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ZSFG Inpatient Beta-Lactam Allergy Test Dose Guidance

Which patients should receive a test dose?

A recent multicenter randomized clinical trial found that oral penicillin challenge (i.e. "test dose") was a safe and effective procedure for patients with a low-risk penicillin allergy, defined as a PEN-FAST score of 0 or 1.[10] In this study, one patient (0.5%) experienced a positive immune reaction following oral penicillin challenge (immediate diffuse rash/urticaria) and 6 patients (3.2%) experienced delayed diffuse rash or urticaria a median 4 hours after the challenge. Half of these patients received medication (antihistamine) and the other half recovered without treatment.

For patient-specific questions, please contact the ID Pharmacist (Epic secure chat "ZSFG ID Pharmacist" group) during normal business hours or the ID consult team (443-2847)

Background:

Penicillin allergies are reported by approximately 10% of all US patients, with higher rates reported by older and hospitalized patients.[1] However, less than 1% of patients are likely to have true, IgE or T lymphocyte-mediated penicillin allergies. **Studies have shown that when tested, >95% of people with reported penicillin allergies were able to tolerate penicillins and other beta-lactams.** Reasons for this discrepancy include: 1) IgE-mediated penicillin allergies can wane over time, with 80% of patients becoming tolerant after 10 years; 2) many penicillin allergies were initially labeled with "unknown" reactions or signs of intolerance that aren't true allergic reactions (such as GI upset or pruritis without rash).[1,2]

Reported but unconfirmed penicillin allergies can lead to an array of undesirable clinical consequences due to avoidance of beta-lactams. **Use of clinically inferior alternative antibiotics can lead to increased risk of readmission for the same infection, prolonged hospital stays, and increased mortality** risk in cases involving MSSA bacteremia.[3,4] Broad-

spectrum alternatives also increase the risk of developing infections with *C. difficile*, MRSA, and VRE, and can contribute to development of antimicrobial resistance.[1,5] Alternatives may also be more expensive, increasing costs to the hospital.[6]

Identifying true penicillin allergies through test dosing can decrease these consequences by reducing unnecessary use of clinically inferior, broad-spectrum antibiotics. **Direct oral challenges (test doses) are a safe and accurate way to de-label penicillin allergies for patients with a remote or unknown history of allergy, or history of mild cutaneous reaction and are supported by multiple national and international guidelines and practice parameters.**[7]

For additional clinical information, please refer to the UCSF Beta-lactam Allergy Guideline, available on the IDMP website (Guidelines --> UCSF Adult Guidelines --> Allergy (Beta-lactam))

Antibiotic Test Dose Procedure:

1. Patient is given the test dose, which is 10% of the target antibiotic dose
2. RN monitors for signs and symptoms of allergic reaction at specified time points during the procedure.
3. If patient does not experience any adverse effects 30 minutes after receiving the test dose, a full dose of the same antibiotic is administered
4. If patient tolerates the full dose, they are not considered to be allergic and can receive ongoing therapy with that antibiotic.
    a. Signs of intolerance: itchy rash, breathing difficulties, facial swelling, hypotension
    b. Patient-reported isolated urticaria, anxiety, or GI upset without any of the above signs should be interpreted as a negative test (e.g. NO allergic reaction)
        i. Isolated urticaria, anxiety, GI upset after the test dose is not a contraindication to administering the full dose.
5. PRN anaphylaxis medications (epinephrine, albuterol, diphenhydramine) are ordered and available for the duration of the procedure.

Best Practices**/Frequently Asked Questions for Test Doses:**

Before the test dose

- **Talking to the patient and/or caregiver about allergies and the test dose:**
    - Many patients with antibiotic allergies as a child can tolerate the same antibiotic later in life without issues
    - Not all antibiotic adverse events are signs/symptoms of an allergy
    - Beta-lactam antibiotics are first-line for many infectious syndromes
    - Test doses are a safe and effective procedure for confirming an antibiotic allergy
        - Based on multiple high-quality studies of drug challenges:[8]
            - Risk of a mild/moderate reaction (e.g. rash, hives) is ~10%
            - Risk of a severe reaction (e.g. anaphylaxis) is ~0.06%
        - Providers are required to document patient and/or caregiver consent via test dose order question
- Preparing for test dosing:
    - Rule out high-risk patients:[1]

        - Record of delayed reactions (>6 hr after exposure) to penicillin with severe cutaneous drug reactions: SJS–TEN, DRESS, or AGEP
        - Exercise caution in patients with documented anaphylaxis to the intended beta-lactam, especially within the last 5 years
    - An allergy history should be performed by interviewing the patient and/or caregiver(s) and reviewing antibiotic history in Epic. The patient's allergy list should be updated with any additional information gained by the allergy history.
    - Pertinent questions:
        - What specific antibiotic did the patient react to?
        - What symptoms did the patient experience? What was the onset? (example: immediately after taking a dose, within 24 hours, several days into course, etc)
        - How much time has passed since the reaction? (< 5 years, 5-10 years, 10+ years?)
        - How did the symptoms resolve? Did the patient require medical care or medications for symptoms to resolve?
        - Has the patient received that antibiotic (or similar antibiotics) since the reaction?

During the test dose

- My patient had increased heart rate after receiving the test dose, does this mean they're allergic?
    - Probably not; close monitoring is recommended but increased heart rate without other signs/symptoms of allergic reaction is not a contraindication to proceeding with the test dose procedure.
- My patient reported itching during the test dose, does this mean they're allergic?
    - Probably not; mild itching without an accompanying rash does not indicate an allergy and is not a contraindication to proceeding with the test dose procedure.

After the test dose

- RN will communicate the results of the test dose procedure to the primary team. If the patient tolerated the antibiotic, primary team to order ongoing dosing, as indicated.
- Updating allergy documentation after the test dose:
    - Patient tolerates drug that they have a documented allergy to: tolerance should be documented AND allergy should be removed from the chart
        - Example: patient with documented amoxicillin allergy but tolerates amoxicillin via test dose. Allergy documentation should be updated ("tolerated amoxicillin via test dose procedure at ZSFG 1/2023) and the allergy should be removed as clinically insignificant.
            - Adding a comment, even if delabeling the allergy, is HIGHLY recommended due to the risk of allergy re-labeling on subsequent encounters
    - Patient tolerates drug that is similar to the documented allergy: add a comment to the allergy stating the results of the test dose procedure
        - Example: patient with documented allergy to "cefepime" but tolerates ceftriaxone via test dose: add a comment "Tolerated ceftriaxone via test dose procedure at ZSFG in 10/2022"

- If patient does NOT tolerate the test dose, the allergy documentation should also be updated!
  - Example: patient with documented amoxicillin allergy did not tolerate amoxicillin via test dose. Allergy should be dated & labelled with the specific reaction(s) observed: “Did not tolerate amoxicillin via test dose procedure at ZSFG in 10/2022 (reaction: rash, facial swelling).

References:

1. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019;321(2):188-199. doi:10.1001/jama.2018.19283
2. Blumenthal KG, Shenoy ES, Wolfson AR, et al. Addressing Inpatient Beta-Lactam Allergies: A Multihospital Implementation. J Allergy Clin Immunol Pract. 2017;5(3):616-625.e7. doi:10.1016/j.jaip.2017.02.019
3. McDanel JS, Perencevich EN, Diekema DJ, et al. Comparative effectiveness of beta-lactams versus vancomycin for treatment of methicillin-susceptible Staphylococcus aureus bloodstream infections among 122 hospitals. Clin Infect Dis. 2015;61(3):361-367. doi:10.1093/cid/civ308
4. MacFadden DR, LaDelfa A, Leen J, et al. Impact of Reported Beta-Lactam Allergy on Inpatient Outcomes: A Multicenter Prospective Cohort Study. Clin Infect Dis. 2016;63(7):904-910. doi:10.1093/cid/ciw462
5. Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. J Allergy Clin Immunol. 2014;133(3):790-796. doi:10.1016/j.jaci.2013.09.021
6. King EA, Challa S, Curtin P, Bielory L. Penicillin skin testing in hospitalized patients with β-lactam allergies: Effect on antibiotic selection and cost. Ann Allergy Asthma Immunol. 2016;117(1):67-71. doi:10.1016/j.anai.2016.04.021
7. Castells M, Khan DA, Phillips EJ. Penicillin Allergy. N Engl J Med. 2019;381(24):2338-2351. doi:10.1056/NEJMra1807761
8. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. J Allergy Clin Immunol. 2022;150(6):1333-1393. doi:10.1016/j.jaci.2022.08.028
9. Healthcare Improvement Scotland. Frequently Asked Questions to support use of the penicillin allergy de-labelling algorithm and oral challenge test. SAPG. 2021. https://www.sapg.scot/media/5581/faqs-pen-allergy-delabelling.pdf
10. Copaescu AM, Vogrin S, James F, et al. Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy: The PALACE Randomized Clinical Trial. *JAMA Internal Medicine*. 2023;183(9):944-952. doi:10.1001/jamainternmed.2023.2986

Approved by ZSFG AMSC 5.2023