the label of “PCN Allergy”

Case 2 – not so quickie

- 77-year-old woman who presents for evaluation of multiple antibiotic allergies
- Her current problem is that she has had a resistant *klebsiella pneumoniae* urinary tract infection for 3 months
- This is resistant to several antibiotics but is sensitive to quinolones and amoxicillin/clavulanic acid
- Internist was considering placing PICC line for IV aminoglycoside therapy

Case 2

- Drug Allergy History:
  - **Penicillin**: She notes that in her early 20s, she had some type of reaction to penicillin. She does not recall what the reaction was, but does not think it was serious.
  - **Cipro/Keflex**: More than 10 years ago she had reactions to two different antibiotics. One caused an urticarial reaction and the other caused gastrointestinal upset. She does not know which antibiotics caused which reaction but believes these were Cipro and Keflex.
  - **Bactrim**: Listed but no idea of reaction history
- She has tolerated azithromycin, doxycycline, and nitrofurantoin

Approach to Multiple Drug " Allergy"

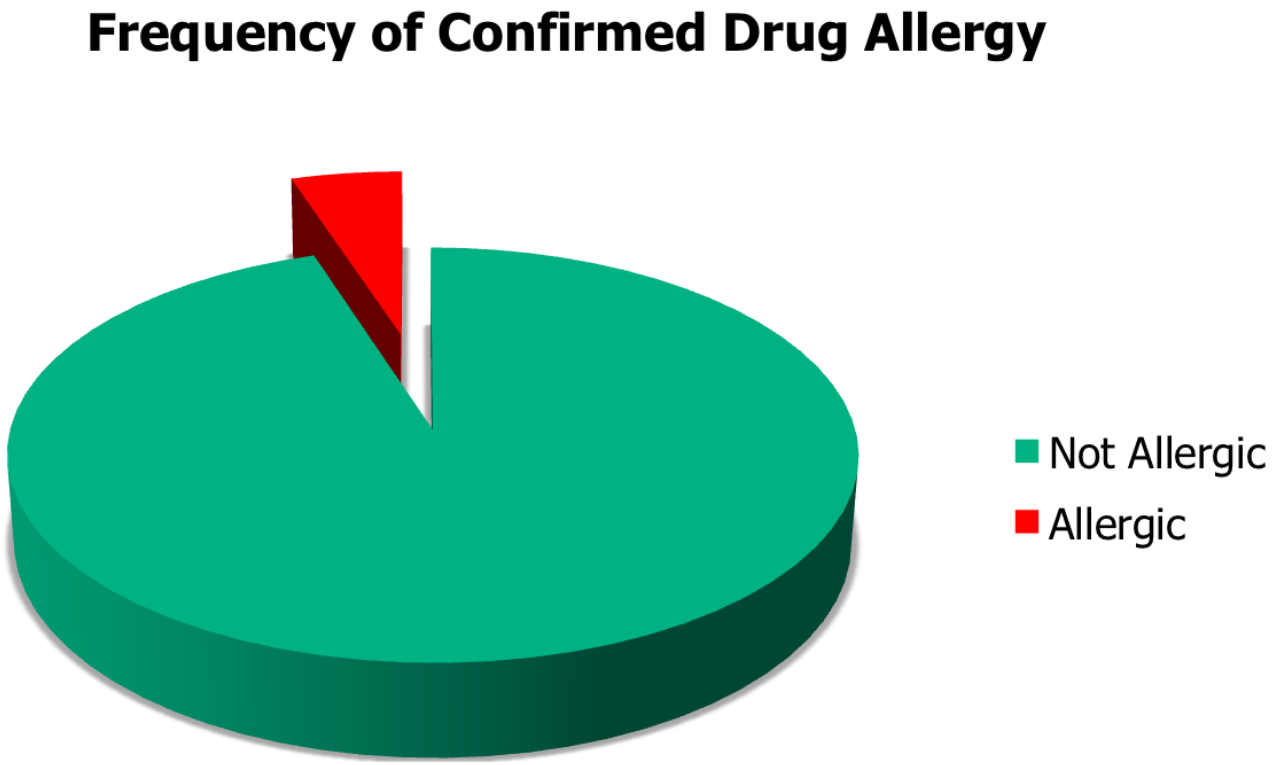
Step 1 – Get a detailed history
–Obtain a detailed history of listed drug allergies
–Determine potential need for future medications

Step 2 - Consider appropriate testing
–Identify medications for drug skin testing
–Identify medication requiring drug challenge

Step 3 - Provide guidance for patients
–Develop a list of medications that safe to use
–Develop a list of medications to avoid
–Develop list of medications that can be considered future testing or challenge ONLY IF/WHEN THE DRUGS ARE NEEDED

History Taking in Drug Allergy

Vast Majority of Patients with Drug Allergy Histories are Not Allergic



Drug Challenges confirm "not allergic": ok to treat with drug
Skin tests and history confirm "allergic": avoid drug or desensitize

Key Features of Drug Allergy History

Question	Relevance
How long ago was reaction?	Some drug allergies tend to wane over time (e.g. penicillin)
Description of "rash" or "hives" (showing pictures sometimes helps)	Most patients can't differentiate urticaria from other rashes Urticaria more suggestive of IgE-mediated reaction. Blistering? Mucosal? Targetoid?
Symptoms objective or subjective?	Subjective symptoms often anxiety-related
When did reaction occur?	Immediate vs. delayed reaction

Khan DA, Solensky R. J Allergy Clin Immunol 2010;125:S126-37.

Features Suggestive of True Drug Allergy

- Objective findings
  - Rash
  - Wheezing
  - Angioedema
- Rational temporal relationship to drug
- “allergy-prone” drug
  - Bactrim very common, Nexium not
- Resolution with discontinuation
  - Typically within weeks

Features Less Suggestive of Drug Allergy

- Subjective symptoms only
  - “swelling”, pruritus
  - isolated throat symptoms (panic)
  - mild GI symptoms
- High number of listed drug allergies
  - The longer the list, the more likely they are false
- History of a childhood reaction
  - Kids gets rashes!

Testing in Drug Allergy

Skin Testing

Reliable testing is limited to penicillin and very few others

Drug Challenges – you can do these!

Reliable for any drug and useful as long as reaction history is not serious

(e.g. EM/SJS, urticaria/AE/ANA)

Drug Challenges

Gold standard for determining tolerance to a drug

Terminology

- Drug Challenge – synonyms
  - Drug provocation test
  - Graded dose challenge
  - Incremental challenge
  - Test dosing

Drug Challenges

- Intended for patients who are unlikely to be allergic to the given drug
- May be done in a graded manner or 1 step (full dose)
  - Graded challenges often start at 1/100th or 1/10th of final dose
- The intention of a drug challenge is to verify that a patient will not experience an adverse reaction to a given drug
- It's under-utilized!

Solensky R, Khan DA et al. Ann Allergy Asthma Immunol 2010;105:273e1-e78.

Safety of Drug Challenges

ELSEVIER

Contents lists available at SciVerse ScienceDirect

Adverse reactions during drug challenges: a single US institution's experience

Leon Kao, MD*; Jessica Rajan, MD*; Lonnie Roy, PhD†; Eric Kavosh, MD*; and David A. Khan, MD*

*Division of Allergy and Immunology at the University of Texas Southwestern Medical Center at Dallas, Dallas, Texas
†Health Systems Research Department, Parkland Health & Hospital System, Dallas, Texas

- 1/123 challenges positive (no treatment required)
- Subjective symptoms in 20 and were higher with
  - Historically subjective symptoms
  - Female gender
  - >10 listed drug allergies associated

Kao L et al. Ann Allergy Asthma Immunol 2013;110:86-91.

CPT code for ingestion challenge

95076 Ingestion Challenge (foods, drugs)

Minimum of 61 minutes required

No E&M should be billed in conjunction with this code

Skin Testing for Drugs

- Typically done by specialists
- Positive and negative controls
  - Histamine and saline
- Must know non-skin irritating concentrations and drug metabolites
- Limited to penicillin and very few others
  - Neuromuscular blocking, a few chemotherapeutics

Most patients who think they are allergic to penicillin are not

Key Point #4

Most patients who really were allergic to penicillin in the past, lose their allergy over time

Key Point #5

Penicillin Skin Testing

- Penicillin skin testing using PRE-PEN® and PCN-G has good negative predictive value (96-99%) in excluding penicillin allergy
- PRE-PEN®, or benzylpenicilloyl polylysine, is the metabolite of PCN which is responsible for most IgE-mediated reactions
- Simple skin prick and intradermal test with positive and negative controls
- Available serum testing ("RAST") has poor NPV

Macy E et al. JACI In Practice 2013;1:258-63.
delReal GA, et al. Ann Allergy Asthma Immunol 2007;98:355-9.
Green GR, et al. J Allergy Clin Immunol1977;60:339-45.
Brown BC, et al. JAMA1964;189:599-604.

PCN Allergy Label Associated with Higher Serious Infections

Food, drug, insect sting allergy, and anaphylaxis

Health care use and serious infection prevalence associated with penicillin ''allergy'' in hospitalized patients: A cohort study

Eric Macy, MD, MS,[a] and Richard Contreras, MS[b] *San Diego and Pasadena, Calif*

Patients labeled with PCN allergy more likely to receive quinolones, clindamycin and vancomycin

These patients had higher prevalence of C.difficile, MRSA and VRE infections

J Allergy Clin Immunol 2014;133:790-6.

Case 2: Penicillin Skin Testing

- Skin testing to penicillin reagents was negative
- Confirmatory challenge with amoxicillin was well tolerated

- Recommendation
  - Patient should now tolerate amox-clav to which the organism was sensitive
  - Likely OK for her to take other beta-lactams in future, but may want to drug challenge with keflex with her history

Skin Testing to Non-Penicillin drugs

- The predictive value with skin testing to most other drugs is unknown
  - We don't know the metabolites
- A negative skin test cannot be relied upon as evidence of drug tolerance

So, what if a there is no alternative to a drug and a history of "Drug Allergy?"

- If skin testing is positive and no adequate alternatives(e.g. neurosyphyllis) desensitization ("temporary induction of tolerance")
- If skin testing not possible, and reaction history not serious – drug challenge
- If skin testing not possible and reaction c/w anaphylaxis, presume allergy and desensitize

Drug Challenge vs Drug Desensitization

	Challenge	Desensitization
Likelihood of drug allergy	low	high
# steps (starting dose)	1-3 (1/100)	➢12(1/10,000)
Dosing increments	≥10-fold	2-fold
Diagnostic test	yes	no
Induces drug tolerance	no	yes
Must be repeated prior to drug readministration	no	yes
Reactions with procedure	< 10%	~ 30%

Graded Challenge Vs. Desensitization

- Clinical Question: **Will this patient tolerate this drug?**
  - Graded challenge will answer this question

- Clinical Question: **How do I treat this patient who is (or might be) allergic to this drug?**
  - Drug desensitization is a procedure to address this question

Case 2 – Review

- 77-year-old woman who presents for evaluation of multiple antibiotic allergies
- Her current problem is that she has had a resistant *klebsiella pneumoniae* urinary tract infection for 3 months
- This is resistant to several antibiotics but is sensitive to quinolones and amoxicillin/clavulanic acid
- Internist was considering placing PICC line for IV aminoglycoside therapy

Case 2 Review

- Drug Allergy History:
  - **Penicillin**: She notes that in her early 20s, she had some type of reaction to penicillin. She does not recall what the reaction was but does not think it was serious.
  - **Cipro/Keflex**: More than 10 years ago she had reactions to two different antibiotics. One caused an urticarial reaction and the other caused gastrointestinal upset. She does not know which antibiotics caused which reaction but believes these were Cipro and Keflex.
  - **Bactrim**: Listed but no idea of reaction history
- She has tolerated azithromycin, doxycycline, and nitrofurantoin

Case 2: Final Recommendations

- Give amox-clav for UTI
- If amox-clav ineffective for UTI, consider oral challenge with quinolone
- For future, penicillins and macrolides all ok and should be sufficient to treat most infections as an outpatient
- Avoid sulfonamide antibiotics
- Avoid cephalosporins and quinolones
  - Consider oral challenge to a Cephalosporin if necessary in the future

Key Points of Case

- Multiple Antibiotic Allergy Patients can be managed successfully
- Penicillin skin testing and selected drug challenges will result in a good antibiotic armamentarium for most patients

Cephalosporins and Carbapenems

- There is some limited cross-reactivity with penicillin and these drugs
- If reaction to PCN mild, significant reaction unlikely – consider drug challenge
- If there is a concerning history, and PCN skin testing negative, drug challenge appropriate
- If skin testing impossible or skin testing positive, consider empiric desensitization

Risk of reacting to cephalosporins in a patient with a history of a non-severe penicillin allergy is ~ 0.2%

Key Point #5

Goodman EJ et al. J Clin Anesth 2001;13:561-4.
Daulat S et al. J Allergy Clin Immunol 2004;113:120-2.

What about Bactrim?

- Sulfa drugs probably 2nd most common allergy after penicillin
- Can be IgE-mediated or other mechanisms
- No testing available
- "Slow desensitization" protocols available for pts with mild eruptions (HIV pts.)
- Common cause of EM/SJS/TEN
  - NEVER do drug challenge if targetoid lesions, blistering rash, mucosal lesions
- Allergists say "Try not to use it!"

People who are allergic to “sulfa” usually do fine with other “sulfa” medications

Key Point #6

Sulfonamide Allergy

- A sulfonamide is any compound that contains a sulfonamide (SO_2NH_2) moiety
- **Sulfonamide antimicrobial drugs are structurally different from other sulfonamide-containing medications** (furosemide, thiazide diuretics and celecoxib) by virtue of an aromatic amine at the N4 position and a substituted ring at the N1 position

A Worrisome Drug Reaction

Stevens-Johnson's Syndrome, TEN,Erythema Multiforme

- EM and SJS hard to distinguish
- EM mostly due to viral infection, SJS from drugs
  - Aromatic anticonvulsants, sulfa antibiotics, allopurinol
- If history includes antibiotic use, must assume SJS
- Higher risk in HIV+, SLE, Bone marrow TX
- Contraindication for re-challenge, testing
- Potentially fatal

More Drug “Allergy” Cases

- 61 yo AA female with hypertension

ACE-I Angioedema

- 0.1-0.7%, more common in African-Americans
- 1/3 of angioedema in ED
- Typically involves head and neck, especially lips/tongue
  - Urticaria is rare
- **Often delay in onset of > 1 year**
  - mean 1.8 yrs (Malde 2007)
  - Can take months to resolve after discontinuation

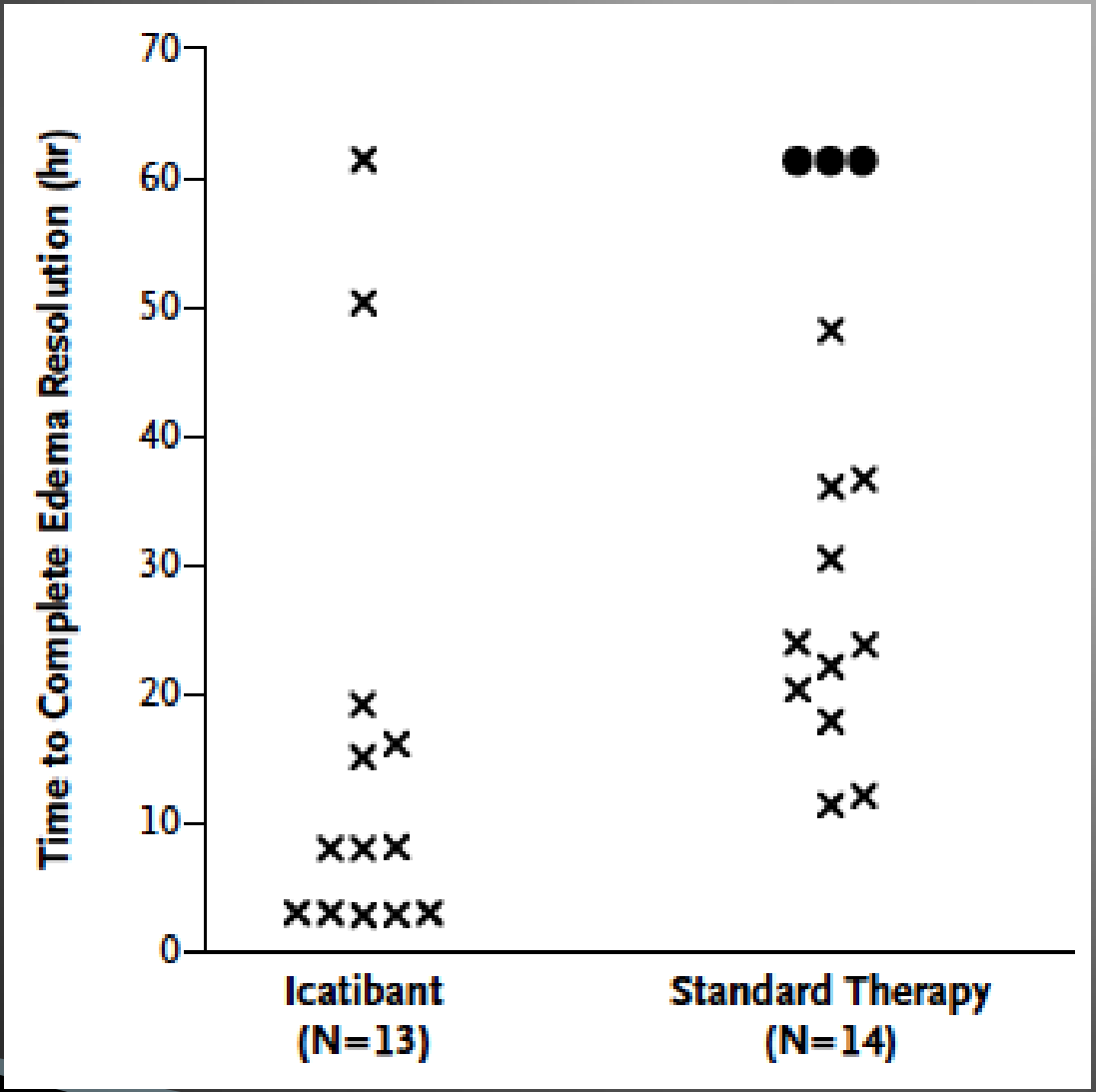
No testing available for ACE-I angioedema or ACE-induced cough

ACE-I Angioedema

- Likely induced by ↑ bradykinin levels
- ACE-I contraindicated in hereditary angioedema
- ARBs typically well-tolerated
- Treatment supportive
- Icatibant (bradykinin receptor 2 antagonist) recently shown to be effective
- Should icatibant be stocked in EDs???

Bas M et al. N Engl J Med 2015;372:418-25.

Icatibant Resolves Angioedema More Rapidly than Placebo



Bas M et al. N Engl J Med 2015;372:418-25.

Aspirin Allergy Case

- 62 year old with DM presents with angina and found to have CAD in need of coronary stent
- 15 years ago developed hives and mild lip edema after taking 650 mg of aspirin
- Cardiology consults for aspirin desensitization

Reactions to ASA/NSAIDs

- Urticaria/AE can be isolated or exacerbate chronic urticaria
- Can also exacerbate asthma
- Somewhat dose-related
- Cross-Reactive Reactions
  - Likely due to COX-1 inhibition and generation of cys-Leukotrienes
    - Most tolerate tylenol and many tolerate cox-2 inhibitors
- If drug is definitely needed:
  - Drug challenge – “Hey cardiologist, is 81 mg enough.”

Rapid ASA Challenge-Desensitization Protocol Summary

- A two step protocol (40 mg, wait 60-90 min then additional 40mg given) will likely successful
- If needed, higher dose "desensitization" protocols exist
- Whether these protocols truly induce drug tolerance or are simply a graded challenge is unclear

Wong JT et al. J Allergy Clin Immunol 2000;105:997-1001.
Silberman S et al. Am J Cardiol 2005;95:509-10.
Rossini R et al. Am J Cardiol 2008;101:786-9.
White AW et al. Allergy Asthma Proc 2013;34:138-42.

Approach to patients with aspirin hypersensitivity and acute cardiovascular emergencies

Andrew A. White, M.D., Donald D. Stevenson, M.D., Katharine M. Woessner, M.D., and Ronald A. Simon, M.D.

"However, despite an extensive literature search and careful review, peer consultation throughout multiple medical systems, and an exhaustive review of the cases of aspirin reactions in the Scripps Medical System **we are unable to find even one convincing case of an anaphylactic reaction to aspirin**."

Allergy Asthma Proc 2013;34:138-42.

Radio contrast media reactions

- 1-3% ionic contrast, 0.5% non-ionic contrast
- "Anaphylactoid" reactions
  - Non-specific mast cell release
- Contact dermatitis to iodine irrelevant
- "shellfish allergy" – IgE to tropomycin
- THIS IS AN "OLD DOCTOR'S TALE"
- Use non-ionic contrast and consider prednisone and Benadryl prior to study

Drug Allergy Case

Desensitization

Case of Macrolide Allergy

- A 68-year-old woman developed urticaria and shortness of breath six days into a course of clarithromycin for *Mycobacterium avium intracellulare* infection
- Her pulmonologist advised her to take a "test" dose of azithromycin 250 mg. Within an hour she developed urticaria, shortness of breath, and throat tightness resulting in an emergency department visit.

Swamy N et al. Ann Allergy Asthma Immunol 2010;105:489-90.

Antibiotic Desensitizations

- Indicated for patients with:
  - High likelihood or confirmed antibiotic allergy
  - In need of culprit antibiotic where no alternative exists

Antibiotic Drug Desensitization

- Typical starting dose is 1/10,000th of target therapeutic dose
- Can also use calculated dose from skin test as starting point
- Further dosage increases are typically twice the previous dose
- Administered at 15-20 minute intervals until therapeutic dosage achieved
- Can be performed with oral or IV medications

Take Home Points

- Most patients who believe they are drug allergic are not
- Misdiagnosis of penicillin allergy leads to inappropriate and costly broad-spectrum antibiotic use
- Penicillin skin tests and drug challenges are very useful diagnostic tests
- Penicillin allergic subjects (especially those with non-severe reactions to penicillin) typically tolerate cephalosporins and carbapenems
- Patients allergic to sulfamethoxazole can tolerate other non-antibiotic sulfonamides

Take Home Points

- ACE-I angioedema can be delayed
  - icatibant may be useful
- ASA/NSAID sensitive patients may tolerate low dose aspirin and cox-2 inhibitors
- Antibiotic desensitizations can be used when needed for IgE mediated reactions to most antibiotics