Consequences of an Unconfirmed Penicillin Allergy with Public Health Implications

- Unconfirmed penicillin allergies and the use of alternative (second-line) and/or broader-spectrum antimicrobial agents such as fluoroquinolones, clindamycin, vancomycin, and aztreonam have been associated with:
  - More treatment failure
  - Serious adverse effects
  - Higher incidences of Clostridium difficile, vancomycin-resistant enterococci (VRE) and methicillin-resistant Staphylococcus aureus (MRSA)
  - Longer hospital stays
  - Rising antimicrobial-related healthcare costs
- The CDC, NQF, ABIM, alongside the IDSA and AAAAI, have recognized unconfirmed penicillin allergies as a public health concern.

Prevalence and Mislabelling of Penicillin Allergies

- Approximately 10-20% of hospitalized patients self-report a penicillin allergy with 15-24% requiring antimicrobial therapy.
- Less than 10% of these individuals when tested have a positive penicillin skin test and over 90% have been shown to tolerate penicillins without an immediate IgE-mediated hypersensitivity reaction.
- Reported allergies to penicillins are often mistaken for non-IgE-mediated adverse reactions: maculopapular/morbilliform rash due to underlying viral or bacterial infections, gastrointestinal intolerance, dizziness, and headache.
- IgE antibodies associated with a positive penicillin skin test wanes over time, with 80% of patients becoming tolerant after 10 years.
  - 50% of sensitivity lost by 5 years and 80% by 10 years.

β-Lactam Cross-Reactivity Due to Antibody

- The cross-reactivity between β-lactams with IgE-mediated hypersensitivity may be predicted by similarities of R-side chains. [β-lactam Allergy Side Chain Chart]
- The rate of cross-reactivity between a penicillin and cephalosporin due to antibody recognition:
  - <2% in those who are skin test positive; <1% in patients not skin tested.
- Non-IgE-mediated hypersensitivity reactions (maculopapular rash, acute interstitial nephritis, immune-mediated hepatitis) have been reported with anti-staphylococcal penicillins (e.g. nafcillin).
  - Cefazolin is an option as it has a dissimilar R1 side chain to penicillins and cephalosporins.19
- Cross-reactivity with carbapenems is very unlikely (<1%).
- Cross-reactivity with aztreonam is absent, except for ceftazidime.

Allergy Assessment Methods and Northwestern β-Lactam Allergy Clinical Pathway

Conducting a risk assessment with allergy history leads to fewer treatment failures and deaths compared to giving an alternative antibiotic.23

- Penicillin Skin Testing (PST) 9,13,16,23
  - Required to evaluate a penicillin allergy in patients with a moderate to high-risk for IgE-mediated hypersensitivity reaction:
    - Urticaria, angioedema, bronchospasm, anaphylaxis. [β-Lactam Allergy Guideline: Clinical Pathway]
    - Contact Allergy and Immunology for PST
  - Has a negative predictive value (NPV) of 95% and approaches 100% when followed with an oral amoxicillin challenge.
  - A positive skin test, however, does not necessarily predict challenge reactions for benign skin rashes.
  - PST is not reliable to predict low-risk, non-IgE-mediated reactions.

- Direct Graded Challenges (GC) 9,16,21-22,23
  - Recommended to verify penicillin tolerance in patients with a low-risk (or unlikely) IgE-mediated reaction using a β-lactam with a dissimilar R1 side chain.
    - Contact Antimicrobial Stewardship for GC instructions & order set (pager 55955)
  - Direct GC (without prior skin testing) has been shown to be safe in patients with a non-life threatening, low-risk history for an IgE-mediated reaction.
  - Tolerance verifies that a patient will not experience an immediate adverse reaction from the challenged agent with no increased risk for future reactions compared with the general population.
  - Allergy profiles should be updated to reflect tolerance to the challenged agent.
References


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