

NC CLASP OUTPATIENT STEWARDSHIP YEAR 2, SESSION 8

Antibiotic Allergies April 24, 2024



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- These slides contain materials from a variety of colleagues, as well as the CDC, WHO, AHRQ, etc.



INTRODUCTIONS

Please put your name, clinic, and location in the chat!







CME AND CE CREDIT



CME & CE for participants

- Attendance and active participation per learning session
- Click the link in the chat during the session to document your attendance
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TODAY'S OVERVIEW

Quick Review:

Skin and Soft-Tissue Infections

- Antibiotic Allergies
 - Impact of reported allergies on antibiotic stewardship
 - Penicillins and Cephalosporins
 - Allergy assessment and resources
 - Other antibiotic classes



THREE WAYS TO OVERUSE ANTIBIOTICS

1. Prescribing antibiotics when none are indicated

2. Using an antibiotic that is too broad for the infection (or otherwise suboptimal)

3. Using an excessive duration



CELLULITIS: OPTIMAL TREATMENT

Narrow spectrum of therapy

- Without MRSA risk factors, cephalexin highly effective
- ► 5-day duration as effective as 10 days
- Awareness of cellulitis mimics



ABSCESS: ANTIBIOTIC SELECTION

~100% (Always active)
90-99% (Almost always active)
50-89% (Resistance more frequent)
<50% (Usually or always inactive)

Clindamycin

cephalexin					
Pneumococcus	H. flu, Moraxella		Atypicals		
Group A Strep		Oral anaerobes			
MSSA		MRSA			
E. coli, K. pneumoniae		Pseudomonas			
Trimethoprim-Sulfamethoxazole					
Pneumococcus	H. flu, Moraxella		Atypicals		
Group A Strep		Oral anaerobes			
MSSA		MRSA			
E. coli. K. pneumoniae		Pseudomonas			

Conhalovin

Pneumococcus	H. flu, Moraxella		Atypicals	
Group A Strep		Oral anaerobes		
MSSA		MRSA		
E. coli, K. pneumoniae		Pseudomonas		
Doxycycline				
Pneumococcus	H. flu, Moraxella		Atypicals	
Group A Strep		Oral anaerobes		
MSSA		MRSA		
E. coli, K. pneumoniae		Pseudomonas		

- MSSA and MRSA coverage warranted
- Highly reliable: TMP-SMX, doxycycline; clindamycin a little less so
- Target based on cultures (as appropriate)
- Duration: 5 days



SSTI: ANTIMICROBIAL STEWARDSHIP OPPORTUNITIES

Best studies: guideline implementation for cellulitis and abscess

- Differentiate cellulitis from noninfectious conditions
- Rule out severe infection and risk factors for unusual pathogen
- Early source control of pus
- Targeted antibiotics based on antibiogram (e.g., cephalexin for cellulitis, doxycycline for abscess)
- ► 5-day durations
- Consider not using antibiotics if adequate I&D done



PENICILLIN ALLERGIES: IMPACT



Risk of meticillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study

OPEN ACCESS

Kimberly G Blumenthal assistant professor of medicine¹²³, Na Lu biostatistician¹, Yuqing Zhang professor of medicine¹³, Yu Li research assistant¹², Rochelle P Walensky professor of medicine²³⁴, Hyon K Choi professor of medicine¹³

- Population study in the UK
- Penicillin allergy associated with:
 - MRSA infection: adjusted HR 1.69 (95% CI: 1.51-1.90)
 - C. difficile infection: adjusted HR 1.26 (95% CI: 1.12-1.40)

Patients reporting penicillin allergy were 69% more likely to have an MRSA infection and 26% more likely to have a C-diff infection

BMJ, 2018



The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk

Kimberly G. Blumenthal,^{1,2,3,4} Erin E. Ryan,^{5,6} Yu Li,^{1,2} Hang Lee,^{4,7} James L. Kuhlen,⁸ and Erica S. Shenoy^{2,4,5,6}

¹Division of Rheumatology, Allergy, and Immunology, Department of Medicine, ²Medical Practice Evaluation Center, and ³Edward P. Lawrence Center for Quality and Safety, Massachusetts General Hospital, Boston, ⁴Harvard Medical School, Boston, ⁵Division of Infectious Disease, Department of Medicine, ⁶Infection Control Unit, and ⁷Biostatistics Center, Massachusetts General Hospital, Boston; and ⁸Acadia Allergy and Immunology, Department of Medicine, University of South Carolina School of Medicine, Greenville, South Carolina

Analysis of patients undergoing one of 5 common surgeries at Mass Gen

▶ Penicillin allergy: adjusted OR of 1.51 (1.02-2.22) for surgical site infection

- Only 12% received cefazolin (92% of penicillin non-allergic)
- 49% of penicillin-allergic received clindamycin and 35% received vancomycin

Patients reporting penicillin allergy had 51% higher odds of surgical site infection.

Clinical Infectious Diseases, 2017



Recorded Penicillin Allergy and Risk of Mortality: a Population-Based Matched Cohort Study

Kimberly G. Blumenthal, MD, MSc^{1,2,3,4}, Na Lu, MPH^{1,5}, Yuqing Zhang, DSc^{1,3,4,5}, Rochelle P. Walensky, MD, MPH^{2,3,4,6}, and Hyon K. Choi, MD, DrPH^{1,3,4}

► 63,690 patients with penicillin allergy; 237,167 patients without

- Median follow-up: 6 years
- Adjusted hazard ratio for mortality: 1.14 (1.12-1.17)

Patients reporting penicillin allergies were 14% more likely to die

Journal of General Internal Medicine, 2019

PENICILLIN ALLERGIES: IMPACT

- ▶ 10% of all patients report a penicillin allergy
- Only 10% of allergy reporters are *actually* allergic
- Penicillin allergy is associated with increased risk of surgical-site infection, MRSA infection, C-diff, and possibly death
- Alternative antibiotics are often:
 - Broader-spectrum: vancomycin, fluoroquinolones, carbapenems
 - Less effective: vancomycin, clindamycin, oral cephalosporins
 - ▶ More likely to cause C-diff: carbapenems, 3rd and 4th gen cephalosporins, fluoroquinolones



EPIDEMIOLOGY AND NATURAL HISTORY OF PENICILLIN ALLERGY

Reactions reported by 10% of patients

- Incidence of anaphylaxis with amoxicillin: 1 per 200,000 administrations
 - But very commonly used!

About 10% of patients lose their penicillin allergy each year

- After 10 years, 80-90% of true penicillin allergies have resolved
- Don't assume it's resolved though!
 - If many years have passed, testing is reasonable



WHY ARE PENICILLIN ALLERGIES OVER-REPORTED?

Many childhood illnesses are fever plus rash

- Erythema infectiosum, roseola infantum, scarlet fever
- Fever + antibiotics + rash = perceived reaction

Antibiotic-infection interactions

- Jarisch-Herxheimer reaction: fever, chills, headache, tachycardia, flushing
 - Occurs 1-2 hours after treatment of spirochete (i.e., syphilis) with penicillin
- ▶ EBV plus amoxicillin \rightarrow diffuse morbilliform rash

Perception that penicillin allergy is familial



CHALLENGES

Penicillin (and to a lesser extent cephalosporin) allergies are among the most common serious drug reactions

Allergy labels are used for various intolerances

Allergy documentation does not require detailed history

Clinicians reasonably fear overriding or removing a documented allergy

Pretty sure it's not a true allergy vs risk of anaphylaxis



ASSESSING PENICILLIN ALLERGY



PENICILLIN INTOLERANCES: 4 POSSIBILITIES

1. Non-severe, non-allergic

- Non-urticarial early-onset rash, GI symptoms only, behavior change, etc.
- Unlikely to repeat
- 2. True allergy, still allergic
- 3. True allergy, allergy resolved
- 4. Severe, non-allergic reaction



KEY HISTORICAL DETAILS

- When did the patient have the reaction?
- What was the reaction?
 - Non-reaction: family history; patient denies history
 - Intolerance: GI upset, headache, fatigue, etc.
 - Low-risk: itching alone, rash without hives, flushing/redness
 - High-risk Allergy: face/lip/tongue swelling, wheezing, shortness of breath, flushing
- What was the treatment for the reaction?
- Has the patient taken that class since then? Similar classes?
 - Penicillin allergy but tolerated cephalosporins?



PATIENT NOT ALLERGIC (ZERO RISK)

Family history

Specific allergies are not familial

Tolerated the penicillin *since* initial reported reaction

▶ We often find penicillin-allergic patients who took a full course of a penicillin recently

Intolerance, not allergy (Non-allergic, non-severe)

- Reaction was GI upset, nausea, vomiting, diarrhea, otherwise unrelated
- Non-urticarial, early-onset rash in childhood



TRUE ALLERGY

- IgE-mediated reaction
- Onset: <1 hour, up to 6 hours</p>
- Symptoms: itching, palmar erythema, wheezing, hives, angioedema, and/or anaphylaxis
- Treatment often required
 - Antihistamines, beta-agonists for wheezing, epinephrine if anaphylaxis
- Assessment:

HIGH RISK: AVOID FOREVER

High-risk reactions are severe and are not allergic

Reaction types:

- Stevens-Johnson Syndrome (SJS)
- Toxic Epidermal Necrolysis (TEN)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
 - Now called Drug-Induced Hypersensitivity Syndrome (DIHS)
- Serum Sickness
- Hemolytic anemia
- Acute Interstitial nephritis
- OK to use beta-lactams that were previously tolerated. Never give the offending agent; generally avoid all beta-lactams that are not known to be tolerated



Page 1 Toolkit A Patient ID/ Sticker: Page 1 Date of reaction:	Toolkit A (continue Page 2	Patient ID/ Sticker:
Reaction details (check all that apply): Intolerance histories Isolated Gl upset (diarrhea, nausea, vomiting, abdominal pain) Chills (rigors)	Timing/onset: Immediate (< 4 hrs) Intermediate (4-24 hrs) Delayed (> 24 hrs)	Treatment: None/penicillin continued Antihistamines Steroids (IV or PO) Epinephrine Penicillin discontinued IV Fluids
Low-risk allergy histories Family history Itching (pruritus) Unknown, remote (> 10 yr ago) reaction Patient denies allergy but is on record Moderate-high risk allergy histories (potential IgE reactions) Anaphylaxis Anaphylaxis Angioedema/swelling Bronchospasm (chest tight Courth Nasal symptoms Arrbythmia	Unknown How long ago was the reaction: C < 6 mo 6 mo-1 yr Other beta-lactam use: Previous use of a penicillin or bef	Other: Content of the content of th
Obsign Index symptoms Fundation Throat tightness Hypotension Flushing/redness Shortness of breath Rash Syncope/pass out Wheezing Type of rash (if known): Dizzy/lightheadedness	If yes, please list drugs:	beta-lactam (after the course that caused a reaction)
HIGH RISK: Contraindicated penicillin skin testing/challenge (potential severe non-immediate regimes in the	actions) ever hemia History taken by Print name:	Signature: Date:

Other symptoms:

EPIC EXAMPLE

- Patient reports penicillin allergy in 2012. Has penicillin-susceptible infection, started on meropenem at outside hospital.
- Can they take cephalosporins?
- Step 1: Go to Chart Review, Medications
 - Apply Antibiotics Filter



EPIC EXAMPLE

IP		meropenem (MERREM) 1 g in sodium		
IP	8	clindamycin (CLEOCIN) 18 mg/mL inje		
AMB	8	ofloxacin (OCUFLOX) 0.3 % ophthalmi		
		ofloxacin (OCUFLOX) 0.3 % o		
AMB	8	azithromycin (ZITHROMAX) 200 mg/5		
AMB		cefdinir (OMNICEF) 250 mg/5 mL sus		
AMB	8	azithromycin (ZITHROMAX) 200 mg/5		

Step 2: Review antibiotic history

- Patient took cefdinir in 2016!
- Patient reports no problem with that

Almost certainly will tolerate cephalosporin now



PENICILLIN ALLERGY TESTING

Can determine if patient is currently truly allergic

As opposed to non-allergic intolerance or resolved allergy

Limitations: Can not detect non-IgE mediated reactions

Serum sickness, Stevens-Johnson, DRESS, drug-induced liver injury, etc.

Skin testing:

- Scratch or prick testing, followed by intradermal injection
- Commercially available penicillin allergens; also can use specially prepared penicillin G

Graded oral challenge:

- Used if considered low-risk scenario (>10 years ago or probably not an allergic reaction)
- Take 10% of dose under close observation. If tolerated \rightarrow take full dose under observation



EXAMPLE ALGORITHM





PENICILLIN ALLERGY: CAN THEY TAKE CEPHALOSPORINS?

Classic teaching: 10% of penicillin-allergic patients will react to cephalosporins

► Truth: probably 1-5%

Usually determined by side chains, not beta-lactam ring

Some drugs share side chains

► Example:

Amoxicillin shares R1 side chain with cephalexin and cefadroxil. Cross-reaction more likely

But a patient who is allergic to amoxicillin will <u>likely</u> tolerate cefdinir or ceftriaxone (no shared side chains)

Management:

- ▶ If true allergy to a penicillin, graded IV or oral challenge with cephalosporins
- If unlikely true allergy, can usually just give full dose under observation

Randomized Multicenter Trial for the Validation of an Easy-to-Administer Algorithm to Define Penicillin Allergy Status in Sexually Transmitted Infection Clinic Outpatients

Rebecca A. Lillis,¹ Lindley A. Barbee,² Candice J. McNeil,³ Lori Newman,⁴ J. Dennis Fortenberry,⁵ Santiago Alvarez-Arango,^{6,7} and Jonathan M. Zenilman^{8,®}

Patients reported penicillin allergy

- Considered high-risk if immediate, IgE-mediated reaction
 - Hives only if within past 5 years
- Also high-risk if non-IgE mediated reaction such as Stevens-Johnson

Non-high-risk patients randomized to either:

- Formal penicillin allergy testing
 - ▶ If negative \rightarrow oral amoxicillin challenge (250 mg)
- Graded oral challenge
 - 25 mg of amoxicillin, 30 min of observation (vital signs, observation)
 - ▶ If no symptoms \rightarrow 250 mg amoxicillin

96/99 patients passed allergy testing; 95/99 patients passed graded oral challenge



ALLERGY LABELS

"Sticky penicillin allergy labels"

- Patients are tested, educated and delabeled
- Allergy labels may persist in other EHRs
- Patients may continue to report penicillin allergy



Olds G and Chow T, Ann Allergy



NON-BETA-LACTAM ANTIBIOTICS

IgE-mediated reactions are very uncommon for antibiotics other than penicillins and cephalosporins

Examples:

- Non-allergic rashes: TMP-SMX (may be severe!)
- Non-IgE-mediated infusion reactions: Vancomycin, fluoroquinolones
 - Similar effect as with IV opiates in some patients
- Drug-induced liver injury: rifampin, TMP-SMX, minocycline

Management:

- Idiosyncratic severe reactions: avoid!
- Infusion reactions: usually tolerable with pre-treatment and slower infusions



PENICILLIN ALLERGY SOLUTIONS



HOW CAN AMBULATORY PROVIDERS HELP PATIENTS REPORTING ANTIBIOTIC ALLERGY?

1. EASY: Refer beta-lactam-allergic patients to an Allergist

- Confirm that they do penicillin allergy testing
- Prioritize patients likely to require beta-lactams in the future
- 2. MEDIUM: Take detailed histories and de-label zero-risk patients
 - Family History
 - Tolerated the antibiotic since the reaction was observed
 - Intolerance only (e.g., mild-moderate GI symptoms)
- 3. HARD: Perform amoxicillin or cephalosporin graded oral challenges
 - Requires ability to recognize and treat symptoms of Type I hypersensitivity



WHAT CAN ALL PROVIDERS DO?

Gather detailed history when recording or reviewing allergies

If the patient has documented tolerance of a medication to which allergy is listed, <u>remove</u> the allergy label. <u>Document</u> the rationale for this change for future reference.

If a patient reports an allergy but it's not true, <u>educate</u> the patient and family



BREAKOUT SESSION

Do you often see patients impacted by penicillin allergies?

Do you have any options for handling those, other than avoidance?

What patient populations are most affected?



Summary

- Penicillin allergies are commonly reported and potentially harmful
 - C-diff, surgical site infections, mortality
- Reported intolerances can be grouped into:
 - Non-severe, non-allergic
 - Likely true allergy
 - Severe, non-allergic
- Patients with reported allergy may:
 - 1. Still be truly allergic
 - 2. Not have a true allergy
 - 3. Have a true allergy that resolved (>90% after 10 years)

- Patients can be de-labeled if:
 - They pass an oral or IV challenge OR
 - They tolerated the same drug since they reported the allergy!
- Resolving allergies takes work but can protect patients!
- Non-severe, non-allergic reactions
 OK to give that drug
- Severe, non-allergic reactions:
 - AVOID that drug (and often, entire class)



FINAL MESSAGE

The goal is not for you all to do your own penicillin allergy testing

Some patients are truly penicillin-allergic! Leave this to the allergists please!

The goal is for you to know that:

- Penicillin allergy is often falsely reported
- Inaccurate penicillin allergy labels are <u>harmful</u>
- You can identify patients who are likely to benefit from penicillin allergy testing
- Penicillin allergy testing is NOT a waste of time, effort, or money. It is very helpful for patients and they appreciate it!
- After testing, most patients reporting a penicillin allergy can safely take beta-lactams



THE NORTH CAROLINA CLINICAL ANTIBIOTIC STEWARDSHIP PARTNERS (NC CLASP)

All the information from today's session will be on our website <u>https://spice.unc.edu/ncclasp/</u>











Antibiotic Stewardship Conference



5.22.24 | 8:30 AM - 4 PM The Enterprise Conference & Event Center Winston-Salem, NC



North Carolina Clinical Antibiotic Stewardship Partners

More information at spice.unc.edu/ncclasp/

RESOURCES

CDC Penicillin Allergy Fact Sheet: <u>https://www.cdc.gov/antibiotic-use/community/pdfs/penicillin-factsheet.pdf</u>

AAAAI Penicillin Allergy Center

Resources, questionnaires, etc.

Great review: Blumenthal KG, Peter JG, Trubiano JA, Phillips EJ. Antibiotic allergy. The Lancet. 2019 Jan 12;393(10167):183–198.

