Beta-Lactam Toolkit

Presenter's Name

Title
Professional Association

ACAAI Drugs & Anaphylaxis Committee 2015

Maria Gonzalez

- Maria is a 55 year-old female with recurrent acute sinusitis
- She lives about 15 minutes from [***city near presentation***]
- A good ENT referral source has referred her to your office as he would like to use a penicillin or a cephalosporin drug

Maria Gonzalez

- **Penicillin:** Maria states that in her 20s, she had some type of reaction to PCN. She does not recall what the reaction was but her PCP told her to never take PCN again
- **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 antibiotic caused which reaction but believes these were Cipro and Keflex
- **Bactrim:** Listed as drug allergy but patient has no idea of her reaction history
- She has tolerated azithromycin, doxycycline, and nitrofurantoin but these drugs seem to have quit working

- Hypersensitivity reactions to antibiotics are commonly **reported** both in adults and children, with a prevalence of approximately **10%**
- In U.S., antibiotic-associated adverse events have been implicated in **19.3% of all emergency department visits** for drug-related adverse events

Legendre D. et al. Clin Infect Dis 2013:1-9
Romano A. and Caubet J. J Allergy Clin Immunol Pract 2014;2:3-12

Penicillin (PCN) "allergy" Leads to Use of alternative agents

The effect of using alternative agents to PCN:

- The use of broader-spectrum antibiotics, e.g., vancomycin and fluoroquinolones, leads to more **resistant organisms**
- **Increased cost** of alternative antibiotics
- Significant **comorbidities**
  - Vancomycin-resistant enterococcus
  - Clostridium difficile-associated diarrhea

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73
Picard M, et al. JACI Practice. 2013;252-257
Sade K, et al. Clin Exp Allergy. 2003; 33:501-506
Reddy V., et al. JACI. 2013;131:AB170

The dangers & Costs of being labeled "Penicillin Allergic"

- Retrospective matched cohort study of 51, 582 "Penicillin Allergic" patients hospitalized in Kaiser Foundation South California Hospitals 2010-2012
- Longer hospital stays (.59 day/person)
- Treated with more fluoroquinolones, clindamycin, and vancomycin
- 23.4% more C difficile
- 14% more MRSA
- 30% more vancomycin-resistant Enterococcus
- $20 Million increase cost/year for this group of patients

Macy E, Contreras R. JACI. 2014;133(3):790-6

Educational slides for PCP audiences

Adverse drug reactions (ADRs)

Type A: predictable reactions

- Usually *dose dependent*, related to the known pharmacologic actions of the drug, occur in otherwise healthy individuals
- Approximately *80% of all ADRs*

Type B: unpredictable reactions

- ***Dose independent***, unrelated to the pharmacologic actions of the drug, occur only in ***susceptible individuals***
- Unintended response to a drug taken at a dose normally used in humans

Demoly P. et al. Allergy 2014; 69: 420–37
Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Type B: unpredictable reactions

- Drug intolerance
- Drug idiosyncrasy
- Drug allergy
- Pseudoallergic (anaphylactoid) reactions

Drug allergy

- **An immunologically mediated response to a pharmaceutical and/or formulation (excipient) agent in a sensitized person**

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Classifications of Drug Allergy by clinical presentation

Immediate

- Typically occur within 1– 6 h after the last drug administration,but could start up to 24 hours

Non-immediate

- Occur at any time, from 1 h to several days after the initial drug administration

Demoly P. et al. Allergy 2014; 69: 420–37

Classifications of Drug hypersensitivity reactions

Immediate

- Urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms, nausea, vomiting, diarrhea, abdominal pain, anaphylactic shock

Non-immediate

- Delayed urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, TEN/SJS, DRESS, AGEP, symmetrical drug-related intertriginous and flexural exanthemas (SDRIFE)
- Hepatitis, renal failure, pneumonitis, anemia, neutropenia, thrombocytopenia

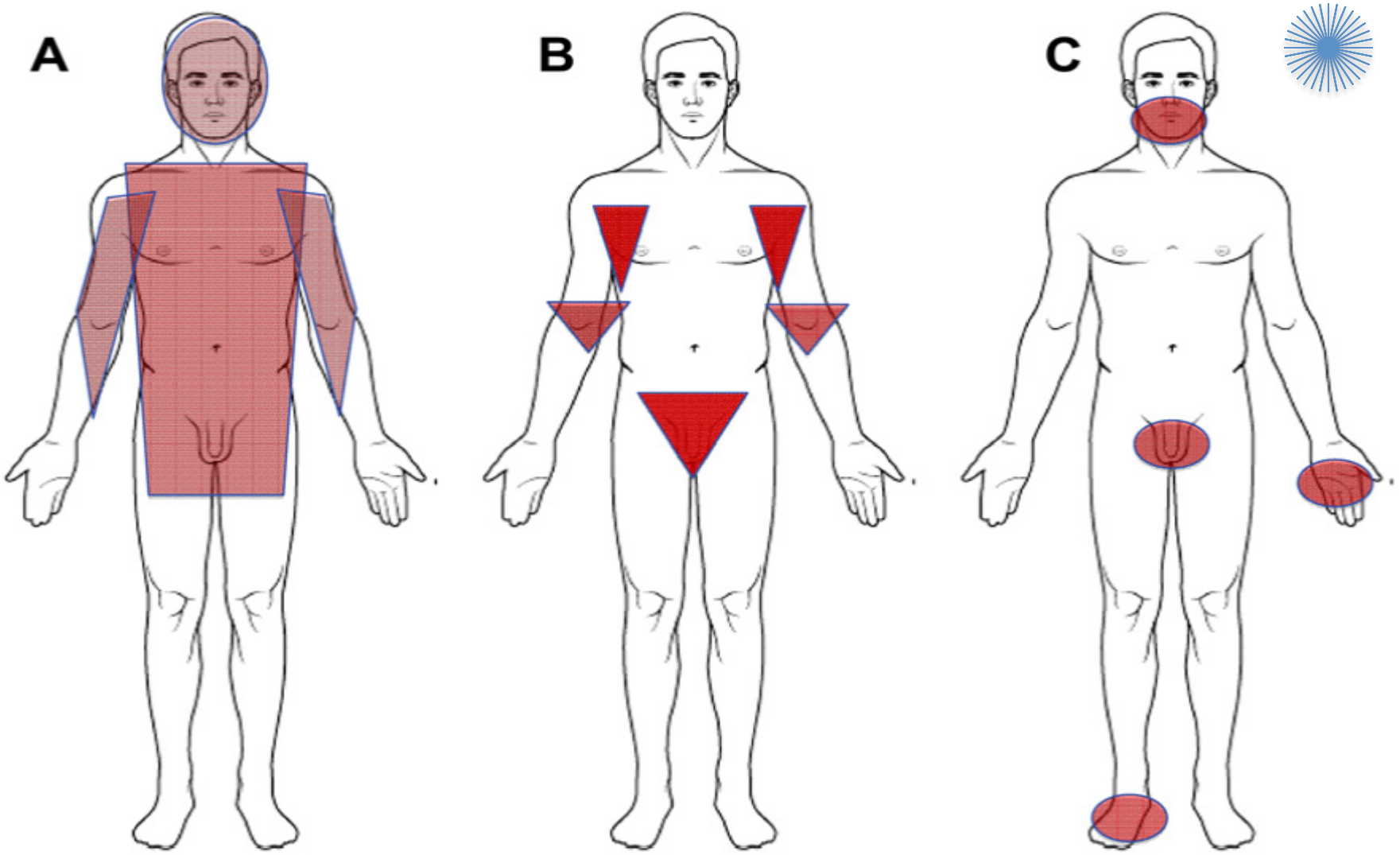
Drug hypersensitivity reactions (DHRs)

- Adverse effects of pharmaceutical formulations (including active drugs and excipients) that clinically resemble allergy
- **Drug allergies** are DHRs for which a definite immunological mechanism is demonstrated
- For general communication, when a drug allergic reaction is suspected, **DHR is the preferred term**, because true drug allergy and nonallergic DHR may be difficult to differentiate based on the clinical presentation alone

Demoly P. et al. Allergy 2014; 69: 420–37

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 or changes in pigmentation



Urticarial/maculo-papular

Intertriginous & Flexural examthemas

Fixed drug eruption

Bircher A. and Scherer K. Med Clin N Am 94 (2010) 711–725

Symmetrical drug-related intertriginous and flexural exanthem (SDRIFE)

Sharply demarcated erythema in the gluteal/perianal area in a patient with SDRIFE. Note the involvement of the popliteal folds.

Non- immediate reactions

- Identification of a non-immediate reaction is sometimes difficult because of the heterogeneity of the clinical manifestations, which can be quite similar to the symptoms of infectious diseases
- Moreover, these reactions may be favored by a concomitant viral infection, such as those caused by HIV,CMV, HHV-6, or EBV

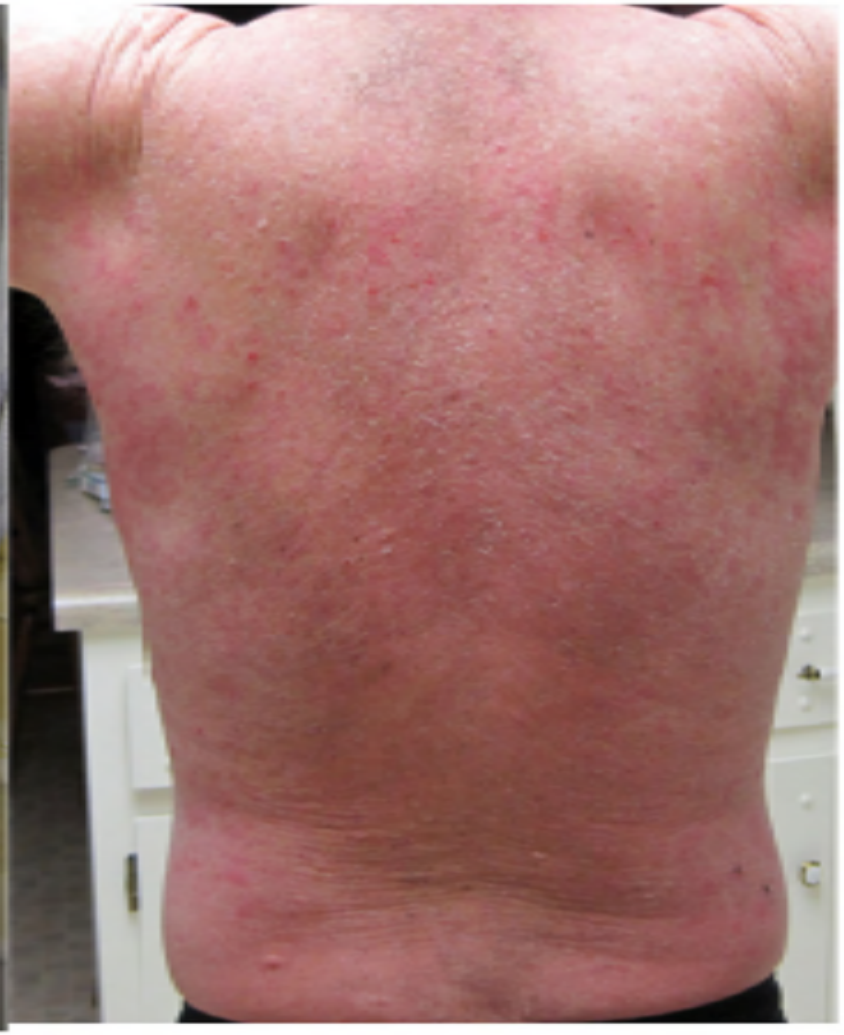
Ampicillin and Amoxicillin

- Amoxicillin and ampicillin are associated with the development of a **delayed maculopapular rash** in approximately **5% to 10%** of patients
- These reactions are **usually not related to IgE-mediated allergy**, and they are postulated in many cases to require the presence of a concurrent viral infection or another underlying illness
- But serious subsequent reactions have been reported. Thus, **PCN testing is recommended.**

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Hospital

4 Days later



Maculopapular Eruptions

- Most common drug allergic reaction
- Pathophysiology is mixed
  - Often T-cell mediated
- Onset variable, often within days or longer
- Erythema, fine papules, pruritus
- Usually begins on trunk, spreads to extremities, typically symmetric
- Often resolves with scaling/peeling
- Does not evolve into anaphylaxis

Antibiotic Allergic Drug Reactions
By classification

Table 5. Antibiotics that caused of drug hypersensitivity

Antibiotics	n (%)
Penicillin	15 (24.59%)
Cephalosporin	10 (16.39%)
Quinolone	6 (9.83%)
Clindamycin	6 (9.83%)
Sulfonamide	5 (8.19%)
Antiretroviral drugs	3 (4.91%)
Glycopeptide	3 (4.91%)
Anti TB drugs	3 (4.91%)
Antifungal drugs	2 (3.27%)
Macrolide	2 (3.27%)
Aminoglycoside	1 (1.63%)
Tetracycline	1 (1.63%)
Carbapenem	1 (1.63%)
Metronidazole	1 (1.63%)
Unknown	1 (1.63%)
Other	1 (1.63%)

Sangasapasviliya A. et al. J Med Assoc Thai 2010; 93: S106-11

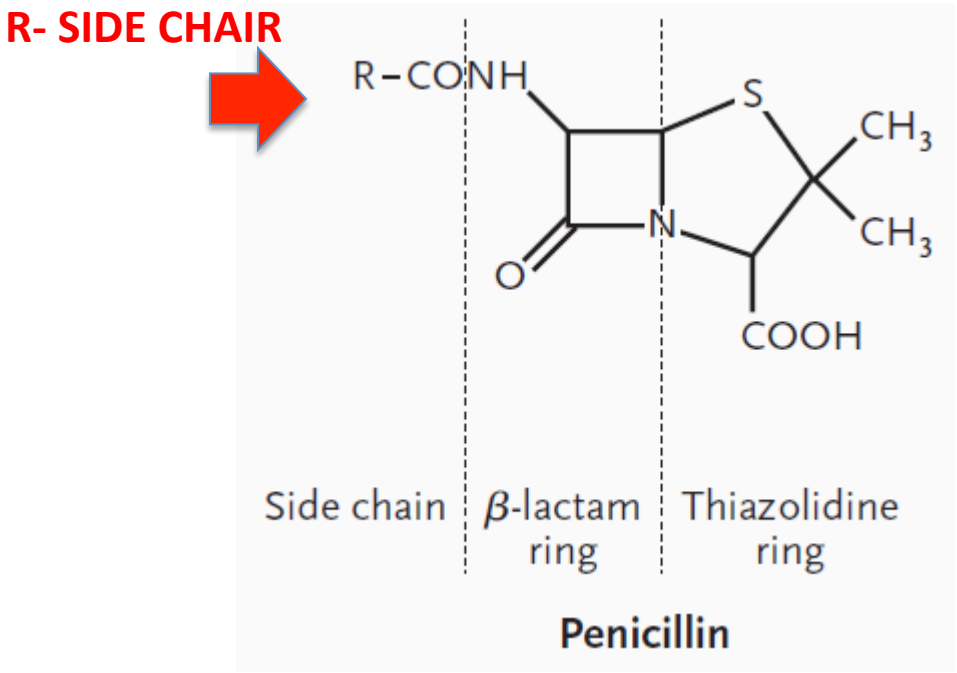
Beta-lactam antibiotics

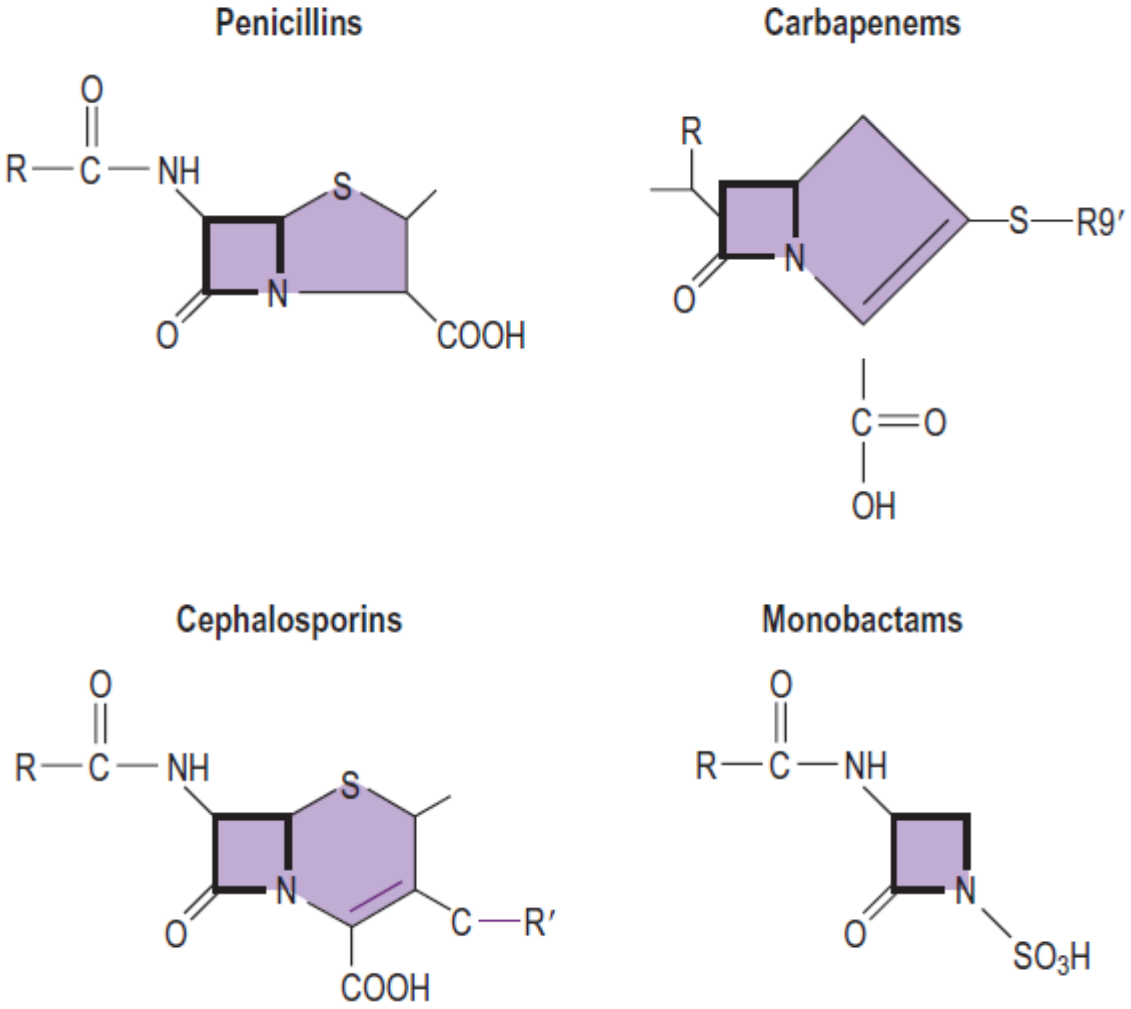
2 major classes

- Penicillins
- Cephalosporins

4 minor classes

- Carbapenems
- Monobactams
- Oxacephems
- Clavams





Celik G., Pichler W. and Adkinson F. Middleton's Allergy 8th edition,1274-95

Non- Beta-lactam antibiotics

- Quinolones
- Sulfonamides
- Macrolides
- Aminoglycosides
- Rifamycins
- Glycopeptides
- Clindamycin

Romano A. and Caubet J. J Allergy Clin Immunol Pract 2014;2:3-12

Overview of Beta-lactam Allergy

- Penicillin Allergy Background
- Mechanism
- Testing
- Use of other beta-lactams
- Cephalosporin Allergy
- Sample Cases

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.

ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY

VOLUME 105, OCTOBER, 2010

Penicillin allergy

Penicillin (PCN) allergy

- 7.8-10% of all patients in the United States (approximately 25-32 million) report a history of PCN allergy, Only approximately
- Only 27,665 patients/year are tested for PCN allergy (based upon number of PRE-PEN ampules sold in 2011)[2]

1.Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73
2. Macy,E. JACI in practice 2013;1:258-63.

Kaiser Permanente PCN allergy Demographics 2011

- Health plan members
  - Reporting PCN allergy: 51,978
  - Not Reporting PCN allergy: 478,656
- Age **46.6 yrs** ± 22.2 yrs (vs 38.9 ± 22.2 yr for all covered lives)
- Age range= 2 months to 101 years
- PCN allergic reporting group=64.4% Female
- Number of drug allergies reported
  - One= 58.9% (PCN only)
  - Two= 22.8%
  - Three or greater =18.3%
- Multiple Drug Intolerance Syndrome= ≥ 3 drug allergies

Macy,E. JACI in practice 2013;1:258-63

Penicillin (PCN) allergy
Not really that high

- 10% of patients report a history of PCN allergy, but 90[1]-98%[2] of these individuals are not allergic.[1]
- Rate of anaphylaxis to IV administration is 1-2/10,000 patients.
- Since the 1970's a progressive decline in number of positive PCN skin tests

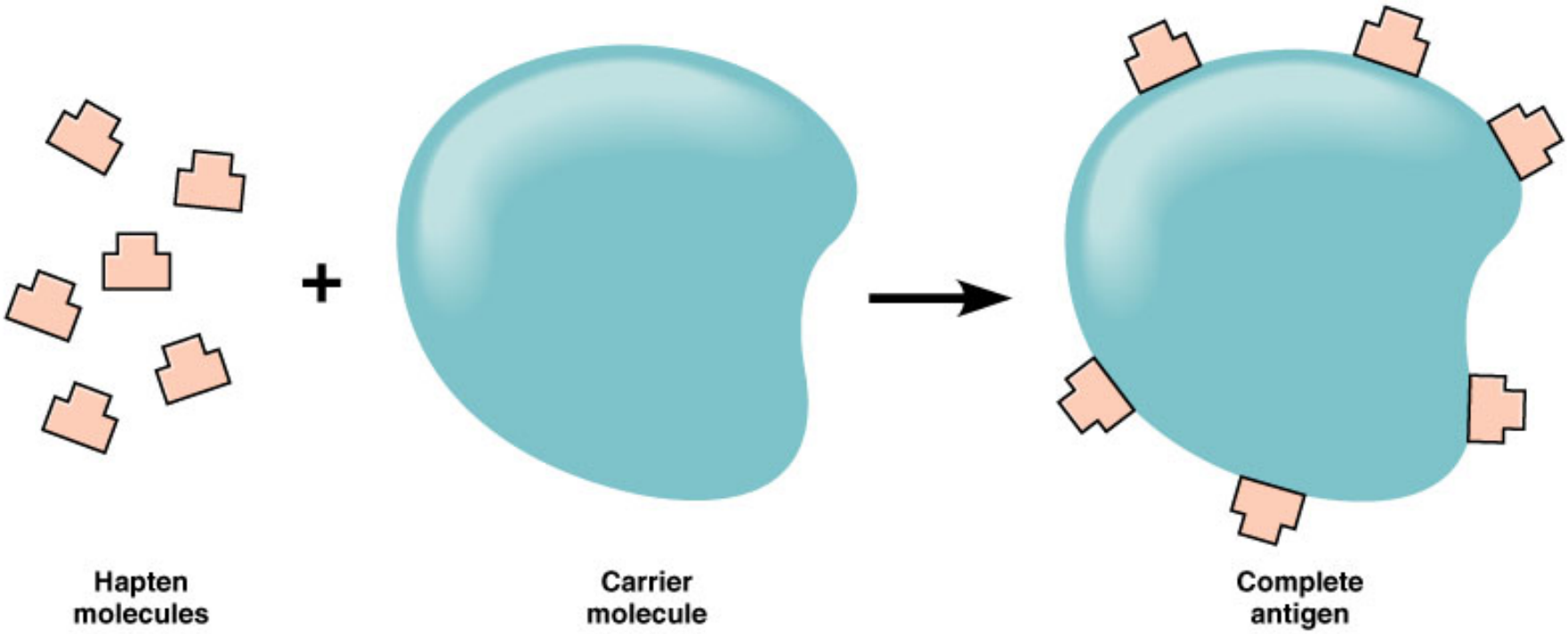
1. Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

2. Macy,E. JACI in practice 2013;1:258-63

Possible Reasons for such a low rate of true "Allergy" to PCN

- Penicillin allergy and specific IgE antibodies to PCN wane over time
- A viral or bacterial infection may have caused the rash or reaction
- Another drug taken concurrently may have ben responsible
- The reaction may have been an adverse reaction, e.g., diarrhea or nausea, and not true allergic
- Hx may have been obtained by a parent when the patient was too young to remember
- Assumption by patient or physician that PCN allergy was inherited from a parent with PCN allergy

Haptenation



- PCN is immunologically inert, but haptenates form reactive intermediates

http://classes.midlandstech.edu/carterp/Courses/bio225/chap17/study2.htm

PCN Skin testing and Challenge

skin testing For PCN Allergy

- PCN allergy wanes with time.
  - 50% lose their sensitivity at 5 years
  - 80% lose their sensitivity at 10 years.
- Patients with vague histories of a reaction >10 years ago may be candidates for graded challenge.
- If history is convincing or reaction severe, they may be candidate for desensitization/induction of tolerance.

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Contraindications for pcn testing and challenge

- Stevens Jonson syndrome
- Hemolytic anemia
- Hepatitis
- Nephritis
- Oral or skin blisters

Macy,E. JACI in practice 2013;1:258-63

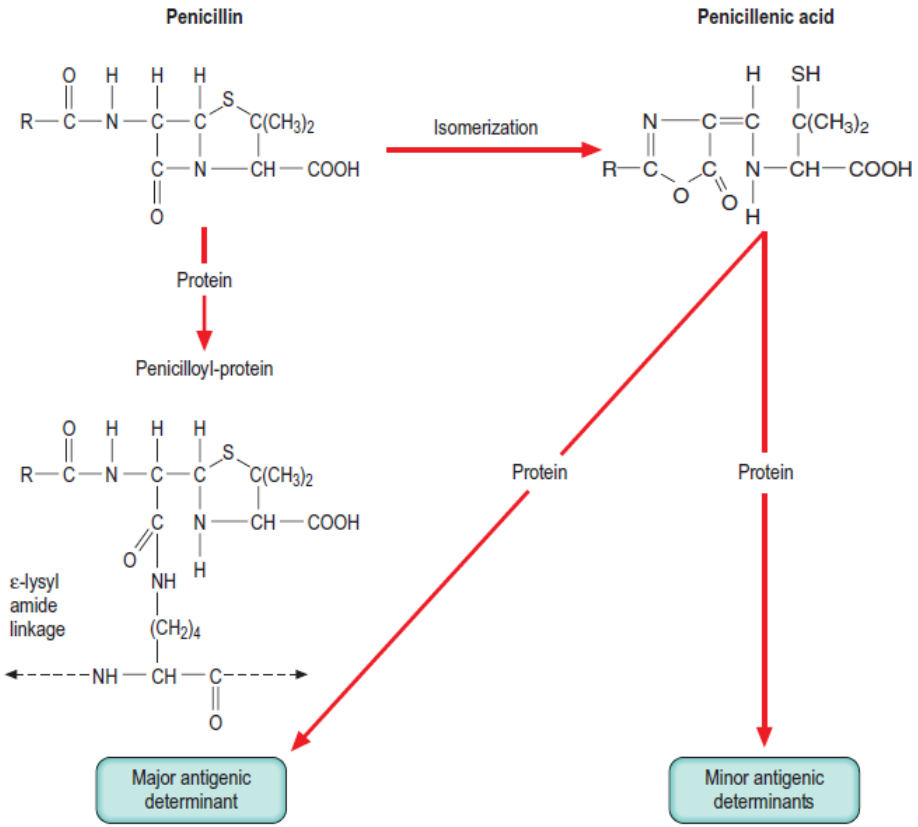
Contraindications for skin testing & Drug Challenge

- **Autoimmue Diseases**
  - Bullous pemphidoid, Pemphigus vulgaris, Linear IgA bullous disease, Drug-induced lupus
- Neutrophilic Dermatosis
  - Acute generalized exanthematous pustulosis (AGEP)
  - Sweets syndrome
- Severe Cutaneous Drug Reactions
  - SJS/TEN
  - DRESS
  - Exfoliative dermatitis

Contraindications for skin testing & Drug Challenge

- Drug- induced vasculitis
- Serum sickness
- Organ specific drug reactions
  - Cytopenia
  - Hemolytic anemia
  - Hepatitis
  - Nephritis
  - Pneumonia

PCN Structure



Celik G., Pichler W. and Adkinson F. Middleton's Allergy 8th edition,1274-95

DRUG Testing- IMMEDIATE & DELATED

TABLE I. Diagnostic tests of hypersensitivity reactions to drugs

Type of reaction		Type of tests
Immediate	*In vitro*	Specific IgE assays
		Flow cytometric BATs
	In vivo	Skin tests
		Provocation tests
Nonimmediate	*In vitro*	LTTs or LATs
		ELISPOT assays for analysis of antigen-specific, cytokine-producing cells
	In vivo	Delayed-reading intradermal tests
		Patch tests
		Provocation tests

(Not recommended)

(Experimental)

Good option

Choice for PCN, ? cephalosporins

When skin testing is not available

(Experimental)

Penicillin specific IgE

- High specificity (97%-100%) but lower sensitivity (29%-68%)
- Therefore, although a positive in vitro test result for penicillin specific IgE is highly predictive of penicillin allergy, a negative in vitro test result does not adequately exclude penicillin allergy

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Penicillin skin testing

- Most reliable method for evaluating IgE-mediated penicillin allergy
- When performed by skilled personnel using proper technique, serious reactions are extremely rare
- Several studies, including those looking at drug provocations, have shown a similar rate of reactions in patients who display negative skin prick tests to the major determinants PPL and BP) compared with patients with negative skin prick tests to the full set of major and minor penicillin determinants

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

PCN skin testing

- **Major determinants** penicilloylpolylysine (**PrePen**) and a minor determinant- benzyl penicillin (PCN G) should be used for all PCN allergy skin testing
- **Minor Determinant Mix** is not commercially available for skin testing but it is not felt to be required
- Skin testing of all reagents involves both **prick and intradermal testing**

Interpretation of the PCN Skin testing results

PCN skin testing

- **Negative predictive value approaches 100%**
- Positive predictive value between 40% and 100%
- If negative on prick testing patients should receive a penicillin challenge (Provocative Drug Testing)
  - If challenge not performed, patients and providers may still fear administration.

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

San Diego Kaiser Permanente PCN allergy testing 6/2010-4/2012

- Subjective challenge reactions reported were itching (without rash) and dizziness
- 11/15 reporting subjective but no objective symptoms were ‘Multiple Drug intolerance Syndrome” patients defined as reporting 3 or more drug allergies
- Itching which started immediately to 58 minutes reported by 13/15 patients
- Dizziness which started Immediately to 55 minutes in 2/15 patients
- None of these patients required any treatment
- These patients were advised that they were not allergic to PCN

Macy,E. JACI in practice 2013;1:258-63

Drug provocation test (DPT)

- Gold standard to establish a firm diagnosis in subjects with clear-cut histories and negative allergy tests
- Is intended for patients who, after a thorough evaluation, are unlikely to be allergic to the given drug

Graded challenge or test dosing

- Administration of progressively increasing doses of a medication until a full dose is reached
- The medication is introduced in a controlled manner to a patient who has a low likelihood of reacting to it.
- Unlike procedures that induce drug tolerance, graded challenges usually involve fewer doses, are of shorter duration, and are not intended to induce drug tolerance

Common Clinical INDICATIONS FOR DRUG CHALLENGES

- To exclude a drug allergy in patients with histories that are unconvincing
- To exclude cross-reactivity of structurally related drugs
- To exclude cross-reactivity of non-structurally related drugs to reassure patients (e.g., multiple drug allergic patients)

Role of drug challenges

- At times allergy skin testing is not a viable option in drug allergy
- Drug challenges are important tool in diagnosis and management of drug allergic patients
- With careful assessment of patients and appropriately designed protocols, drug challenges can be safety performed in the allergist's office
- Patients with > 10 listed allergies and subjective symptoms are at higher risk for subjective symptoms with a drug challenge
- Placebo-controlled drug challenges may be needed in some patients.

Drug provocation test: PCN

- If PCN allergy testing is negative go to DPT
- Administer an initial dose of 1/10 of the therapeutic dose of Amoxicillin
- Observe for 30 minutes
- If no reaction, then a full dose of Amoxicillin is administered
- Patient is observed for one hour

When PCN skin testing & challenge are negative

When PCN Skin Testing and Drug Provocation test are negative

- Assure the patient that they are safe to take any beta-lactam medication (PCN or Cephalosporin) as long as this is the only known beta-lactam allergy
  - 2.9-4.5% chance with each future course of a PCN class medication of developing a new allergy to PCN[1]
  - Similar rate of developing a future allergic reaction to a sulfonamide[1]
- For select patients (e.g., very anxious or concern about a delayed reaction) consider a 5 day course of the antibiotic following the testing
- Send consultation letter to PCP, other treating physicians, and patient's pharmacy indicating that patient should no longer be considered to be allergic to PCN[2]

1.Macy,E. JACI in practice 2013;1:258-63
2.Gerace, K. Abstract 366. AAAAI 2015 Annual meeting

DRUG DESENSITIZATION: INDUCTION OF TOLERANCE

- Penicillin **skin test–positive** patients should **avoid penicillin**, but if they develop an absolute need for penicillin, rapid induction of drug tolerance may be performed
- Often referred to as “drug desensitization”
- A temporary induction of drug tolerance
- Involve administration of incremental doses of the drug
- Can involve IgE immune mechanisms, non- IgE immune mechanisms, pharmacologic mechanisms, and undefined mechanisms

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Drug desensitization

- One form of induction of immune drug tolerance by which effector cells are rendered less reactive or nonreactive to IgE-mediated immune responses by rapid administration of incremental doses of an allergenic substance
- This can be used for severe PCN allergy when there are no alternative agents
- This is a hospital procedure usually conducted in the ICU

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Beta-lactam Drug Desensitization

- Typical starting dose is 1/10,000 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 under therapeutic dosage is achieved.

Outcomes and Safety of PCN desensitizations

- Most all patients can be desensitized
- About 1/3 of patients have mild cutaneous reactions during desensitization
- Severe reactions extremely rare
- Delayed reactions < 10%
- Long-acting benzathine PCN may be administered after desensitization safely at intervals of 1- weeks

Wendel GD et al. New Eng J Med 1985;312:1229-32.

PCN allergy and other drugs

- Monobactams (Aztreonam): Does not cross react with penicillins or cephalosporins (except ceftazidime) and may be given without PCN skin testing.
- Carbapenems: PCN skin testing should be performed if possible, otherwise may receive via graded challenge.

TESTING FOR DELAYED REACTIONS TO BETA-LACTAMS

Skin testing for delayed reactions

- Skin testing using both intradermal and patch tests has been utilized for certain delayed immunologic drug reactions
- The negative predictive values for these techniques have not been well established and therefore a negative test does not preclude a drug allergy
- Some allergists may suggest testing select patients when it is urgently necessary to use a drug that resulted in a delay reaction in the past

Delayed Intradermal drug tests

- Delayed intradermal tests may be useful for drug-induced maculopapular rashes and eczema but are not generally recommended for other cutaneous reactions
- Intradermal drug tests appear to be more sensitive than patch tests in most circumstances
- Beta-lactams have been reported to be positive in delayed cutaneous reactions

USE OF CEPHALOSPORINS IN PCN ALLERGIC PT

Cephalosporin administration in PCN History positive patients

- **Prior to 1980** cephalosporins were often **contaminated** with penicillin
  - Partially responsible for the 1st & 2nd generation cephalosporin package inserts that state that there is "up to 10% cross-reactivity" to cephalosporins in PCN-allergic patients **(NOT TRUE TODAY)**

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73
Solensky, R (2015). Penicillin-allergic patients: Use of cephalosporins, carbapenems, and monobactams. In D.S. Basow (Ed.), UpToDate. Retrieved from http://www.uptodate.com/home/index.html.

Cephalosporin administration in PCN History positive patients

- There is “moderate cross-reactivity” in vitro between cephalosporins and penicillins.
- In PCN allergic patients, clinical sensitivity to cephalosporins occurs in 0.1% to 2%, some with anaphylaxis.
- Therefore PCN skin testing is recommended prior to cephalosporin administration in PCN allergic patients

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Cephalosporin administration to patients with history of penicillin allergy

- **Penicillin skin testing should be considered before administration of cephalosporins**
- If skin test results are negative there is minimal risk for an allergic reaction to a cephalosporin.
- The committee recommends test dose challenge with the cephalosporin to be used for treatment
- Note: PCN test dose challenge would still be needed prior to PCN use in future

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Cephalosporin administration to patients with history of penicillin allergy

- Patients allergic to **amoxicillin** (or augmentin) should avoid cephalosporins with identical R-group side chains (cefadroxil, cefprozil, cefatrizine) or receive them via rapid induction of drug tolerance
- Note: future testing with amoxicillin and test dose challenge would need to be completed prior to using a cephalosporin with identical R-group side chain

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

R-chains

Table 16. Groups of β-Lactam Antibiotics That Share Identical R_1-Group Side Chains[a]

Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			

[a] Each column represents a group with identical R_1 side chains.

Table 17. Groups of β-Lactam Antibiotics That Share Identical R_2-Group Side Chains[a]

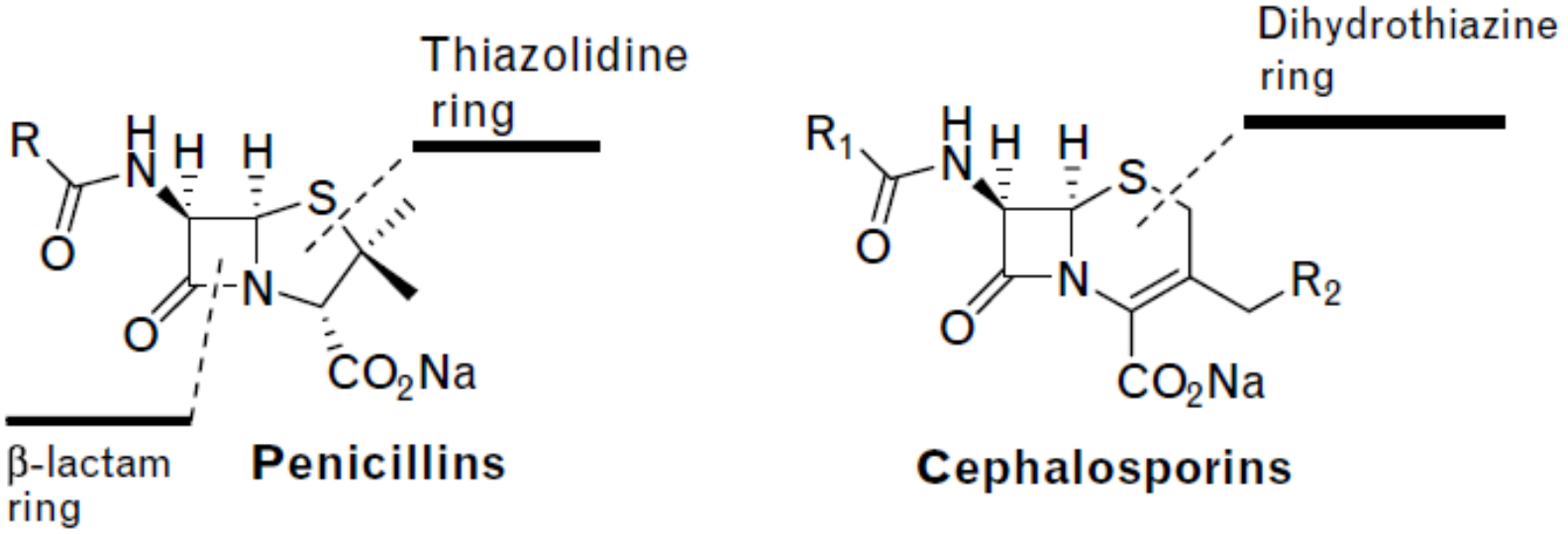
Cephalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten
Cefadroxil	Cephalothin	Cefoxitin	Cefamandole	Loracarbef	Ceftizoxime
Cephradine	Cephaloglycin		Cefmetazole		
	Cephapirin		Cefpiramide		

[a] Each column represents a group with identical R_2 side chains.

- With a reported cephalosporin allergy, testing and oral challenge should be with a cephalosporin that **does not share the same R-chain**

CEPHALOSPORIN ALLERGY

Cephalosporins



Perez-Inestrosa E. et al. Curr Opin Allergy Clin Immunol 5:323–330

Cephalosporin allergy

- 10-fold less common than PCN allergy (as reported)
- Most hypersensitivity reactions are probably directed at R-group side chain rather than core beta-lactam structure, though this is uncertain.
- Skin testing with native cephalosporins is not standardized, but a positive skin test result using a nonirritating concentration suggests the presence of drug specific IgE antibodies
- A negative skin test result does not rule out an allergy because the negative predictive value is unknown

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Cephalosporin administration With Cephalosporin Allergy History

- Complete cephalosporin **skin testing using a non-irritating concentration** of the selected cephalosporin taking into account if the specific cephalosporin responsible for the adverse reaction shares the same R1 or R2 side chain as the drug that that needs to be used
- Administer graded dose challenge with oral form of drug used for skin testing

R-chains

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Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			

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Cefadroxil	Cephalothin	Cefoxitin	Cefamandole	Loracarbef	Ceftizoxime
Cephradine	Cephaloglycin		Cefmetazole		
	Cephapirin		Cefpiramide		

[a] Each column represents a group with identical R_2 side chains.

- With a reported cephalosporin allergy, testing and oral challenge should be with a cephalosporin that does not share the same R-chain

Cephalosporin administration to patients with hx of amoxicillin/ampicillin allergy

- Patients allergic to **amoxicillin** (or augmentin) should avoid cephalosporins with identical R-group side chains (cefadroxil, cefprozil, cefatrizine) or receive them via rapid induction of drug tolerance
- Patients allergic to **ampicillin** should avoid cephalosporins and carbacephems with identical R-group side chains (cephalexin, cefaclor, cephradine, cephaloglycin, loracarbef) or receive them via rapid induction of drug tolerance

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

SUMMARY

1	Confirm history is a drug allergic reaction
2	Classify drug allergic reaction
3	Determine likelihood of drug(s) in question to cause reaction
4	Determine elements that may influence drug allergy history
5	Evaluate if subsequent exposure to drug
6	What is likely future need of drug?

Khan DA. Drug Allergy. In Manual of Allergy & Immunology 5th Ed. 2012

Diagnostic evaluation of children

- Using the same diagnostic protocol as adults
- Several studies confirmed the safety of skin tests in children, with a rate of 1% to 3% of systemic reactions to skin testing
- Negative predictive value of the Drug Provocation Testing has been shown to be high

Romano A. and Caubet J. J Allergy Clin Immunol Pract 2014;2:3-12

Case # 1

- Drug Allergy History of 55 year old female:
- Penicillin: Pt states that in her 20s, she had some type of reaction to PCN. She does not recall what the reaction was but dues not think that 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 antibiotic caused which reaction but believes these were Cipro and Keflex
- Bactrim: Listed as drug allergy but patient has no idea of reaction history
- She has tolerated azithromycin, doxycycline, and nitrofurantoin

Assessment of Case

- Penicillin
  - Likely benign reaction
  - Likely remote
  - Likelihood of current penicillin allergy is low
- Ciprofloxacin/cephalexin
  - Adverse reaction to one
  - Urticarial reaction to the other
    - Potentially IgE mediated
  - Remote
- Sulfonamides
  - Unknown

Approach to patients with multiple drug intolerance syndrome

Step 1 (history)	• Obtain detailed history of listed drug allergies • Determine potential need for future medications
Step 2 (testing)	• Identify medications for drug skin testing • Identify medications requiring drug challenge
Step 3 (guidance)	• Develop list of medications that are safe to use • Develop list of medications to avoid • Develop list of medications that can be considered for future testing or induction of drug tolerance

Khanm DA. Ann Allergy Asthma Immunol 110: 2e6 (2013)

Conclusion of case

- Patient was negative to Pre-Pen and PCN-G
- Patient was administered Amoxicillin 500 mg in a 2-dose challenge in the office and observed
- Recommendation:
  - OK to receive penicillins in the future
- Patient wants to discuss future testing and/or challenge to cephalosporins in the future

Case 2

- 35 year old healthy female who reports that when she was a child, she had a reaction to “a penicillin” and was told to never take this medication again.
- Reaction: stomach upset, diarrhea, and “acting confused” which resolved after stopping the medication
- She tolerated Augmentin without difficulty at age 20 for a sinus infection

Questions

- What kind of adverse drug reaction did she possibly have?
  - A. Anaphylaxis
  - B. Anaphylactoid reaction
  - C. Side Effect
  - D. School avoidance-itis
- What are your recommendations in this patient about penicillin/penicillin derivatives?
  - Patient has tolerated penicillin derivative since her initial “reaction” and therefore is at no higher risk than the general population to have anaphylaxis to penicillin

Case 3

- 47 year-old male with well-controlled moderate persistent asthma and AR who reports a history of penicillin allergy when he was 11 years old.
- Reaction: He was not sure why he was prescribed the penicillin. He recalls feeling that he throat was closing and had shortness of breath within 30 minutes after taking a dose. He doesn't recall hives or GI issues, but states that he was intubated in the ER.
- He has not had any penicillin/penicillin derivatives since that time.

Questions

- Are you concerned about a penicillin allergy?
  - Yes
- What are you going to tell him about taking penicillin?
  - Don't do it
- Can he lose his sensitivity to penicillin?
  - Yes
- Would you recommend a cephalosporin?
  - No. Recommend skin testing to PCN first. If negative OK to take cephalosporin. If positive would consider graded challenge or desensitization.
- What antibiotics would have the lowest risk of anaphylaxis for him?
  - Aztreonam and Non-beta-lactams.

Case 4

- 20 yo woman with cystic fibrosis is started on an extended course of piperacillin/tazobactam.
- 2 weeks into course she develops fevers, rashes, and arthritis. She is changed to cefepime with resolution of her symptoms.
- The next year she is treated with piperacillin and develops the same symptoms in 4 days before the antibiotic is changed.
- Is this an allergy? Would you skin test? What would you advise?
- Yes, but not IgE. (Coombs III – Immune complex). No skin testing. Avoid penicillins.

Case 5

- A 40 year old woman reports a lifelong history of penicillin allergy. She has no recollection what may have happened, but reports her mother always just told her she was allergic to penicillin.
- Is this an allergy? Would you skin test? What would you advise?
- The history in this case is not helpful. Yes, skin testing is recommended. If skin test is negative, should undergo oral challenge. If skin test positive, recommend alternate antibiotics in future or desensitization if penicillin is needed.

ACAAI Drug Allergy & Anaphylaxis Committee
Beta-Lactam Toolkit Contributors 2014-2015:

- Dana Wallace, MD – Beta-Lactam Toolkit Project Leader
- Scott Commins, MD – Committee Chair
- Anne Ellis, MD – Committee Vice-Chair ??
- Marcella Aquino, MD
- Aleena Banerji, MD
- Howard Crisp, MD
- Paul Dowling, MD
- Stanley Fineman, MD
- Autumn Guyer, MD
- Fred Heish, MD
- James L. Kuhlen, MD
- David Lang, MD
- Philip Lieberman, MD
- Mohsen Nasir, MD
- Wes Sublett, MD

American College of Allergy, Asthma & Immunology | allergist

THE END OF PCP PRESENTATION

SLIDES FOR ALLERGISTS AS AUDIENCE

2014-2015 ACAAI Drug Allergy & Anaphylaxis Committee Beta-Lactam Toolkit

- Physician and nursing testing protocols for Immediate and Delayed reactions
  - **Penicillin**
  - **Cephalosporins**
- **Skin Testing forms/consent form**
- **Ordering** of testing supplies/**insurance coding** & reimbursement expected
- **Patient education** handout on PCN and Cephalosporin drug allergy & “Frequent Q & A on PCN Allergy”
- Educational **PowerPoint presentation for PCP and insurers audiences** + added slides for presenting to groups or allergists

2014-2015 ACAAI Drug Allergy & Anaphylaxis Committee Beta-Lactam Toolkit

- **Marketing & educational materials** for PCP, medical staff, local medical societies, news media, insurance companies
- **Letter templates** to send to patients in allergists' & PCPs' practice who are labeled as "Penicillin allergic" recommending PCN skin testing and challenge
  - Letter templates for medical professional groups (non-allergy) offering formal lecture presentation by allergist or requesting the placement of an article as a newsletter or a website posting
  - **Summary article on safety and economic advantages of PCN**/cephalosporin testing for population health (insurers as key target)

2014-2015 ACAAI Drug Allergy & Anaphylaxis Committee Beta-Lactam Toolkit

- **Ad Copy** for newspaper, health magazine, website placement
- **Reference list** & open access articles for allergists on PCN & Cephalosporin allergy
- ACAAI **CME program** on the website *Learning Center*
- **Webinar** for ACAAI members **summer 2015**
- **Workshop at ACAAI 2015** annual meeting
- **Toolkit** will be available on ACAAI Members' secure website (www.acaai.org)

Reasons for underutilization of PCN testing in Allergy offices

- PRE-PEN not available
  - Sept. 2000-Nov. 2001
  - Sept. 2004-Nov. 2009
- Many allergists never trained to do PCN testing as not available during their fellowship years
- Older allergists got out of practice of performing PCN testing
- Fear of completing without having minor determinants
- Reimbursement was too low to cover cost of PRE-PEN without oral challenge
- Time consuming, labor intensive
- Most PCN testing has been in academic centers or integrated health care programs

Macy,E. JACI in practice 2013;1:258-63

PCN SKIN TESTING AND CHALLENGE

AAAAI PCN Allergy 2014 Survey

- 642 allergists (62% private practices) responded to the survey
- 90% performed beta-lactam skin testing
- 75.2% of all allergists do skin test using Penicillin G
- 38.3% of all allergists also skin tested with MDM (44% of allergists at academic centers)
- Pre-Pen was overall the most prevalent positive skin test in patients with a positive test (66% reported)
- 15% of those who skin tested using ampicillin, reported ampicillin to be the most prevalent positive skin test
- Oral challenges were more likely to be performed by allergists in practice <10 years (93% vs. 85%)

Gerace KS. J Allergy Clin Immunol Pract. 2015 Sep-Oct;3(5): 791-3.

AAAAI PCN Allergy 2014 Survey

- Allergists performing both skin testing and oral challenges were more likely to advise patients that they could safely take all beta-lactams (36%) than those performing only skin testing (21%)
- 32.8% of allergists only performing skin testing advised patients to take only the drug for which they had tested negative while only 8.8% of allergists also performing oral challenges gave this same advice

Gerace KS. J Allergy Clin Immunol Pract. 2015 Sep-Oct;3(5): 791-3.

AAAAI PCN Allergy 2014 Survey

- 72% of allergists preferred using both skin testing and oral challenges
- 4% of allergists performed only oral challenges
- 76% allergists did not feel confident that the PCP received and followed recommendations following PCN skin testing
- Authors called for more standardization for beta-lactam testing

Gerace KS. J Allergy Clin Immunol Pract. 2015 Sep-Oct;3(5):791-3.

2015 Drug & Anaphylaxis Committee Questionnaire on Beta-lactam Testing and challenge

- Wide variation on how to conduct PCN/Cephalosporin skin testing including:
  - Which agents to use for testing: Penicillin G, Minor determinant Mix, Pre-Pen, Amoxicillin, and/or Ampicillin, Clavulanate
  - Concentration of agents to use for testing
  - Amount of each agent to inject for ID testing
  - Reading time and criteria for a positive prick and intradermal test
  - Concentration of histamine control, amount to inject, when and how to read

2015 Drug & Anaphylaxis Committee Questionnaire on Beta-lactam Testing and challenge

- Differing opinions on when & how to conduct PCN/ Cephalosporin testing and challenge including:
  - Indications for sIgE testing to PCN
  - Testing options for maculopapular rash to PCN or amoxicillin/ampicillin
  - When to use oral challenge
  - Preferred drug for oral challenge
  - # of doses of oral challenge drug
  - Observation time following oral challenge

PCN skin testing

- **Major determinants** penicilloylpolylysine (**PrePen**) and a minor determinant- benzyl penicillin (PCN G) should be used for all PCN allergy skin testing
- **Minor Determinant Mix** is not commercially available for skin testing but it is not felt to be required
- Skin testing of all reagents involves both **prick and intradermal testing**

Minor determinant mix
Is it needed?

- 2010 Drug Allergy PP --- EVIDENCED BASED
  - *"Ideally, penicillin skin testing should be performed with both major and minor determinants."*
  - *"Skin testing with the major determinant (Pre-Pen) and penicillin G only (without penicilloate or penilloate) may miss up to 20% of allergic patients, but data on this are conflicting."*
  - *"Penicillin G left in solution ("aged" penicillin) does not spontaneously degrade to form antigenic determinants and has no role in penicillin skin testing."*
  - *"Penicillin challenges of individuals skin test negative to penicilloylpolylysine and penicillin have similar reaction rates compared with individuals skin test negative to the full set of major and minor penicillin determinants."*

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Minor determinant mix
Is it needed?

- 2010 Drug Allergy PP --- EXPERT OPINION
  - *"Therefore, based on the available literature, skin testing with penicilloylpolylysine and penicillin G appears to have adequate negative predictive value in the evaluation of penicillin allergy."*

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

PCN Testing Protocol
2015 Drug & Anaphylaxis Committee

- Complete prick and ID testing (if prick is negative) with:
  - **Penicillin G 10,000 U/ml**
  - **PrePen** (benzylpenicilloyl polylysine) full strength
  - **Negative Control**: Sodium chloride solution without preservative
  - **Positive Control**:
    - Percutaneous: histamine base 6 mg/ml (histamine dihydrochloride 10 mg/ml)
    - Intradermal: histamine base 0.1 mg/ml (histamine phosphate 0.275 mg/ml)

PCN Testing Protocol
2015 Drug & Anaphylaxis Committee

- For ID testing administer 0.02-0.03 ml
- Read all prick/ID tests at 15 minutes
- Positive Prick & ID is ≥3 mm diameter with equivalent or greater erythema (flare) compared to the saline control
- Duplicate testing not recommended
- Oral Challenge with Amoxicillin
  - 1st dose (optional) 25 to 50 mg Amoxicillin
  - 2nd dose (or only dose) 250 mg Amoxicillin
- Observe for 30 and 60 minutes after 1st & 2nd dose, respectively

Pre-Pen Testing/Reading
Per package Insert

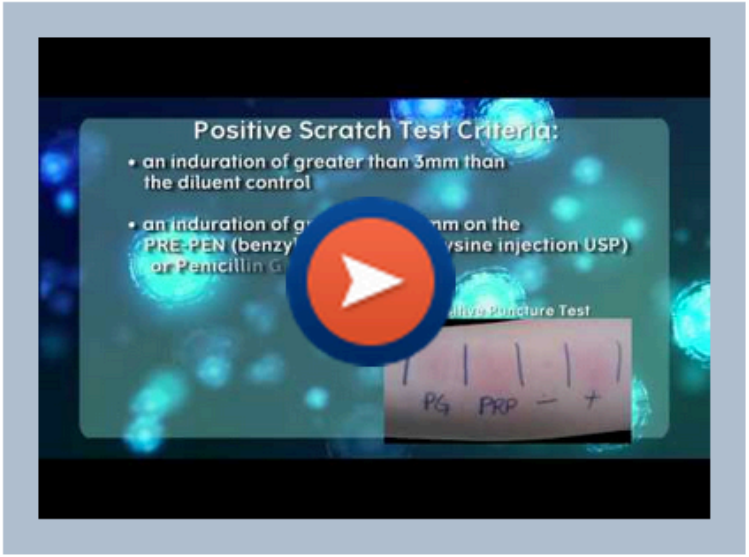
- Puncture testing: Development within 10 minutes of a pale wheal, sometimes with pseudopods, surrounding the puncture site with varying diameter from 5-15 mm, … surrounded by a variable diameter of erythema and … variable degree of itching.

- Intradermal testing: Inject bleb of about 3 mm in diameter, in duplicate, Read at 20 minutes– positive is itching and significant increase in size of original bleb to at least 5 mm

https://docs.google.com/viewer?url=http%3A%2F%2Fwww.pre-pen.com%2Ffiles%2Fdocument_25.pdf

Pre-Pen

Videos



http://www.pre-pen.com/physician-tools

WHEN SHOULD AMOXICILLIN OR AMPICILLIN BE INCLUDED IN SKIN TESTING?

Amoxicillin is the #1 Rxed PCN Drug In US and Southern Europe

- In Southern Europe, up to 1/3 of PCN allergic patients are allergic to the R chains of PCN
  - 90% of the PCN prescribed is amoxicillin[1]
- In 2010, top 5 Antibiotic Rx (outpatients) in the US were for 1) Amoxicillin or 2) Augmentin (230); 3) Azithromycin (166); 4) Ciprofloxacin (66) and 5) Cephalexin (65) all listed per 1000 persons[2]
- In 2010, Southern US had 936 antibiotic Rx/1000 persons, 2x the number in other geographical areas[2]
- Use of Amoxicillin/Augmentin Rxed antibiotics seems to be approaching Southern Europe

1. Solensky, R (2015). Penicillin-allergic patients: Use of cephalosporins, carbapenems, and monobactams. In D.S. Basow (Ed.), UpToDate. Retrieved from http://www.uptodate.com/home/index.html. 2. N Engl J Med 2013; 368:1461-1462

San Diego Kaiser Permanente PCN allergy testing 6/2010 - 4/2012

- 500 patients tested
- Adverse reaction reported by patients
  - **Rash- not hives 41%**
  - **Rash- hives/angioedema 34%**
  - Unknown- 15%
  - Other adverse reaction 8%
  - **Anaphylaxis 2.8%**
- Reported onset of adverse event after last PCN exposure
  - **Unknown-30%**
  - 1-24 hours-23%
  - > 73 hours- 21%
  - 25-72 hours-16%
  - < 1 hour-10.5%

Macy,E. JACI in practice 2013;1:258-63

San Diego Kaiser Permanente PCN allergy testing 6/2010-4/2012

- Skin testing agents for prick and ID testing
  - **PRE-PEN** (used according to package insert- see below)
  - **Na Penicillin G** -0.01 molar = 5941 U/ml
  - **Na Amoxicillin** prepared from Sigma-Aldrich chemical supplies- 3.6 mg/ml
- For ID testing **0.02 ml injected**
- Positive skin test (read at 15 minutes) defined as:
  - PRE-PEN= > **5 mm wheal with surrounding erythema** (as per package insert)
  - All other agents for prick and ID testing were considered positive if **> 5 mm wheal with surrounding erythema**
  - Note: Author disagrees with using the lower 3-4 mm wheal size as this will identify too many false positives

Macy,E. JACI in practice 2013;1:258-63

San Diego Kaiser Permanente PCN allergy testing 6/2010-4/2012

- **4**/500 (**0.8%**)patients had positive skin test to **Pre-Pen**
  - # 1 Pre-Pen ID 20/30 mm (1.7 yr old)
  - # 2 Pre-Pen ID 12/30 mm (57 yr old)
  - # 3 Pre-Pen ID 15/20 mm (64 yr old)
  - # 4 PCN ID 8/12 (86 yr old)
- **4/500** (0.8%) with **negative** skin test had **positive challenge** to amoxicillin 250 mg (125 mg in child)
  - #1 Hives at 20 minutes (38 yr old)
  - #2 Hives at **60 minutes** (6 yr old)
  - #3 hives at **50 minutes** (5 yr old)
  - #4 Hives at **50 minutes.** Hypertension (53 yr old)
- All positive oral challenges above were **treated with antihistamines** and symptoms cleared in 60 minutes
- 2 patients had significant delayed reactions, #1 GI upset and #2 migraine

Macy,E. JACI in practice 2013;1:258-63

San Diego Kaiser Permanente PCN allergy testing Conclusions

- Macy E., et al. recommend testing only with:
  - **Pre-Pen**
  - **Na Penicillin**
- If negative on skin testing, **do amoxicillin oral challenge on everyone**
- Testing with **amoxicillin not needed**
- Strongly recommends using the weaker Na Penicillin 6000 U/ml for prick and ID testing (vs 10,000 U/ml)
- Recommends 5 mm with greater erythema be considered a positive prick or ID test

Macy,E. JACI in practice 2013;1:258-63

Testing for Amoxicillin/Ampicillin
2015 Drug & Anaphylaxis "Expert Opinion"

- **Amoxicillin and Ampicillin ARE different drugs** and there is the possibility of reacting to one and not the other
- **Ampicillin IV** is the only available commercial product in US that can be used for skin testing
- When the suspected or confirmed allergic reaction was to Amoxicillin or Ampicillin, and this drug will likely be needed in the future, consider skin testing with **Ampicillin**
- Test using **Ampicillin 20 mg/ml for Prick/ID testing**[1,2]
  - Note: Some US drug allergy experts recommend 2.5 mg/ml but no published studies could be located
- **When Augmentin is the allergic drug**, clavulanate (not commercially available) is not a required skin testing agent. However, consider using **Augmentin for oral challenge.**

1.Blanca M. Allergy. 2009;64(2):183-93.
2.Padial A, Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2008;38(5):822-8.

San Diego Kaiser Permanente PCN allergy testing 6/2010-4/2012

- Over the 100 days following testing, 4 (4.5% of 88 penicillin courses) who had tested negative had a new reaction to a PCN class drug
- Previous studies have shown that (given a hx of PCN allergy) following negative PCN testing, patients have a 2.9% adverse reaction rate following each future therapeutic course of PCN class antibiotic
- The above group with a history of PCN allergy + negative PCN testing have about a 2.9% chance of reacting to a sulfonamide antibiotic
- Routine clinical practice 1.5% women and 1.1% men will report a new penicillin allergy after each use of a PCN class antibiotic

Macy,E. JACI in practice 2013;1:258-63

PCN Allergy De-labeling Required

- Retrospective chart review of 100 patients from tertiary outpatient clinic who were skin tested to PCN 1/2010-5/2014
- 37.7% (26/69) of patients who were skin test negative to PCN remained labeled “PCN allergy” in the the EHR
- These 26 returned to the clinic and all tolerated an oral challenge or treatment course of PCN
- 19.2 % of the 26 still did not have their label of “PCN allergy” removed.
- 100% of these patients acknowledged, when questioned, that they had tested negative to PCN
- 38% (9/23) with negative PCN testing have kept their allergy label or continued to avoid PCN

Gerace KS. J Allergy Clin Immunol Pract. 2015 Sep-Oct;3(5):815-6.

When PCN Testing is positive

- If a PCN skin test (major or minor determinant) is positive, there is approximately 50% chance of an immediate reaction to PCN
- Many patients with a positive PCN skin test will have a negative challenge, indicating sensitization rather than true clinical allergy
- A positive in vitro specific IgE to PCN or major determinant or basophil activation tests indicates significant risk for an immediate reaction, but a negative test results lacks adequate sensitivity
- Patients with a both a positive history and skin test to PCN have a 2% chance of being allergic to cephalosporins

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73

Allergic reaction to the PCN structure & other drug allergies

- In US, majority of PCN-allergic patients, at least historically, have been allergic to the core ring structure of the beta-lactam and less than 0.5% are sensitized to R group side chain
- Beta-lactam ring found in cephalosporins, carbapenems, and monobatams
- If PCN testing is negative, may receive carbapenem
- If PCN testing is positive, give carbapenem by graded challenge
- If PCN allergic, may receive Aztreonam, a momobactam as no cross-reactivity

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73
Solensky, R (2015). Penicillin-allergic patients: Use of cephalosporins, carbapenems, and monobactams. In D.S. Basow (Ed.), UpToDate. Retrieved from http://www.uptodate.com/home/index.html.

Cephalosporin administration in PCN History positive patients

- **Prior to 1980** cephalosporins were often **contaminated** with penicillin
  - Partially responsible for the 1st & 2nd generation cephalosporin package inserts that state that there is "up to 10% cross-reactivity" to cephalosporins in PCN-allergic patients **(NOT TRUE TODAY)**
- A limited number of well-controlled studies of cephalosporin use in PCN-allergic patients are available
- Cephalosporin challenge studies in patients with both 1) Positive PCN history & skin test and 2) Positive cephalosporin skin test are lacking

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73
Solensky, R (2015). Penicillin-allergic patients: Use of cephalosporins, carbapenems, and monobactams. In D.S. Basow (Ed.), UpToDate. Retrieved from http://www.uptodate.com/home/index.html.

Cephalosporin administration With Cephalosporin Allergy History

- Complete cephalosporin **skin testing using a non-irritating concentration** of the selected cephalosporin (usually 10-fold dilution of standard IV dose – see chart)
- If the specific cephalosporin responsible for the adverse reaction **is known** select a drug that **does not share the same R1- or R2-side chains** as the cephalosporin that caused the allergic reaction
- If the specific cephalosporin responsible for the adverse reaction is **unknown**, skin test use a 2nd or 3rd generation cephalosporin, e.g., cefuroxime (available IV and oral forms)
- Administer graded dose challenge with oral form of drug used for skin testing (1/10 to ¼ , full dose over 1 1/2 hours)

Non-irritating concentrations of cephalosporins for skin testing

Table 18. Nonirritating Concentrations of 15 Antibiotics[428]

Antimicrobial drug	Full-strength concentration	Dilution from full strength	Nonirritating concentration
Azithromycin	100 mg/mL	10^{-4}	10 μg/mL
Cefotaxime	100 mg/mL	10^{-1}	10 mg/mL
Cefuroxime	100 mg/mL	10^{-1}	10 mg/mL
Cefazolin	330 mg/mL	10^{-1}	33 mg/mL
Ceftazidime	100 mg/mL	10^{-1}	10 mg/mL
Ceftriaxone	100 mg/mL	10^{-1}	10 mg/mL
Clindamycin	150 mg/mL	10^{-1}	15 mg/mL
Cotrimoxazole	80 mg/mL	10^{-2}	800 μg/mL
Erythromycin	50 mg/mL	10^{-3}	50 μg/mL
Gentamicin	40 mg/mL	10^{-1}	4 mg/mL
Levofloxacin	25 mg/mL	10^{-3}	25 μg/mL
Nafcillin	250 mg/mL	10^{-4}	25 μg/mL
Ticarcillin	200 mg/mL	10^{-1}	20 mg/mL
Tobramycin	80 mg/2 mL	10^{-1}	4 mg/mL
Vancomycin	50 mg/mL	10^{-4}	5 μg/mL

Solensky R. et al. Ann Allergy Asthma Immunol 2010; 105:259-73