Too Many Penicillin Allergies! Overview, Assessment and Action Plan for Success Within Antimicrobial Stewardship

Christopher M. Bland, Pharm.D., FCCP, FIDSA, BCPS
Clinical Associate Professor
University of Georgia College of Pharmacy
Clinical Pharmacy Specialist
St. Joseph’s/Candler Health System
Savannah, GA
Disclosures

• Grant Funding
  • ALK Abello
Objectives

• Provider overview regarding detrimental outcomes of self-reported penicillin allergies
• Analyze current literature supporting penicillin allergy assessment and intervention
• Explore steps for an individual facility to establish an algorithm to address the penicillin “allergic” patient
Are you allergic to penicillin?

- Yes
- No
Where are you currently with penicillin allergy assessment and skin testing?

- Allergy reconciliation only
- Graded/Direct Challenges
- Penicillin Skin Testing
- Desensitization
PCN “Allergy” Case

- 67 year old male admitted with presumed sepsis syndrome
- PMH: HTN, OA, GAD, GERD
- Medications PTA: Clonidine patch, Acetaminophen, Lorazepam, Hydralazine, Omeprazole
- Allergies: Penicillin (Unknown)
- Discharged from hospital 1 week prior
- Vitals: 110/80; Pulse 110; RR 20. T: 101.4°F
- Pertinent Positive Labs: SCr: 1.6 mg/dL (baseline 1.0 mg/dL); WBC 18.4 X 10³
- Patient receives 2L NS and is hemodynamically stable
PCN “Allergy” Case

• Because of patient’s PCN allergy, the providers prescribe meropenem and vancomycin which are given after cultures are drawn and the patient is being transferred to the medicine floor for further management.

• How would you handle this patient’s penicillin allergy?
What is Antimicrobial Stewardship?

“Antimicrobial stewardship includes not only limiting inappropriate use but also optimizing antimicrobial selection, dosing, route, and duration of therapy to maximize clinical cure or prevention of infection while limiting the unintended consequences, such as the emergence of resistance, adverse drug events, and cost.”

Antibacterial Approvals by FDA

Approvals by the US Food and Drug Administration (FDA), 1983-2007

Background

• Penicillin allergy is one of the most frequently reported drug allergies
  • Approximately 10% of patients report hypersensitivity
  • Results in limited treatment options, increased healthcare costs, and increased resistance with the use of broad-spectrum agents
• Up to 90% of patients reporting hypersensitivity do not truly have a penicillin allergy
• Many patients therefore do not receive optimal therapy for infecting pathogen

Clinical Indications where 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

Clinical pathogens where Beta-lactams are best

- Viridans Group Streptococci
- *Listeria Monocytogenes*
- *Actinomyces*
- *Cutibacterium acnes*
- *Pasteurella multocida*
- *Neisseria Meningitidis*

Implications of PCN “Allergy”

• Increased adverse effects
• Increased hospital stays
  • Approximately one-half day longer
  • 30,000 hospital days/65 million in expenditures
• Development of MDR infections
  • 23.4% increase in CDI
  • 14.1% more MRSA
  • 30.1% increased VRE

Penicillin Allergy Assessment and Skin Testing (PAAST)

• Many facets all with benefit
• PAAAST has many potential options depending on resources
  • Allergy record confirmation
  • Detailed allergy interview with EHR biopsy
  • Side Chain Assessment for Cephalosporins
  • Graded Challenge
  • Direct Oral Challenge
  • Desensitization
  • Penicillin Skin Testing
Potential Benefits of PAAST

• Increased usage of drugs of choice where superior outcomes exist
• Decreased usage of more expensive antimicrobials
• Avoidance of broad-spectrum antimicrobials
• Acute and long-term benefit potential on resistance
• Preserve newer agents
Patients who report a PCN allergy experience....

• 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

Consequence: Increased Costs

- Mean antibiotic cost for patients allergic to penicillin is 63% higher than those not allergic to penicillin.
  - Cost of drug
  - Additional lab work
  - Nurse and pharmacist time
  - Management of side effects
  - Increased LOS
Quick Refresher on Classifications

<table>
<thead>
<tr>
<th>Gell-Coombs Classification</th>
<th>Immune Cause</th>
<th>Typical Manifestations</th>
<th>Examples of Associated Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I (Immediate)*</td>
<td>IgE</td>
<td>Anaphylaxis, laryngeal edema, urticaria, hives</td>
<td>(\beta)-lactams</td>
</tr>
<tr>
<td>Type II (Cytotoxic)</td>
<td>IgG, IgM</td>
<td>Cytopenia</td>
<td>Penicillin, heparin, quinidine</td>
</tr>
<tr>
<td>Type III (Immune Complex)</td>
<td>IgG, IgM</td>
<td>Serum sickness</td>
<td>Thymoglobulin, penicillin, phenytoin</td>
</tr>
<tr>
<td>Type IV (Delayed)</td>
<td>T-Lymphocytes</td>
<td>Contact dermatitis</td>
<td>Latex, sulfa, penicillin</td>
</tr>
<tr>
<td>SJS and TEN (miscellaneous)</td>
<td>T Cells</td>
<td>Erythema with necrosis and detachment</td>
<td>Sulfonamides, cephalosporins, anticonvulsants, NSAIDs</td>
</tr>
<tr>
<td>DRESS syndrome</td>
<td>Eosinophils</td>
<td>Cutaneous eruptions, multi-organ failure</td>
<td>Anticonvulsants, sulfonamides</td>
</tr>
</tbody>
</table>


SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrolysis; NSAID = nonsteroidal anti-inflammatory drug; DRESS = drug rash with eosinophilia and systemic symptoms.

\*Candidate for penicillin allergy skin testing.

PCN Anaphylaxis: Major Concern?

• Important to quantify true risk
• Historical data of poor quality
• 100,000,000 amoxicillin courses over 35 years in Great Britain
  • 1 fatality (PO) with total of 7 deaths parenteral or “unknown routes”
• 2.1 million individuals with 4.5 million oral courses
  • 22 cases confirmed anaphylaxis (1 in 207,191; 0.0005%)
• ~200,000 individuals with ~300,000 IV courses
  • 3 cases confirmed anaphylaxis (1 in 95,298; 0.001%)

Cephalosporin Anaphylaxis: Absolute Low Risk

- Kaiser Permanente database 3-year period 2010-12
- ~600K exposed to ~900K courses oral cephalosporins
  - Anaphylaxis in 5 patients
- ~325K exposed to ~500K courses parenteral cephalosporins
  - Anaphylaxis in 8 patients

Beta-Lactam Serious Cutaneous Allergic Reactions (SCARs)

• Less common than anaphylaxis
• Population-based data nonexistent on incidence
• ~5 million exposures to PCNs
  • 2 total cases
• ~1.4 million exposures cephalosporins
  • 3 total cases
  • All reported with additional antibiotic

Allergy Assessment

• Detailed Patient/Family Interview
  • Not all patients need testing
  • Ask Brand/Generic names (Interrogation)
  • Get specific
• Previous hospital stay medication history
• Use your pharmacist (local pharmacies)

Allergy Assessment: Use your trainees!

• Quasi-experimental study using 4th year APPE pharmacy students
• 6 month study October 2018-March 2019
• Preceptor (ID pharmacist) trained students in allergy assessment and interviewing skills
• Template sheet given to interview patient
• Results of allergy assessment interview discussed with preceptor

Jones BM et al. Submitted to IDWeek 2019.
Allergy Assessment: Use your trainees!

• Preliminary results using 12 APPE students
  • Many non-allergic ADRs found (e.g. nausea/vomiting)
  • Mild allergies (itching/rash)
  • Moderate-Severe allergies (Urticaria/Anaphylaxis)
• 162 interventions performed
  • 154 verbal (95 updated, 34 removed, 33 confirmed)
  • 2 re-challenges
  • 6 PSTs

• Pharmacy students can serve as extenders for PAAST
  • Great option for resource strapped institutions

Jones BM et al. Submitted to IDWeek 2019.
Cross-Reactivity Assessment

• Penicillin cross-reactivity lower in recent assessments
  • Cephalosporins (<2%)
  • Carbapenems (<1%)
• May obviate need for direct penicillin challenge/skin testing
• Side chains key tool in determining risk
• Shared R1 and R2 side chains good predictor
• Cefazolin=Unique Side Chain=Low cross reactivity with PCN

<table>
<thead>
<tr>
<th>Cross-reactive beta-lactams</th>
<th>Penicillin</th>
<th>Amoxicillin</th>
<th>Ampicillin</th>
<th>Cephalexin</th>
<th>Cefuroxime</th>
<th>Cefoxitin</th>
<th>Ceftriaxone</th>
<th>Cefotaxime</th>
<th>Cefepime</th>
<th>Ceftazidime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Direct Oral Amoxicillin Challenge

- Represent ~50% of "PCN allergic" patients low risk
- Nearly 1/3rd have been challenged without updating record
- Low risk patients viable option
  - Non-allergic symptoms
  - Pruritis only
  - Benign rash
  - Indeterminate history (> 10 years with non suggestive IgE-mediated hypersensitivity reaction
- Typically 250mg amoxicillin given
- Risk of anaphylaxis extremely low
- Resource poor areas without allergy testing services

Direct Oral Amoxicillin Challenge

- 3299 patients given direct oral amoxicillin challenges
- 6 healthcare groups over 3 year period
- 42 patients (1.3%) had acute positive challenge reactions
- 130 (3.9%) had delayed positive challenge reactions

- Overall direct challenge without skin testing was effective strategy to clear patients of penicillin allergies

Direct Oral ”Penicillin” Challenge: Oncology Patients

• 2 tertiary referral centers in Australia in low risk patients

• Low-risk patients identified as one of the following:
  • Unknown reaction > 10 years ago
  • ADR not allergy
  • Hx of benign childhood rash, non-urticarial rash, or maculopapular exanthem > 10 years ago

• Exclusion: Anaphylaxis, SCARs, pregnancy, cognitive impairment, ABX-induced AKI or hepatic injury

• ID physician verified allergy

• RN supervised oral challenge

Direct Oral “Penicillin” Challenge: Oncology Patients

- PCN VK 250mg or Amoxil 250mg based on when allergy occurred
- Single dose for most: Monitor for 2 hours
- Delayed hypersensitivity: 5-day challenge
- All 46 patients (50% oncology) meeting criteria tolerated oral challenge
- Significant 90-d ABX usage (67.4% pre-test vs. 60% post-test)
- 84.6% PCN in post-test period vs. 3.2% pre-test period (p<0.001)
- Less 3rd/4th gen. ceph in post-test period (8.7% vs. 69.6%; p=0.0001)

Graded Challenge

• Option for “medium” risk histories
  • Typically when PST not available
• Urticaria or other Pruritic reactions
• IgE features but NOT anaphylaxis
  • Itching, Flushing, GI symptoms
• Administer $1/10^{th}$ to $1/4^{th}$ full dose with 30-60 minutes monitoring
• Follow with full dose with additional 30-60 minute monitoring period

PCN Desensitization

• Indicated for high risk patients (e.g. anaphylaxis) with likely allergy
• PCN or beta-lactam DOC
• Recent, severe, life-threatening immediate hypersensitivity
• Positive PST
• Uninterpretable PST (nonreactive histamine)
• Not able to undergo PST (e.g. hemodynamic compromise)
• Typically done with IV penicillin in ICU setting for 1:1 nursing
• Classic example: Neurosyphilis

Penicillin Skin Testing (PST)

• Objective measure for determining hypersensitivity in moderate-high risk reported allergies
  • IgE mediated
• Requires training
• Time~2 hours including optional oral challenge
• Competes with other good initiatives!
• Resource intensive
  • Components
  • People
PST: Key Questions Before Implementing

- Why is your institution interested?
- Who should be tested (and not tested)?
- What are potential pitfalls after negative PST?
- How will components of test be prepared and stored?
- Who will take ownership and lead the program?
- Who should be trained?
- What is best approach for structuring PST?

Patient populations for PST

- Outpatient
  - Home infusion/infusion centers
  - Preoperative patients
  - Clinic
- Inpatient
- LTAC
Who should we consider for skin testing... Patient characteristics

- Type I reaction to PCN
- Superior outcomes would be produced
  - MSSA bacteremia
- $$$$
- Frequent fliers
- Resistance pattern of organism
- Facilitation of discharge
PST Methods: Many successful models

• Allergist Led with many specialties
• State Laws Crucial with Pharmacist Models
• Non-Allergist
  • Pharmacist with Nursing
  • Pharmacist +/- PGY-1/PGY-2 residents
  • Pharmacist with ID Physicians (including fellows)

Telemedicine for PST

• Allergist resources limited
• Allergy PA trained to perform PST services at outlying hospital
• 50 patients consented with total time of consultation of 128 minutes
  • PA travel time (46 minutes)
  • Clinical (82 minutes)
  • Physician time only about 5 minutes
• Patients rated their experience 4.5 out of 5 on average
• 33/46 PST negative patients changed to beta-lactam
• More than 30K cost savings

Pharmacists and PST: State Laws

- Varies tremendously state by state
- Recent survey showed only 19 out of 50 were definitive “Yes”
- Lots of maybes
- 16 states did not respond despite multiple efforts to contact via phone or email
- Interesting considering vaccination allowed in all 50 states plus D.C.
- Bottom line: If pharmacist performing PST, check with state board of pharmacy first

Reappearance of PCN Allergies: déjà vu’

• Not the actual allergy that reappears
• Electronic Health Record Entry...
• Many opportunities for reappearance
  • Hospital tested
  • Another local hospital
  • Dentist (10% of antibiotics prescribed in U.S.)
  • Primary Care
  • Specialist
  • Pharmacy
Re-Labeling: Major Issue

• Varying data regarding incidence of re-labeling over time
• One study demonstrated 49% with negative PST still had allergy listed at time of discharge
• Another showed 36% had allergy added back within 1 year
• PCN Allergy Education Crucial
  • 42% of healthcare providers in one study had never received formal allergy education

Jones BM et al. Curr Treat Options Infect Dis. 2019 (Online First)
Re-labeling and Patient Education

• Patient major source of ultimate re-labeling
• Keys include to sustained re-labeling:
  • Verbal and written components on appropriate education level
  • Educate on importance of verifying allergy (pre-test)
  • Educate post-test with emphasis on results
  • Patient Handout
  • Laminated wallet card preferred

Jones BM et al. Curr Treat Options Infect Dis. 2019 (Online First)
PAAST Exercise: Thinking through implementation

• You are considering implementing penicillin allergy and assessment services at your 200 bed community hospital based on recent data showing benefit.

• What are important questions to ask before beginning?
• What are important ways to measure benefit?
Questions to Ask

Who will lead the program?
  • Does not have to be ID-trained person necessarily
• What FTE resources are available?
  • Trainees?
• Who is your target population for PAAST?
• Pharmacy State Laws if PST
• Are allergists available for PST or training of PST?
• What can you do now vs. ultimately want to achieve?
• How many committees will it take to make it happen?
Concluding Case: Thanks Twitter!

• 56 year old male scheduled for TKR with documented penicillin allergy (anaphylaxis with amoxicillin 10 years ago). Which of the following would you recommend?
  • Cefazolin
  • Vancomycin or Clindamycin
  • Direct Amoxicillin challenge
  • Penicillin skin test
  • Other?
Concluding Case Responses

- Twitter responses:
- Cefazolin
- PST if time followed by oral challenge and then cefazolin
- Vanc or Clinda if no time before surgery then schedule for outpatient PST
PAAST- How to get more educated

• PAAST Certificate Program
• University of South Carolina College of Pharm
• 15 hour ACPE, ACCME, ANNC credits
  • 11 hour home study recorded material
  • 4 hour live component
• 10 faculty (8 Pharm.D.s/2 MDs)
• bit.ly/PAASTCertificateProgram
• Or just Google “PAAST University of South Carolina”
Conclusion

• PAAST is a valuable tool within the stewardship toolbelt
• There are many different ways to provide PAAST services
• Institutions should decide which aspects of PAAST are best
• Education with record updating are key aspects of de-labeling
• Re-labeling is a longitudinal concern after determining patient not allergic to penicillin
Questions?