The role of antibiotic allergies in antimicrobial stewardship in long-term care facilities

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Objectives

• Understand the potential harms of penicillin allergy labels and the relationship with antimicrobial stewardship

• Introduce strategies to optimize treatment of penicillin allergic patients as an antimicrobial stewardship initiative

• Describe processes to de-label patients of a penicillin allergy in long-term care facility patients.
Beta-lactams

- Beta-lactams are the most commonly used antibiotic group in the U.S.
- Core structure is the $\beta$-lactam ring with variable side chains at the R site
- Different side chains provide variation in the spectrum of activity and duration of action

[Chemical structures of Penicillins, Cephalosporins, and Carbapenems]

Drug Related Allergies

• Type 1 – IgE mediated
  – Usually occur within 1 hour of drug exposure, but may occur up to 72 hours afterwards
  – Urticaria, angioedema, bronchospasm, shortness of breath, rash with pruritus, and/or anaphylaxis

• Type 2 – cytotoxic
  – PCN induced hemolytic anemia

• Type 3 – Immune Complex
  – Serum sickness

• Type 4 – Cell mediated (delayed)
  – Contact dermatitis
PCN Allergy – How common

• PCN & other beta-lactams are the most frequent cause of medication-induced anaphylaxis

• Up to 10% of patients report a penicillin allergy
  – Most reports reflect historical childhood events, family history, or non-allergic adverse effects

• Highest rates reported by older and hospitalized patients
PCN Allergy – Overstated?

- Even with a well documented allergy, hypersensitivity may not persist over time due to loss of anti-PCN IgE antibodies (up to 80% over 10 years)
- 9 out of 10 patients who claim to be allergic to penicillin are not truly allergic when assessed by skin testing
- Preferred beta-lactam therapy is avoided in >50% of patients even when a non-severe prior reaction is reported
Beta-lactams are best!

- Surgical Prophylaxis
- Methicillin-susceptible *Staphylococcus aureus*
  - Superior to vancomycin for MSSA bacteremia
- Severe *Pseudomonas* infections
  - Often backbone at many institutions
- Group A streptococcal infections
  - Including invasive necrotizing infections
- Several STIs
  - Syphilis, PID, Gonococcal infections
# Commonly Prescribed Antibiotics in LTCFs

<table>
<thead>
<tr>
<th>Antibiotic Name</th>
<th>% of Treatment Courses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>28%</td>
</tr>
<tr>
<td>Beta-lactams</td>
<td>27%</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>15%</td>
</tr>
<tr>
<td>SMX-TMP</td>
<td>14%</td>
</tr>
<tr>
<td>Macrolides</td>
<td>6%</td>
</tr>
</tbody>
</table>

Antibiotic Prescriptions from Ontario LTCFs

Beta-lactams are safe(r)!

- Fluoroquinolones
  - QTc prolongation
  - Tendinitis/tendon rupture
  - Hypo/Hyperglycemia
  - CNS toxicities including insomnia and hallucinations, particularly in elderly
  - Drug interactions

- Beta—lactams
  - Generally well tolerated!
  - Main side effects: GI upset, rash

- Macrolides
  - QTc prolongation
  - Drug interactions (less with azithro)
  - GI

- SMX-TMP
  - Drug interactions
  - Hyperkalemia
  - Decreased tolerance in elderly
Implications of PCN “Allergy”

• Increased adverse effects
• Longer hospital stays, more readmissions
  – Two days longer in a study of geriatric inpatients, less likely to be discharged home
  – 30,000 hospital days/65 million in expenditures
• Development of MDR infections
  – 23.4% increase in *C. difficile* infection
  – 14.1% more MRSA
  – 30.1% increased VRE
• 50% increased odds of surgical site infection

Baman, N. JACI 2012; 389
Implications of PCN “Allergy”

• Increased usage of broad-spectrum antibiotics
  – FQ, Clindamycin, Vancomycin

• Increased antibiotic costs
  – 63% higher than those without reported allergy

• Antibiotic regimens deviate from standard of care (as defined by national guidelines, protocols or ID consults) in ~40% of patients with a reported PCN allergy

PCN Allergy - Documentation

- Allergy history documentation is poor
- Often lack documentation of nature and severity of reaction
- One retrospective cohort found only 39.8% of records had a specific allergen identified and only 22.7% had reaction characteristics identified
- Appropriate history can improve classification of mild versus life-threatening reactions
- Rechallenge with beta-lactams is more likely when allergic reactions are well documented

PCN Allergy - Documentation

- Allergy records are rarely updated to demonstrate tolerance
- ONLY 18% of patients with a documented penicillin allergy who received a penicillin antibiotic without incident had their records updated at UMMC
- Rarely updated to indicate tolerance of other beta-lactams
- Algorithms to guide penicillin allergy histories can improve documentation

Oliver WD. JACI In Practice 2017;5:184-6.
Staicu ML. ID Week 2016
 Conducting a Drug Allergy History

• *What is the name of the medication?*

• *How long ago did the reaction occur?*

• *Which systems were involved in the reaction, and what were the characteristics?*

• *When during the course did the reaction occur?*

• *Why was the medication prescribed?*
Conducting a Drug Allergy History

• Was the patient taking concurrent medications at the time of the reaction?

• What was the therapeutic management required secondary to the reaction?

• Had the patient taken the same or a cross-reacting medication before the reaction?

• Has the patient been exposed to the same or similar medication since the reaction?
Conducting a Drug Allergy History

• Has the patient experienced symptoms similar to the reaction in the absence of drug treatment?

• Does the patient have an underlying condition that favors reactions to certain medications?
PCN Allergy - Documentation

Question #1: (all)
What was your reaction to PCN and when did it occur?

- Difficulty breathing, throat closing, tongue/lip/facial swelling
- Don’t Remember
- Rash
- Nausea
- Vomiting
- Diarrhea

Document reaction and when reaction occurred.

Question #2: (all)
Have you taken any beta-lactams in the past without a reaction?

- YES
  - Document which beta-lactams patient tolerated
  - May receive medications in the same class.

- NO
  - Unclear if beta-lactams can be used safely.
  - Consider penicillin skin testing.

Document as a side effect, beta-lactams can be used safely!
PCN Allergy Documentation

Question #3: (only if rash)
Was the rash itchy, bumpy, or did skin peel off AND did the rash occur within 1 hour of taking?

Yes:
Document reaction as severe. If patient has received cephalosporins previously without a reaction, may receive medications in the same class.

No:
Document as low severity. Not a type I reaction. Beta-lactams can be used safely.
Pharmacist Allergy Interviews on FQ Use

Table 2. Primary and Secondary Outcomes.

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 43)</th>
<th>Prospective Group (n = 37)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of fluoroquinolone, mean days (SD)</td>
<td>3.7 (2.2)</td>
<td>2.7 (1.7)</td>
<td>0.027</td>
</tr>
<tr>
<td>Duration of fluoroquinolones, mean hours (SD)</td>
<td>88.4 (52.2)</td>
<td>64.2 (42.0)</td>
<td>0.027</td>
</tr>
<tr>
<td>Length of stay, median days (IQR)</td>
<td>6 (3-9)</td>
<td>5 (4-8)</td>
<td>0.73</td>
</tr>
<tr>
<td>Patient switched to β-lactam antibiotic, n (%)</td>
<td>N/A</td>
<td>18 (49)</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone, n (%)</td>
<td>N/A</td>
<td>16 (43)</td>
<td></td>
</tr>
<tr>
<td>Cefdinir, n (%)</td>
<td>N/A</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Cefepime, n (%)</td>
<td>N/A</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Reason for switch from FQ to β-lactam, n (%)</td>
<td>N/A</td>
<td>17 (94)</td>
<td></td>
</tr>
<tr>
<td>Pharmacy recommendation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician switch without intervention</td>
<td></td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>Pharmacy recommendations accepted, n (percentage recommendations)</td>
<td>N/A</td>
<td>17/18 (94)</td>
<td></td>
</tr>
<tr>
<td>Adverse reaction after switch to β-lactam, n</td>
<td>N/A</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FQ, fluoroquinolone; IQR, interquartile range.
PCN Allergy & Cross-Reactivity

• Cross-reactivity in penicillin-allergic patients is related to side chains

• For first generation cephalosporins, the risk of cross-reactivity is higher (used to be documented in the literature as 8%, newer reports suggest 2%), but risk of cross-reactivity with 2\textsuperscript{nd}, 3\textsuperscript{rd}, 4\textsuperscript{th} generation cephalosporins is negligible

• 1 patient of 300 with a reported PCN allergy had a reaction to cefazolin given for surgical ppx in large retrospective review

PCN Allergy & Cross-Reactivity

| Groups of Beta-lactam Antibiotics That Share Identical $R_1$-Group Side Chains |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Amoxicillin                     | Ampicillin                      | Ceftriaxone                     | Cefoxitin                       | Ceftazidime                     |
| Cefadroxil                      | Cefaclor                        | Cefotaxime                      | Cephalothin                     | Aztreonam                       |
| Cefprozil                       | Cephalexin                      | Cefpodoxime                     |                                |                                |
|                                 | Cephradine                      |                                |                                |                                |
|                                 | Loracarbef                      |                                |                                |                                |

Each column represents a group with identical $R_1$ side chains

- In the subset of patients with a history of true anaphylaxis to penicillin, cross reactivity with cephalosporins ~40% - almost exclusively associated with cephalosporins with shared chemical side chains.
Management of Reported Type 1 PCN Allergy

- Desensitization
- Graded Challenges
- Direct Oral Challenges
- Penicillin skin testing
Desensitization

• Requires inpatient admission – not practical for LTCF

• Time consuming
  – Pharmacy preparation
  – Nursing monitoring

• Requires exquisite compliance with antibiotic administration times

• Effects are not sustained
Graded Challenges

- Not intended to induce drug tolerance
- Demonstrates that administration of a specific drug will not result in an immediate reaction
- Give 1%, then 10%, then 100% of therapeutic doses at 30 minute intervals
- Recommended for inpatient setting
Direct Oral Challenges

• Administer 250-500 mg dose of amoxicillin and observe for 1 hour after dose
• Reserved for patients with a low suspicion for true anaphylactic allergy (e.g., history of mild childhood rash, non-urticarial rash, adverse events such as nausea or vomiting)
• Could be done in select patients in an outpatient or LTCF setting with appropriate monitoring and access to emergency resources
Antimicrobial Stewardship Guidelines

- Penicillin skin testing is now recommended
- “In patients with a history of B-lactam allergy, we suggest that ASPs promote allergy assessments and PCN skin testing when appropriate”
- Largely unstudied as primary ASP intervention
- Weak recommendation, low-quality evidence

PCN Skin testing (PST)

- PCN & other beta-lactams spontaneously breakdown into reactive intermediates that bind with circulating carrier proteins forming haptens – these serve as the reactive allergenic major and minor determinants for skin testing
- Major determinant – benzylpenicilloyl polylysine accounts for 90% of PCN intermediates
- PST antigens react with IgE antibodies, if present, and the interaction results in a skin wheal, flare, or bleb at the injection site
PCN Skin Testing

• When performed in the appropriate setting with proper technique and reagents, the skin test has a negative predictive value of 97-99% and a positive predictive value of 50%

• Patients with a negative skin test are at no greater risk of experiencing an allergic reaction to a beta-lactam than the general population

Who to test?

- Patients that based on history likely experienced an IgE-mediated allergic reaction
- Patients known to be extremely hypersensitive to penicillin (e.g., systemic or anaphylactic reactions) should not be skin tested
- Ensure patient has not been receiving any histamine blockers (H1 – diphenhydramine and H2 – ranitidine and famotidine) within last 24 hours!!
Step 1: Preparation

Mark arm for each reagent – Prepén, PCN G, Histamine (+ control), Normal Saline (-control)
Step 2: Skin Prick

• Place 1 drop of reagent onto forearm and puncture the skin at the drop site with the Duotip device using a slight twisting motion. Use a new duotip for each reagent. Be conservative with the amount of PrePen you use. Wait 15 min, then observe
Step 2 Interpretation

- Positive - presence of a wheal with surrounding erythema ≥3 mm in diameter compared to negative control
- Equivocal – <3 mm wheal with little or no erythema and no itching
- Negative – Absence of wheal <3 mm compared with negative control
- Invalid – no reaction to positive control (histamine)
- If skin prick test positive → do not advance to intradermal test, do not give a beta-lactam
- Equivocal or negative skin prick tests → move on to intradermal test
Step 3: Intradermal testing

• Using a TB syringe, inject 0.02 mL of the reagent (PrePen, PCN G, normal saline) to create a small bleb ~3 mm in diameter on the forearm. Repeat blebs for PrePen and PCN G at least 2 cm apart if enough reagent.

• Draw tight circles around the blebs

• Wait 15 minutes and observe

• Same interpretation criteria as for skin prick test
Patient Education Materials

Penicillin Allergy Testing

You have been tested to see if you are allergic to the antibiotic penicillin.

- Many people think they are allergic to penicillin. In fact, lots of people do not have a true allergy.
- It is important to know the facts. The doctors will have more drugs to treat an infection if you do not have a true allergy.
- Reasons why you may think you have an allergy:
  - You had a rash that was not due to the antibiotic. For example, it may have been due to your illness.
  - Many people outgrow their allergies.
  - Reactions such as a stomach ache or loose bowels are not a true allergy.

How the test works:

- Skin Prick Test: The doctor will scratch/prick the skin on your arm with a small amount of penicillin. This will help them decide if you have a true allergy. If this part of the test is positive you have a penicillin allergy.
- Intradermal Test: If your skin prick test was negative, your doctor will then make a few small injections into your arm just under the skin.
- The entire test takes less than 1 hour.
- The test is safe and you will be watched by the staff during the test.

Test results:

- If both parts of the test are negative, then you do not have a true penicillin allergy. This means you can take penicillin and related antibiotics.
- If either part of the test is positive, then you are allergic. You should not take penicillin and related antibiotics.

If you have questions contact your primary care doctor.

Patient Name: ___________________________

Date of Penicillin Skin Testing: _______________________

On the above stated date, you received a penicillin allergy skin test and the results were negative / positive. Circle One

Physician Signature: ___________________________
Contact Number: 1-888-210-0511

☐ A negative result indicates you may safely receive beta-lactam antibiotics. Please note that no reagent, test, or combination of tests will completely assure that a reaction to penicillin therapy will not occur.
☐ A positive result confirms an IgE-mediated allergy to penicillin
☐ Other: ___________________________

Name of antibiotic received in the hospital (if applicable): ___________________________

Show this card to your doctors and nurses
Models for Allergy Evaluation and PST

• Allergy (when available)
• Infectious Diseases Consultants
• Pharmacist-managed (state law dependent)
• Other physician specialties
• Outpatient
• Peri-operative
Final Step: De-Label!

- After allergy evaluations, the electronic health record should be updated and this information should be communicated to other healthcare providers (e.g., pharmacies)
- Delete the allergy, add qualifying comments such as “penicillin skin test negative” or “tolerated amoxicillin/clavulanate”
<table>
<thead>
<tr>
<th></th>
<th>Low Risk</th>
<th>Medium Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td>• Reactions that are unlikely allergic (e.g., GI symptoms)</td>
<td>• Urticaria or other pruritic rash</td>
<td>• Anaphylactic symptoms</td>
</tr>
<tr>
<td></td>
<td>• Pruritis without rash</td>
<td>• Reactions with features of IgE such as itching, flushing but not anaphylaxis</td>
<td>• Recurrent reactions</td>
</tr>
<tr>
<td></td>
<td>• Remote (&gt;10 y) unknown reactions</td>
<td>• Reactions to multiple beta-lactams</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Family history of penicillin allergy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Action</strong></td>
<td>Direct oral challenge with amoxicillin</td>
<td>Skin test followed by amoxicillin challenge if skin test negative</td>
<td>Allergy referral</td>
</tr>
</tbody>
</table>

Evaluation and Management of Penicillin Allergy
A Review

Erica S. Shenoy, MD, PhD; Eric Macy, MD, MS; Theresa Rowe, DO, MS; Kimberly G. Blumenthal, MD, MSc

Table S2. Cephalosporin cross-reactivity, by R1 groups*

<table>
<thead>
<tr>
<th>Common amino R1 group</th>
<th>Common methoxyimino R1 group</th>
</tr>
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<tbody>
<tr>
<td>Ampicillin</td>
<td>Ceftriaxone</td>
</tr>
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<td>Amoxicillin</td>
<td>Cefotaxime</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Cefuroxime</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>Cefepime</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Ceftazidime</td>
</tr>
<tr>
<td></td>
<td>Cepodoxime</td>
</tr>
</tbody>
</table>

*Beta-lactam antibiotics have shared beta-lactam rings and may have R1 (6/7 position) and/or R2 (3 position) side chains that can be structurally identical or similar. Cross reactivity appears highest for beta-lactams that share identical R1 side chains. More comprehensive cephalosporin cross-reactivity matrices may be used if avoiding identical and similar structures at both side chain locations is desired.
Sulfonamide Allergy

• 3-6% of the general population allergic to sulfonamides (synthetic derivatives of sulfanilamide)

• Structurally defined by the sulfonamide moiety and further divided into antibacterials and nonantibacterials
SMX-TMP
Sulfonamide Cross-Reactivity: Fact or Fiction?

• Comprehensive literature review identified nine case reports supporting possible cross-reactivity

• However, adequate patient testing not completed to firmly establish cross-reactivity

• Lack of convincing evidence of broad cross-reactivity between sulfonamide antibacterials and nonantibacterials

• Hypersensitivity between sulfonamides due to predisposition to allergic reactions rather than cross-reactivity
Take Home Points

• 50-80% of older adults in LTCFs receive at least 1 antibiotic course per year
• Prevalence of reported penicillin allergy increases with age
• Older adults are more likely to suffer from adverse effects associated with the use of non-beta lactam alternative antibiotics
• Penicillin allergy evaluation could have significant benefits for older adults in LTCFs