PENICILLIN SKIN TESTING CURRICULUM

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Penicillin Skin Testing and Cephalosporin Cross-Reactivity

Before you start

- Antihistamines held for at least 5 days.
- Epinephrine and resuscitation equipment at the bedside
- Testing done by personnel trained in the technique and in treating anaphylaxis.
- Do not skin test patients with a history of SJS/TEN, DRESS, serum sickness, or drug-induced hemolytic anemia.

Reagents

Reagent	Concentration	Role
PRE-PEN (benzylpenicilloyl polylysine)	6×10^{-5} mol/L, premixed	Major determinant
Penicillin G potassium	10,000 units/mL	Minor determinant
Amoxicillin, if available	1 to 25 mg/mL	Aminopenicillin side chain
Histamine	1 mg/mL prick, 0.1 mg/mL intradermal	Positive control
Normal saline 0.9%	undiluted	Negative control

Step 1: prick/puncture test

1. Place a drop of each reagent on the volar forearm, at least 2 cm apart.
2. Pierce through each drop with a lancet at a shallow angle. Do not draw blood.
3. Read at 15 minutes. Positive is a wheal at least 3 mm larger than the saline control with surrounding flare.
4. If positive, stop. The patient is sensitized and intradermal testing adds risk without adding information.
5. If negative, go on to intradermal testing.

Step 2: intradermal test

This is the part most people get wrong, and it is worth practicing on the simulation arms first. The goal is a bleb sitting in the dermis. If the fluid ends up in subcutaneous tissue the site is uninterpretable and has to be redone.

Loading the syringe

- Use a 26 or 27 gauge needle on a 1 mL tuberculin syringe.
- Draw up 0.05 to 0.07 mL, then expel the air and the excess so roughly 0.02 mL remains.
- Expelling first means you are not trying to judge a tiny volume while the needle is already in the skin.

Placing the injection

- Stretch the skin of the volar forearm taut with your free hand.
- Hold the needle bevel up and nearly flat, about 10 to 15 degrees to the skin.

- Advance until the bevel is just covered. You should still be able to see the outline of the bevel through the skin.
- Inject slowly. A 3 to 5 mm bleb should rise as you push.
- If no bleb forms, or the fluid disappears, you are subcutaneous. Withdraw and repeat at a fresh site at least 2 cm away.
- Test each reagent in duplicate, with histamine and saline placed intradermally as well.

Reading at 15 minutes

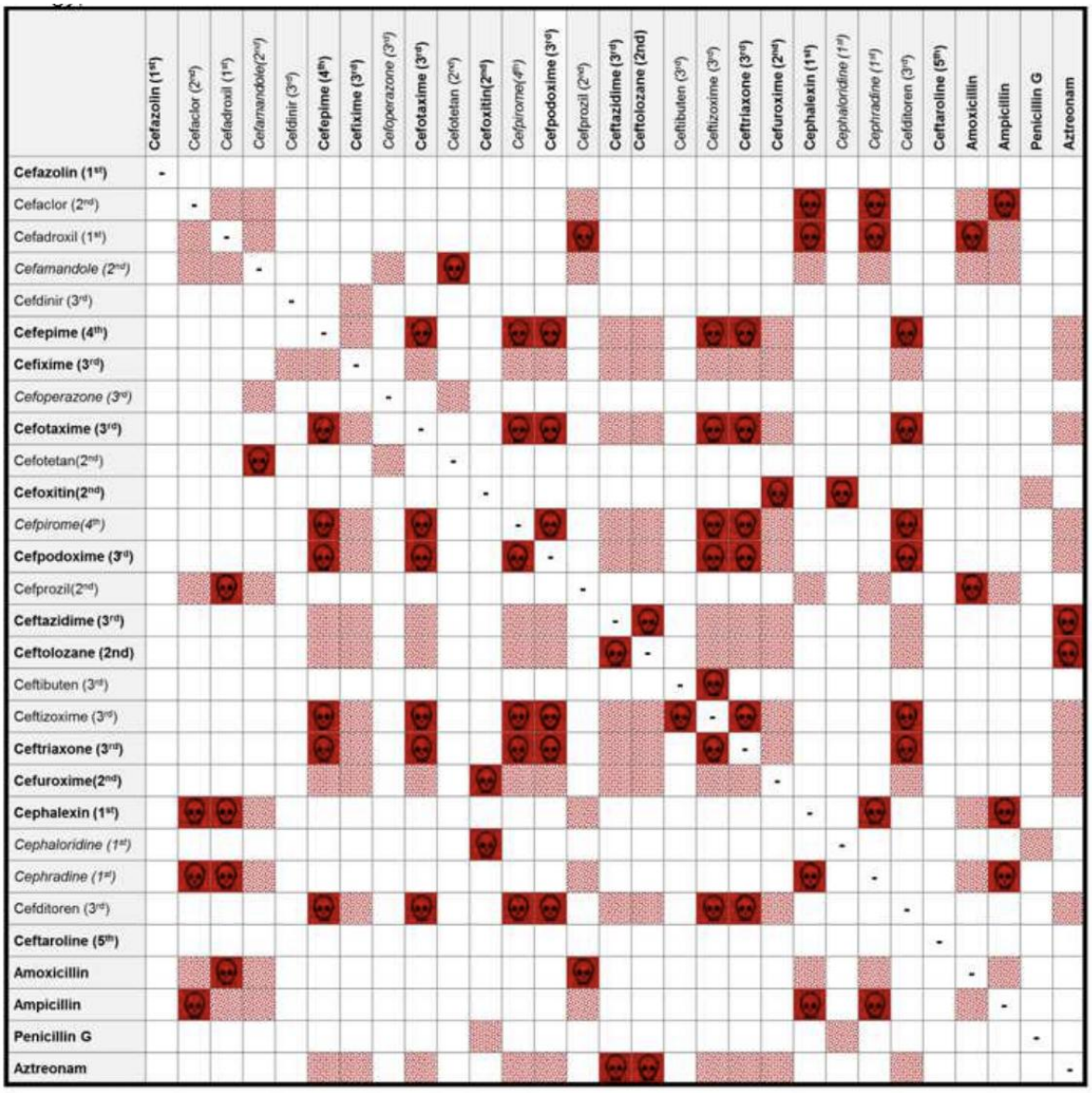
- Outline the wheal and measure two perpendicular diameters.
- Positive is a wheal at least 3 mm larger than the saline bleb with a flare of at least 5 mm.
- The test is only interpretable if histamine produced a wheal and saline did not.

What the result means

- Positive skin test: treat as penicillin allergic. Do not give penicillin or aminopenicillins. Desensitize if a penicillin is essential.
- Negative skin test: proceed to an observed oral amoxicillin challenge, typically 250 mg with 60 minutes of observation. Skin testing plus challenge has a negative predictive value above 95%.
- Both negative: the patient can receive penicillins. Remove the allergy label from the chart before the patient leaves, or it will still be there at the next admission.

Cephalosporins after a penicillin allergy label

Overall cross-reactivity is around 2%. The 8 to 10% figure still quoted on rounds comes from older studies with cephalosporins contaminated by penicillin during manufacture. What drives the reaction is the R1 side chain rather than the beta-lactam ring, which is why cefazolin behaves differently from cephalexin even though both are first generation. [1,2]



How this plays out at the bedside

- Unverified, non-anaphylactic label: cefazolin and third or fourth generation cephalosporins can generally be given. Aminocephalosporins deserve more caution. Carbapenems can be given without testing.
- History of anaphylaxis: skin test or graded challenge before any cephalosporin. Close to 40% react to aminocephalosporins specifically. Cefazolin can still be given by graded challenge because of its unique side chain.
- Confirmed allergy with a positive skin test: avoid anything sharing the R1 side chain. Cefazolin, ceftriaxone, and cefepime can be considered by graded challenge.
- IgE-mediated penicillin allergy fades. About 80% of patients lose sensitization by 10 years, which is why the history alone is rarely enough.

Safety

- Epinephrine 1:1000, 0.3 mL IM, drawn and within reach.
- Observe for at least 30 minutes after the last reagent.
- Document every reagent, every reading, and the final allergy status in the record.

References

1. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: a 2022 practice parameter update. J Allergy Clin Immunol. 2022;150(6):1333-1393.

2. Sousa-Pinto B, Blumenthal KG, Courtney L, Mancini CM, Jeffres MN. Assessment of the frequency of dual allergy to penicillins and cefazolin: a systematic review and meta-analysis. JAMA Surg. 2021;156(4):e210021.