NC CLASP OUTPATIENT STEWARDSHIP
YEAR 2, SESSION 8

Antibiotic Allergies

April 24, 2024
CONFLICT OF INTEREST DISCLOSURES

- The views and opinions expressed in this series are those of the speakers and do not reflect the official policy or position of any agency of the US or NC government or UNC.

- Our speakers have the following financial relationships with the manufacturer(s) and/or provider(s) of commercial services discussed in this activity:
  - Dr. Willis has performed contracted research with: Pfizer (pediatric nirmatrelvir-ritonavir and maternal RSV vaccine), Novavax (pediatric COVID-19 vaccine), and Merck (monoclonal antibody for RSV prevention)

- The speakers do not intend to discuss an unapproved/investigative use of a commercial product/device in this series, and all COI have been mitigated.

- 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
  - Complete surveys as requested
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

- 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
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
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*
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
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 → 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
- 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
Penicillin Allergy History

Reaction details (check all that apply):

Intolerance histories
- Headache
- Fatigue

Low-risk allergy histories
- Itching (pruritus)

Moderate-high risk allergy histories
- Anaphylaxis
- Angioedema/swelling
- Nasal symptoms
- Bronchospasm (start tightness)
- Arterioedema
- Hypotension
- Flushings/redness
- Syncope/pass out

HIGH RISK: Contraindicated penicillin skin testing/challenge
- Stevens-Johnson syndrome (rash with mucosal lesions)
- Drug reaction exanthemas (rash with purpura)

Other symptoms:

Timing/onset:
- Immediate (< 4 hrs)
- Intermediate (4-24 hrs)
- Delayed (> 24 hrs)
- Unknown

Treatment:
- None/penicillin continued
- Antihistamines
- Steroids (IV or PO)
- Epinephrine
- Penicillin discontinued
- IV fluids
- Other.

How long ago was the reaction:
- < 6 mo
- 6 mo-1 yr
- 2-5 yrs
- 6-10 yrs
- > 10 yrs
- Unknown

Other beta-lactam use:
- Previous use of a penicillin or beta-lactam (prior to course that caused reaction)
- Subsequent use of a penicillin or beta-lactam (after the course that caused a reaction)

History taken by
Print name: ____________________ Signature: ____________________ Date: __________
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

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 → take full dose under observation
EXAMPLE ALGORITHM

Assess Reaction Type

Low Risk
- >10 years ago
- Itching only
- Non-allergic, non-severe

Graded Oral Challenge

Possible Allergy
- Hives
- Anaphylaxis
- Syncope
- Angioedema (facial swelling)

Medium or high risk

Skin testing

Graded oral challenge

Lower risk (hives only, reaction >10 years ago)

Skin testing or straight to graded oral challenge

Severe Non-Allergic
- Stevens-Johnson
- DRESS
- Hemolytic anemia
- Etc.

Do not test. Avoid class.
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 likely 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
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 → oral amoxicillin challenge (250 mg)
- Graded oral challenge
  - 25 mg of amoxicillin, 30 min of observation (vital signs, observation)
  - If no symptoms → 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 Asthma Immunol* 2024
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, *remove* the allergy label. *Document* the rationale for this change for future reference.

- If a patient reports an allergy but it’s not true, *educate* 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 harmful
  - 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 https://spice.unc.edu/ncclasp/
Antibiotic Stewardship Conference

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

More information at spice.unc.edu/ncclasp/
RESOURCES

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

- AAAAI Penicillin Allergy Center
  - Resources, questionnaires, etc.