PCN Allergy Testing to Optimize Antimicrobial Stewardship

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Case #1

A 56 year-old female is admitted to your general medicine service with a diagnosis of community-acquired pneumonia. The physician orders ceftriaxone and azithromycin to be initiated. Upon order processing, you note that the patient is “allergic” to penicillin. What would you do at this point?
Assessment Q #1

Approximately what percentage of patients who self-report an allergy to “penicillin” will skin test (ST) positive for a Type 1 (immediate) allergic reaction to penicillin?
Introduction

- PCN allergies are the most commonly reported allergies in the U.S.
  - General Population (5-8%)
  - Hospital Patients (10-15%)
- 80-90% are able to tolerate PCNs after undergoing evaluation for PCN allergy
- Leads to unnecessary use of antibiotic alternatives which may be less effective, broader in coverage, and/or more toxic
Introduction

“Most patients who report penicillin allergy are unnecessarily avoiding penicillin class antibiotics because either their penicillin allergy waned over time or previous reactions should not have been attributed to penicillin”

Drug Allergies

- ADRs with immunologic pathogenesis
- Dose-independent
- Unpredictable (Idiosyncratic)
- Immune mechanisms involve antibodies and/or activated T-lymphocytes directed against specific drugs or metabolites
- Most common reactions are IgE and T-cell mediated
Drug Allergies

- Immediate Reactions:
  - Typically IgE mediated
  - Within minutes to hours after drug admin

- Manifestations:
  - Urticaria (hives)
  - Angioedema
  - Rhinitis; Conjunctivitis
  - Bronchospasm
  - Anaphylaxis; Anaphylactic Shock
Drug Allergies

- Non-Immediate Reactions:
  - T-cell-dependent immune mechanism
  - Occur days to weeks after drug admin

- Manifestations:
  - Uncomplicated cutaneous manifestations (maculopapular rash) – most common
  - Stevens-Johnson syndrome
  - Toxic Epidermal Necrolysis (TEN)
  - DRESS
Drug Allergies

- Why the Overstated Prevalence:
  - Inaccurate reaction documentation
  - Inclusion of non-allergic side effects
  - Delayed hypersensitivity reactions
  - Non-Allergic phenomenon ("ampicillin rash"; "red man syndrome")

- Up to 80% of patients lose sensitivity to PCN over a 10-year period
Assessment Q #2

Upon allergy questioning, if a patient tells you that he or she only had a mild rash that was “no big deal,” how comfortable are you to dispense a cephalosporin to this patient? How about piperacillin-tazobactam?
TABLE. Essential Clinical History Questions for Penicillin Allergy

- What were the signs, symptoms, and timing of the adverse drug reaction?
- Were other medications used concurrently at the time of the adverse drug reaction?
- Had the same or a similar medication been used before the reported adverse drug reaction?
- Has the same or a similar medication been used since the previous adverse drug reaction?
- Why was penicillin or a related antibiotic prescribed?
- Have symptoms similar to the adverse drug reaction occurred in the absence of medication therapy?
- Has the medical record been reviewed for documentation of penicillin allergy and antibiotic use?

Clinical History

- Reaction history alone cannot diagnose or exclude PCN allergy
  - About one-third of individuals with positive PCN allergy skin test (ST) had vague allergy histories (e.g. nonpruritic maculopapular rash; isolated GI symptoms; unknown details of previous reaction)
PCN Skin Testing (ST)

- Penicilloyl Form – major Ag determinant
- Penicilloate/Peniloate Forms – minor Ag determinants
- Prick & intradermal skin testing with both major & minor determinants
- A positive control using histamine and a negative control consisting of saline should be placed during testing
PCN Skin Testing (ST)

- Offers NO predictive value for non-IgE-mediated events such as:
  - Serum sickness
  - Interstitial nephritis
  - Thrombocytopenia
  - Stevens-Johnson syndrome; TEN
  - DRESS

- A history of these non-IgE-mediated reactions requires strict PCN avoidance
PCN Skin Testing (ST)

- First Step – skin prick testing
- If skin prick is negative, follow with intradermal testing
- Negative predictive value for serious immediate-type reactions is 97-99% when major & minor determinants used
- Safe – incidence of systemic reactions to PCN testing is < 1%
ST + Oral Challenge

- Uses major determinant + PCN G for ST
- If ST negative, follow with dose of oral amoxicillin
- In one study, oral challenge reaction rate was 1%; most – urticaria only

Oral Challenge Alone

- May be considered in low-risk patients
- Saves time and avoids false-positive skin test results
- Do NOT use if histories of:
  - IgE-mediated reaction (e.g. anaphylaxis)
  - DRESS
  - Stevens-Johnson or TEN
  - Serum sickness
Oral Challenge Alone

- Prospective study in Israel
- 642 patients (435 children) underwent ST + oral challenge regardless of ST result
- Patients who did not have reaction completed 5-day course at home
- Oral challenge – 2% had immediate reactions; 4% delayed (all mild)
Allergy Management

- When PCN ST is negative, the risk of an immediate-type reaction is 1-3%
- ~ 1-3% risk of PCN allergy in people with no history of allergy to PCNs
- If PCN skin test is positive:
  - Alternative antibiotic
  - PCN desensitization
PCN Desensitization

- Temporary induction of tolerance – will be maintained only as long as specific medication is continuously used
- NOT without risks – should only be used when alternatives cannot be used
- Give increasing doses of PCN at 15-30-min intervals; full dose in 4-12 hrs
- ~ 30-35% of patients experience allergic reactions – close monitoring required
Assessment Q #3

If a patient self-reports an allergy to penicillin, what is the likelihood that the patient will have a reaction secondary to administration of a cephalosporin? What about a carbapenem?
FIGURE. Chemical structures of penicillins and other β-lactam antibiotics.

Cross-Reactivity

- Compared with PCNs, CEPHs have ~10X lower overall reaction rate
- If h/o PCN allergy and +ST, reaction rate to CEPHs is ~ 2%
- Fatal anaphylactic reactions have occurred with CEPH administration in patients with PCN allergy
- Allergy testing should be considered before CEPH in PCN allergic patients
Cephalosporin administration to a patient with a history of penicillin allergy

Option 1
Consider skin testing with cephalosporin (using non-irritating concentration)

Negave
Give cephalosporin via graded challenge

Positive
Options:
1. Give alternate drug
2. Desensitize to cephalosporin

Option 2
Penicillin skin testing

Negative
Give cephalosporin

Positive
Options:
1. Give alternate drug
2. Give cephalosporin via graded challenge; less than 2% will react in 24 hours but reactions may be anaphylactic
3. Desensitize to cephalosporin

Give the cephalosporin directly (only in absence of severe and/or recent penicillin allergy reaction history). Although less than 1% will have a reaction within 24 hours, this is controversial as their reactions may be anaphylactic.

Ann Allergy Asthma Immunol Updated Practice Parameter, Oct 2010
Cross-Reactivity

- In absence of h/o severe or recent PCN reaction, CEPHs often given directly (CAUTION – anaphylactic reactions have been reported)
- Cross-reactivity with carbapenems likely less than 1%
- Patients with negative ST results may safely receive carbapenems
Cross-Reactivity

- If + ST or no ST, patients should receive carbapenems via graded challenge
- Aztreonam (AZ) is less immunogenic than both PCNs and CEPHs
- NO cross-reactivity between either PCNs or CEPHs and aztreonam
- Exception – ceftazidime and aztreonam share identical R side chain
- Has led to overuse of aztreonam
Allergy Knowledge

- Survey of inpatient practitioner knowledge at two community hospitals
- 39% completed surveys; most attending physicians (> 50% more than 10 yr exp)
- ~ 50% unaware of cross-reactivity rates
- Only 41% appropriately considered ST as part of ABX management plan
- 86% never or rarely consult allergist

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

Eric Macy, MD, MS, and Richard Contreras, MS
San Diego and Pasadena, Calif

Background: Penicillin is the most common drug “allergy” noted at hospital admission, although it is often inaccurate. Objective: We sought to determine total hospital days, antibiotic exposures, and the prevalence rates of Clostridium difficile, methicillin-resistant Staphylococcus aureus (MRSA), and vancomycin-resistant Enterococcus (VRE) in patients with and without penicillin “allergy” at hospital admission.

Methods: We performed a retrospective, matched cohort study of subjects admitted to Kaiser Foundation hospitals in Southern California during 2010 through 2012. Results: It was possible to match 51,582 (99.6% of all possible cases) unique hospital subjects with penicillin “allergy” to 2 unique discharge diagnosis category-matched, sex-matched, age-matched, and date of admission-matched control subjects each. Cases with penicillin “allergy” averaged 0.59 (9.9%; 95% CI, 0.47-0.71) more total hospital days during 20.1 ± 10.5 months of follow-up compared with control subjects. Cases were treated with significantly more fluoroquinolones, clindamycin, and vancomycin (P < .0001) for each antibiotic compared with control subjects. Cases had 23.4% (95% CI, 15.6% to 31.7%) more C difficile, 14.1% (95% CI, 7.1% to 21.6%) more MRSA, and 30.1% (95% CI, 12.5% to 50.4%) more VRE infections than expected compared with control subjects.

Conclusions: A penicillin “allergy” history, although often inaccurate, is not a benign finding at hospital admission. Subjects with a penicillin “allergy” history spend significantly more time in the hospital. Subjects with a penicillin “allergy” history are exposed to significantly more antibiotics previously associated with C difficile and VRE. Drug “allergies” in general, but most notably to penicillin, are associated with increased hospital use and increased C difficile, MRSA, and VRE prevalence. (J Allergy Clin Immunol 2014;133:790-6.)

Abbreviations used
ICD-9: International Classification of Diseases, Ninth Revision
MDIS: Multiple-drug intolerance syndrome
MRSA: Methicillin-resistant Staphylococcus aureus
VRE: Vancomycin-resistant Enterococcus species

Penicillin “allergy” is the most common drug-class “allergy” noted in the medical records of subjects using health care, including hospitals, in the United States.12 Most subjects with a history of penicillin “allergy” are not allergic and tolerate future penicillin use.3 In our health plan, over the past 4 years, less than 2% of subjects with a history of penicillin “allergy” had a positive penicillin allergy test result.4,5 Carrying an inaccurate diagnosis of penicillin “allergy” could adversely affect the quantity and quality of health care used. A majority of hospitalized patients are treated with antibiotics.6 Hospitalized patients tend to be older and are less likely to have positive penicillin allergy test results.2,5 Fluoroquinolones, clindamycin, vancomycin, and third-generation cephalosporins are commonly substituted for first-line penicillin-class antibiotics in subjects with an active penicillin “allergy” history.7 Fluoroquinolones, clindamycin, and third-generation cephalosporins have been previously associated with increased rates of Clostridium difficile.8-10 There is still a widespread but mistaken concern about a possible clinically significant increased rate of adverse reactions associated with first- and second-generation cephalosporin use in subjects with a history of penicillin “allergy” that could be driving the use of more fluoroquinolone, clindamycin, vancomycin, and third-generation cephalosporin use when a first- or second-generation cephalosporin could be safely used.11
B-L Avoidance

- Most HCPs avoid prescribing PCNs or related B-L antibiotics in patients with self-reported PCN allergies
- Alternative ABX commonly substituted:
  - Vancomycin
  - Fluoroquinolones
  - Clindamycin
  - Aminoglycosides
  - Aztreonam
B-L Avoidance

- In many cases, broader-spectrum and less appropriate or effective antibiotics are substituted for best studied agents.
- ABX costs 63-158% higher if reported PCN allergy vs. no reported allergy.
- Patients labeled as PCN allergic have longer hospitalizations with related costs.
- One system – ST & consultation saved > $2 million over 3.6 years (Macy et al, 2017)
23% higher incidence of *C. difficile* infection
14% higher incidence of MRSA
30% higher incidence of VRE
50% higher risk of surgical site infection
Higher clinical failure rate
Assessment Q #4

A patient is presenting for pre-op consultation prior to an upcoming surgical procedure. The patient reports a penicillin allergy. What decision is usually made regarding the pre-op antibiotic?
Jeffres MN et al

- *J Allergy Clin Immunol* 2016;137:1148
- Empiric antibiotics for treatment of GNB BSIs in B-L allergy patients
- Clinical failure higher in NBL group (38.7% vs. 27.4%; P=0.030)
- 13/552 (2.5%) of those exposed to B-L experienced hypersensitivity reaction
- Authors concluded risk vs. benefit may support use of B-L in BSI patients
Ann Allergy Asth Immunol 2006;97:681

- Allergy consultation and ST made available for pre-op patients with self-reported PCN allergies
- Of 1030 patients who underwent ST, 43 (4%) had a positive ST result
- 716 patients received cefazolin; 149 (16%) received vancomycin
- 0.7% of cefazolin patients had reaction
MacFadden DR et al

- Clin Infect Dis 2016;63:904-10
- 95/507 (19%) of patients seen by an ID consult service reported B-L allergy
- B-L therapy preferred in 72 (76%)
- 25 (35%) did not receive preferred therapy; 13 reported non-severe rxn
- Patients who received non-preferred ABX had greater risk of adverse effects
Assessment Q #5

Who should do PCN skin testing within the hospital; or, a part of an antimicrobial stewardship program?
Chen JR et al

- *J Allergy Clin Immunol Pract* 2017;5:686
- Established physician-pharmacist team model to ID and ST PCN allergy patients
- Trained clinical pharmacist performed STs preemptively or by provider request
- Goals of program:
  - Removing inaccurate allergy information
  - Reducing the use of B-L alternatives
  - Educating patients & clinicians
Chen JR et al - Cont

- *J Allergy Clin Immunol Pract* 2017;5:686
- 252 direct evaluations conducted over 18 months
- 228/252 (90.5%) had their PCN allergy removed (de-labeling); 223 via ST
- Among patients testing negative, 85 (38%) subsequently received B-L’s, preventing 504 inpatient days and 648 outpatients days of NBL therapy
Retrospective analysis of inpatients who had ST+ OC by an allergist
- 50% of patients had AZ prescribed
- 49/50 patients were ST or OC negative
- 37/50 (75.5%) were changed to B-L
- Overall cost savings - $11,000; 22/31 subsequent admissions were prescribed B-L (147 days of therapy)
Leis JA et al

- *Clin Infect Dis* 2017;65:1059
- ASP teams at 3 hospitals received ST training by allergists
- 827 patients reported B-L allergy over 15 months; B-L preferred for 632 (76%)
- Patients receiving preferred B-L therapy INC from 50% to 81% with use of ST
- Intervention period – 4.5-fold INC odds of preferred therapy (P< 0.0001)
Trubiano JA et al

- Clin Infect Dis 2017;65:166
- B-L ST was implemented into ASPs at two Australian hospitals
- Upon completion of study, 84% with B-L allergies had been de-labeled
- Follow-up showed prescribing of narrow-spectrum B-L’s were more likely (aOR = 3.54) as was prescribing of appropriate antibiotics (aOR = 12.27)
Sacco KA et al

- *Allergy* 2017;72:1288
- Systematic review to examine whether inpt PCN ST affects clinical outcomes
- Population weighted mean for a negative ST was 95.1%
- ST led to a change in ABX selection that was greater in the ICU
- INC use of PCNs and CEPHs
- DEC use of vancomycin and FQs
Sacco KA - Cont

- *Allergy* 2017;72:1288
- Author Conclusions:
  - Inpatient ST is safe and effective in ruling out PCN allergies
  - Patients with PCN allergy history should be tested if they require treatment with a PCN
Jones BM, Bland CM

- Am J Health-Syst Pharm 2017;74:232
- As part of an ASP, a community health system launched ST initiative to optimize treatment, reduce ADEs and drug costs, and minimize resistance
- 36/36 – negative ST result
- 27/36 – appropriate therapy conversion
- A DEC in drug costs was demonstrated
Pharmacists took opportunity to establish ST program following a request from ID consultant

Patients are interviewed first; testing primarily done when there is uncertainty after the interview

Department had previously managed successful immunization programs
Craig Hospital Protocol
Englewood, CO.
Estep PM et al

- AJHP Residents Edition
- 186 patients with self-reported B-L allergies were prescribed AZ over 36 mo
- Used intensive interviewing; not ST
- Percentage of patients who received AZ for full duration was cut by 50%
- AZ days of therapy per 1000 pt-days DEC from 3.6 to 1.8 during study period
Figure 1. This flow chart depicts our institution's approach to efficiently incorporating allergists-immunologists into the antibiotic stewardship program, assessing inpatients with a reported or documented penicillin allergy. Allergy refers specifically to penicillin reaction. Evaluation can determine patients' status as well as impact current or future management.
Case #1

A 56 year-old female is admitted to your general medicine service with a diagnosis of community-acquired pneumonia. The physician orders ceftriaxone and azithromycin to be initiated. Upon order processing, you note that the patient is “allergic” to penicillin. What would you do at this point?
Case #2

A 44 year-old male is admitted to your general medicine service with an apparent intraabdominal infection. The physician orders piperacillin-tazobactam to be initiated. During an allergy intake interview, the patient states that he developed “kidney problems” after taking a penicillin seven years earlier. Should you dispense the piperacillin-tazobactam?
A 62 year-old female, who was recently discharged from the hospital, is readmitted with a diagnosis of pneumonia. The physician orders meropenem to be initiated. During an allergy interview, the patient states all she had was a “rash” when she received penicillin about 20 years ago. She denies hives or anything more serious. Should you dispense the meropenem?
Type II-IV HSR
Serum sickness
Stevens-Johnson Syndrome
Toxic Epidermal Necrolysis
Acute Interstitial Nephritis (AIN)
Drug Rash Eosinophilia Systemic Symptoms (DRESS) Syndrome
Hemolytic anemia

Type I (IgE-mediated) HSR
Anaphylaxis
Angioedema
Wheezing
Laryngeal edema
Hypotension
Hives/urticaria
OR
Unknown reaction WITHOUT mucosal involvement, skin desquamation or organ involvement

Mild Reaction
Itching
Minor rash
(not hives)
Maculopapular rash
(mild Type IV HSR)
EMR lists allergy, but patient denies

OK to:
Use 3rd/4th generation cephalosporins or carbapenems*
by Test Dose Procedure
OR
Use alternative agent by microbial coverages
OR
Aztreonam*

If ID consult determines that PCN or a 1st/2nd generation cephalosporin is the preferred therapy, or that one of the alternative agents is substandard, consult Allergy

OK to:
Use full dose 3rd/4th generation cephalosporin
OR
Use penicillin or 1st/2nd generation cephalosporin by Test Dose Procedure
OR
Use carbapenem*
FIG 2. This flow chart includes all ST period patients. Of 278 patients in the skin testing period, 179 patients were eligible for skin testing. Of the 179 patients for whom skin testing was intended, 43 patients completed ST, and none was allergic.
Guideline for Prescribing Antibiotics to Inpatients with Penicillin Allergy

Why use it? The purpose of this guideline is to provide allergy history-taking support and antibiotic prescribing recommendations for patients reporting penicillin allergy.

How do I access the guideline?
- **Via your smartphone or tablet:**
  - Connect to Partners wifi (phswifi3).
    - You will not be able to access the app via unsecured wifi (phspieguest).¹
  - Access the app at http://id.partners.org/allergy.
    - You will be prompted for your Partners username and password.
- **Via a Partners PC:** just go to http://id.partners.org/allergy

What’s the evidence base? This decision support tool and guideline, based on a pathway that has been used successfully hospital-wide at MGH since 2013,² is supported by drug allergy literature and the practice parameters created by the American Academy of Allergy, Asthma and Immunology.⁶

What if I still have questions? Please watch the educational videos at https://id.partners.org/allergy/videos, contact us at phsallergypathway@partners.org, or involve Infectious Disease and/or Allergy/Immunology consultation services.

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¹ For instructions on accessing phswifi3, see https://id.partners.org/phswifi3.
### Penicillin / Cephalosporin Hypersensitivity Pathway

<table>
<thead>
<tr>
<th>Type II-IV HSR*</th>
<th>Type I (IgE-mediated) HSR*</th>
<th>Mild Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Sickness</td>
<td>Anaphylaxis</td>
<td>Minor rash (not hives)</td>
</tr>
<tr>
<td>Stevens-Johnson Syndrome / Toxic Epidermal Necrolysis (SJS / TEN)</td>
<td>Hypotension</td>
<td>Maculopapular rash (mild Type IV HSR)</td>
</tr>
<tr>
<td>Acute Interstitial Nephritis (AIN)</td>
<td>Angioedema</td>
<td>Medical record lists allergy, but patient denies history of allergy</td>
</tr>
<tr>
<td>Drug Rash Eosinophilia with Systemic Symptoms (DRESS)</td>
<td>Laryngeal edema</td>
<td>Drug Fever</td>
</tr>
<tr>
<td>Hemolytic Anemia</td>
<td>Wheezing</td>
<td></td>
</tr>
<tr>
<td>Drug Fever</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Okay to use:

- **3rd / 4th / 5th generation cephalosporin or carbapenem** by Test Dose Procedure
- **aztreonam**
- **alternative agent by microbial coverage**

**If penicillin or cephalosporin is clinically indicated, please involve the Infectious Disease or Allergy / Immunology services.**

**ALTERNATIVE AGENTS BY MICROBIAL COVERAGE:**

**Gram positive coverage:** vancomycin, linezolid*, daptomycin*, clindamycin, doxycycline, sulfamethoxazole / trimethoprim

**Gram negative coverage:** fluoroquinolones, sulfamethoxazole / trimethoprim, aminoglycosides, aztreonam*

**CEPHALOSPORINS BY GENERATION:**

1st: cephalothin / cefadroxil / cefazolin • 2nd: cefoxitin / cefotetan / cefuroxime
3rd: ceftriaxone / cefixime / cefotaxime / cefodoxime / cefdinir • 4th: cefepime / 5th: ceftolozane

For complete pathway and decision support, visit: [http://id.partners.org/allergy](http://id.partners.org/allergy)
Summary

- Most patients who self-report PCN allergies can safely take PCNs and related antibiotics.
- Active attention should be paid to addressing old and inaccurate information regarding allergies.
- Patients with PCN allergies often do not receive preferred treatment and suffer worse outcomes and more ADEs.
Summary

- PCN ST is evolving as a cost-effective mechanism for improving the use of antibiotics in both inpatient and outpatient settings
- Patients with negative ST should have the PCN allergy information de-labeled
- PCN ST is an excellent role for ASPs to assume because the results should be combined with proper ABX guidance
Summary

- Several studies have documented the effective use of clinical pharmacists as ideal persons to carry out ST protocols within hospitals.
- Could pharmacy technicians assume more of this role in the future?
- Patients with vague or very old PCN allergy information should be encouraged to get ST proactively.
Summary

- Pongdee T & Li JT, Mayo Clin Proc:
  - “Penicillin allergy evaluation and management should be a key component of antibiotic stewardship and can significantly improve health care quality and value for individual patients and health care systems as well as the public at large”
Abbreviations Utilized

- **ABX** = antibiotic
- **ADRs** = adverse drug reactions
- **aOR** = adjusted odds ratio
- **ASP** = antimicrobial stewardship program
- **AZ** = aztreonam
- **B-L** = beta-lactam
- **BSI** = bloodstream infection
- **CEPH** = cephalosporin
- **DRESS** = drug reaction with eosinophilia and systemic symptoms
Abbreviations Utilized

- FQ = fluoroquinolone
- GNB = Gram-negative bacilli
- HCPs = health care professionals
- NBL = non-beta-lactam
- OC = oral challenge
- PCN = penicillin
- SSI = surgical site infection
- ST = skin testing
- TEN = toxic epidermal necrolysis