Pharmacy Update: Truth and Consequences of Beta-Lactam Allergy Management

Penicillin (PCN) Allergy Background

- PCN allergy is the most common drug-class allergy reported
  - ~8-12% of patients self-report a PCN allergy
  - Reported anaphylactic reaction to PCN commonly precludes prescribers from using β-lactams in these patients
- 80-90% of patients reporting a PCN allergy will have a negative response to PCN skin testing

Impact of Penicillin Allergies

- Penicillin "allergies" lead to:
  - More costly, less effective therapy
    - Longer length of stay, more medications used, more treatment failures
  - Worse clinical outcomes
    - Increased mortality, more treatment failures
  - 2nd and 3rd line antibiotics commonly substituted for β-lactams in patients with a penicillin "allergy"
    - Suboptimal use of fluoroquinolones, clindamycin, vancomycin, and aztreonam (e.g. vancomycin for MSSA)
    - Macy et al. *J Allergy Clin Immunol*:
      - Significantly more fluoroquinolone, clindamycin, and vancomycin use
      - 23.4% more *C. difficile* (95% CI: 15.6%-31.7%)
      - 14.1% more MRSA (95% CI: 7.1%-21.6%)
      - 30.1% more VRE infections (95% CI: 12.5%-50.4%)

The Myth of Cross-Reactivity between Penicillins & Cephalosporins

- The widely quoted cross-reactivity rate of 10% was originally reported in the 1960s, studies were flawed due to cephalosporins being frequently contaminated with penicillin
- More recent observational studies have found cross-reactivity rates between 0.17% and 0.7%
- Cephalosporins that share a similar side chain with penicillins are more likely to cross-react
- Second and third-generation cephalosporins (ex>cefuroxime, cefpodoxime, ceftriaxone) have more complex side chains; reduces risk of allergic cross-reactivity

Table 1. FDA-approved Beta-lactam Antibiotics with Similar Side Chains[a]

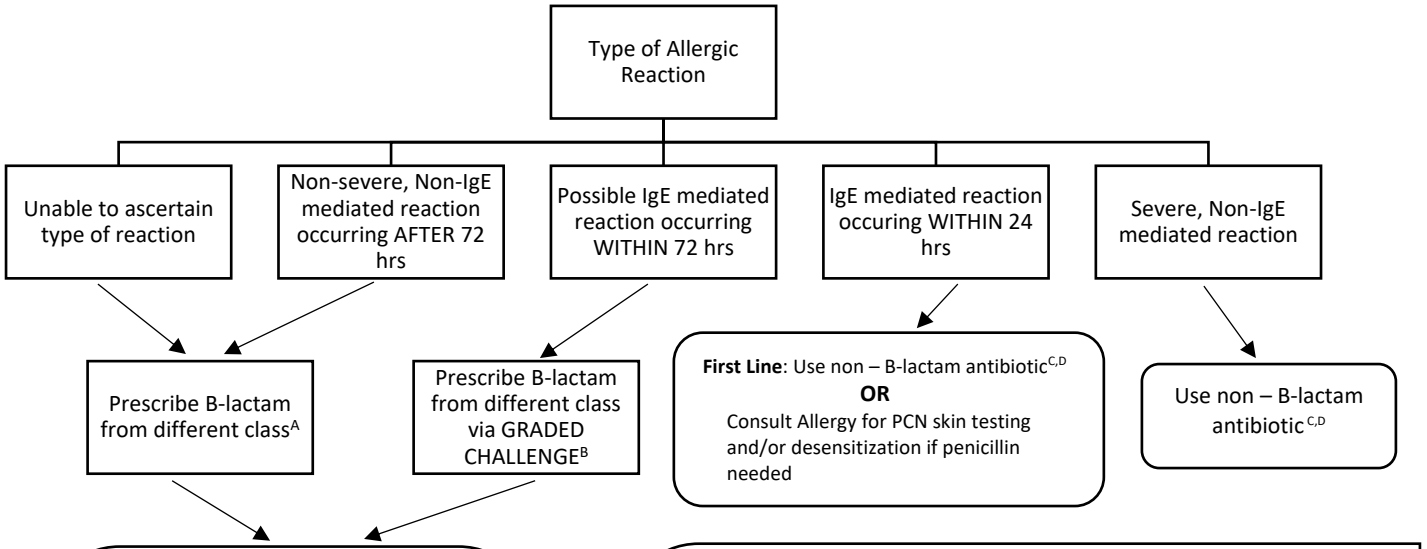
Agent	Agents with Similar Side Chains				
Amoxicillin	Ampicillin	Cefaclor	Cefadroxil	Cefprozil	Cephalexin
Ampicillin	Amoxicillin	Cefaclor	Cefadroxil	Cefprozil	Cephalexin
Aztreonamb	Ceftazidime	Ceftolozane			
Cefaclor	Amoxicillin	Ampicillin	Cefadroxil	Cefprozil	Cephalexin
Cefadroxil	Amoxicillin	Ampicillin	Cefaclor	Cefprozil	Cephalexin
Cefdinir	Cefixime				
Cefditoren	Cefepime	Cefotaxime	Cefpodoxime	Ceftriaxone	
Cefepime	Cefditoren	Cefotaxime	Cefpodoxime	Ceftriaxone	Ceftaroline
Cefixime	Cefdinir				
Cefotaxime	Cefditoren	Cefepime	Cefpodoxime	Ceftriaxone	Ceftaroline
Cefoxitin	Cefuroxime	Penicillin G			
Cefpodoxime	Cefditoren	Cefepime	Cefotaxime	Ceftriaxone	Ceftaroline
Cefprozil	Amoxicillin	Ampicillin	Cefaclor	Cefadroxil	Cephalexin
Ceftaroline	Cefepime	Cefotaxime	Cefpodoxime	Ceftriaxone	Ceftazidime
Ceftazidime	Aztreonam	Ceftolozane			
Ceftolozane	Aztreonam	Ceftazidime			
Ceftriaxone	Cefditoren	Cefepime	Cefotaxime	Cefpodoxime	Ceftaroline
Cefuroxime	Cefoxitin				
Cephalexin	Amoxicillin	Ampicillin	Cefaclor	Cefadroxil	Cefprozil
Penicillin G	Cefoxitin				

[a]Agents not listed are either not approved for use in the US (ceftizoxime, ceftibiprole) or do not share common side chains (e.g. piperacillin, ticarcillin, nafcillin, dicloxacillin)

UW Health: Treatment of Patients with Reported Allergies to Beta-Lactam Antibiotics – Adult – Inpatient Clinical Practice Guideline
Albin S et al. Allergy Asthma Proc. 2014;35(6): 489–494
Huang KG et al. Clin Infect Dis. 2018.

How to Assess & Manage Reported B-Lactam Allergies

- Penicillin Skin Testing
  - Penicillin skin testing is an option for patients with a possible IgE-mediated reaction to penicillin
    - No commercially available skin test for cephalosporins, carbapenems, or monobactams
  - Risk of having an adverse reaction to a penicillin skin test is less than 1%
  - Patients with negative penicillin skin test results can receive penicillin via a graded challenge and can safely receive cephalosporins or carbapenems
  - If the penicillin skin test is positive, the patient should **NOT** receive penicillins or a beta-lactam antibiotic with a similar side chain
- Graded Challenge
  - Performed in patients who have a low probability of an immediate allergic reaction
  - Oral graded challenge:
    - Used if oral therapy is desired
    - Give 1% of dose, then in 30 to 60 minutes give 10% of dose, then in 30 to 60 minutes give full dose
  - Intravenous graded challenge:
    - Used if IV therapy is desired
    - Give 1% of dose, then in 30 to 60 minutes give 10% of dose, then in 30 to 60 minutes give full dose



Penicillin Allergy:
- First Line: Cephalosporin
- Second Line: Carbapenem

Cephalosporin Allergy:
- First Line: Penicillin
- Second Line: Carbapenem

Carbapenem Allergy:
- First Line: Penicillin or Cephalosporin

Aztreonam Allergy:
- First Line: Penicillin or Cephalosporin
- Second Line: Carbapenem

Footnotes

[A]May give via graded challenge if reaction history was recent

[B]Graded challenge: use oral challenge if oral therapy is desired; use IV challenge if IV therapy is desired

- Graded challenges are intended for patients with low probability of an immediate allergic reaction.
- Patients do not need to increase their level of care during a graded challenge
- Patients should be monitored for immediate hypersensitivity reactions (hives, clearing of throat,coughing, dyspnea, abdominal pain, uneasiness) for up to 60 minutes after the full dose is administered

[C]Do not use aztreonam in ceftazidime-allergic or ceftolozane-allergic patients

[D]If no alternatives are available, aztreonam may be considered for Gram-negative infections