BREAKOUT SESSION: INTEGRATING PENICILLIN ALLERGY ASSESSMENTS INTO YOUR PRACTICE

GENERAL AND COMMUNITY CURRICULUM

Leah Ishmael, DO
Beth Timmer, APRN
Allison Ramsey, MD

Case 1: The Classic Pediatric Amoxicillin Rash

Narrative vignette

A 4-year-old presents for a well-child visit. The chart carries a "penicillin allergy" label from age 2: on day 6 of a 10-day amoxicillin course for otitis media, the child developed a mild, non-urticarial, maculopapular rash on the trunk and extremities. There was no facial or mucosal swelling, no blistering or skin sloughing, no fever, and no respiratory or cardiovascular symptoms. The pediatrician at the time advised finishing the course, which the family did without any worsening of the rash. The label has never been revisited in the two years since. The parents are anxious about "testing" and assume any future reaction would be worse than the first.

Background literature & evidence

- In a cohort of 818 children referred for suspected amoxicillin allergy, a graded oral provocation challenge (10% of the dose, then the remaining 90% after an observation period) accurately and safely distinguished true reactors from non-reactors, with a high negative predictive value 89.1%. (PMID: 27043788)
- In a cohort of pediatric patients with penicillin allergy labels and low-risk histories (nonspecific rash or urticaria, no mucosal/respiratory involvement), direct oral amoxicillin challenge without preceding skin testing was performed safely, supporting skin-test-free challenge as a reasonable approach in appropriately selected low-risk children. (PMID: 32407949)
- This is supported by a validated 17-item questionnaire that identified low-risk pediatric penicillin allergy symptoms with high sensitivity: 72.6% of screened children had exclusively low-risk symptoms. Of the 100 low-risk children who completed formal 3-tier testing, 100% tested negative for true penicillin allergy and were delabeled. (PMID: 28674112)
- Of 355 adult patients seen by a single allergist, 50 (14%) carried a penicillin allergy label; 38 (76%) met criteria for direct oral challenge, and most index reactions were remote (88% >10 years prior). Four patients (8%) were delabeled on history alone, and 20 (40%) consented to in-clinic challenge: none developed immediate or delayed hypersensitivity reactions, though 3/20 (15%) had self-limited subjective symptoms not consistent with true IgE-mediated allergy. Overall, 24 patients (48%) had their penicillin allergy label removed. (PMID: 30582497)

Points for discussion

- What specific history features: timing of onset, morphology, distribution, mucosal/systemic involvement, and course while continuing the drug, separate a low-risk delayed rash from one requiring caution?
- What is the simplest mental framework to teach a generalist or APP for triaging a pediatric rash history in real time?
- How do you counsel an anxious parent through an in-office challenge, including what reassurance and monitoring look like?

- What does the relabeling documentation need to capture so this doesn't quietly reappear in the chart at the next visit?

Case 2: Adult with a Low PEN-FAST Score

Narrative vignette

A 45-year-old woman is being seen for a respiratory infection and would benefit from amoxicillin. Her chart lists a "penicillin allergy" from an event over 10 years ago. She recalls taking "something for allergies" at the time but never sought medical care, never had breathing difficulty, facial or throat swelling, blistering, or skin peeling, and never required treatment beyond an over-the-counter antihistamine, if that. She's uncertain of the exact timeline but is confident it was "a long time ago."

Background literature & evidence

- Foundational derivation and validation study for the PEN-FAST conducted in Australia, built from a prospective cohort of 622 antibiotic-allergy-tested patients across two Australian sites, with external validation in three additional cohorts (945 patients) including a U.S. site in Nashville. (PMID: 32176248)
- PEN-FAST criteria: Five or fewer years since reaction (2 points if yes); Anaphylaxis or angioedema, OR Severe cutaneous adverse reaction (2 points if either); Treatment required for the reaction, including if unknown (1 point if yes).
  Risk stratification: 0 points is <1% risk of a positive allergy test; 1–2 points approximately 5%; 3 points approximately 20%; 4–5 points approximately 50%. A score below 3 identifies patients at low risk, for whom direct oral challenge (skipping skin testing entirely) has been shown to be a safe, efficacious pathway.
- Applying the tool to this vignette: reaction occurred more than 5 years ago (0 points), no anaphylaxis/angioedema/severe cutaneous reaction (0 points), no treatment required (0 points) — PEN-FAST = 0, placing her in the very-low-risk category.

PEN	*Pen*icillin allergy reported by patient	☐ *If yes, proceed with assessment*
F	*F*ive years or less since reaction[a]	☐ **2 points**
A	*A*naphylaxis or angioedema	
	OR	☐ **2 points**
S	Severe cutaneous adverse reaction[b]	
T	*T*reatment required for reaction[a]	☐ **1 point**
		☐ **Total points**

Interpretation

Points	
0	**Very low risk** of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy)
1-2	**Low risk** of positive penicillin allergy test 5% (1 in 20 patients)
3	**Moderate risk** of positive penicillin allergy test 20% (1 in 5 patients)
4-5	**High risk** of positive penicillin allergy test 50% (1 in 2 patients)

(Trubiano JAMA Internal Medicine)

Points for discussion

- Scoring through PEN-FAST.
- At what point does a low PEN-FAST score translate into "just give the drug" versus "give it under observation," and how does that decision vary by care setting (primary care office vs. hospital vs. ED)?
- What institutional or personal comfort-level barriers come up when clinicians consider skipping skin testing altogether, and how do you address them in the moment?
- How should the label be updated in the record after a successful direct challenge, and who's responsible for making sure that update happens?

Case 3: Adult with a High PEN-FAST Score

Narrative vignette

A 60-year-old man needs a beta-lactam for a new infection. Two years ago, he had a reaction to penicillin that included facial swelling and difficulty breathing, was treated with epinephrine in the emergency department, and was told at the time that he could "never take penicillin again."

Background literature & evidence

- Using the same PEN-FAST framework; reaction within the last 5 years (2 points), angioedema present (2 points), treatment required with epinephrine (1 point): PEN-FAST = 5, placing him in the highest-risk category (approximately 50% probability of a positive allergy test).
- A high PEN-FAST score means the appropriate pathway is formal skin testing (and, if negative, a subsequent graded oral challenge) rather than a direct challenge.
  The evidence base supporting direct challenge for low-risk patients simply doesn't apply once anaphylaxis/angioedema and recency are both present.
- Cross-reactivity between penicillin and cephalosporins is based on side-chain structure, since this comes up constantly in inpatient and perioperative settings when an alternative agent is needed while formal testing is pending.

Points for discussion

- Why does this patient's history change the pathway entirely relative to Case 2, even though both patients are "adults with a penicillin allergy label"?
- What alternative antibiotics are reasonable choices while formal testing/challenge is pending, and how does side-chain similarity (versus core beta-lactam ring structure) factor into that choice?
- When is same-day allergy referral realistic, and what's the fallback plan when it isn't (e.g., rural or resource-limited settings, which several attendees will be practicing in)?
- How do you talk a patient who was told "never again" through the idea that re-evaluation, done properly, is both safe and appropriate?

Case 4: History Inconsistent with True Hypersensitivity

Narrative vignette

A patient's chart lists a penicillin allergy documented simply as "GI upset." On further questioning, the reported reaction was nausea and stomach discomfort that began during a course of antibiotics, with no rash, hives, facial or throat swelling, respiratory symptoms, or hemodynamic instability, and no clear temporal pattern suggestive of an immune-mediated process: the timing and symptom profile are more consistent with a known, common side effect of the medication than with an allergic reaction.

Background literature & evidence

- Clinically significant immediate (IgE-mediated) or delayed (T-cell-mediated) penicillin hypersensitivity is uncommon (<5%), even in those reporting penicillin allergies. Due to the decreased use of parenteral penicillin and about 80% of patients becoming tolerant after a decade, the rate of IgE-mediated penicillin allergies is decreasing.
- Low-risk history refers to those who had isolated nonallergic symptoms (e.g., gastrointestinal symptoms) or patients solely with a family history of a penicillin allergy, pruritus without rash, or remote (>10 years) unknown reactions without features suggestive of an IgE-mediated reaction.
- Moderate-risk history refers to those who have had urticaria or other pruritic rashes or reactions with features of IgE-mediated reactions (e.g., swelling), but not anaphylactic reactions.
- High-risk history refers to reactions, including anaphylaxis, positive penicillin skin testing results, recurrent penicillin reactions, and hypersensitivities to multiple β-lactam antibiotics.
  (PMID: 30644987)

Table 3. Risk Stratification for Penicillin Allergy Evaluation

	Low Risk	Medium Risk	High Risk
History[a]	Isolated reactions that are unlikely allergic (eg, gastrointestinal symptoms, headaches) Pruritus without rash Remote (>10 y) unknown reactions without features of IgE[b] Family history of penicillin allergy	Urticaria or other pruritic rashes Reactions with features of IgE but not anaphylaxis[b]	Anaphylactic symptoms[c] Positive skin testing Recurrent reactions Reactions to multiple β-lactam antibiotics
Action	Prescribe amoxicillin course or perform a direct amoxicillin challenge under observation.[d]	Skin test followed by amoxicillin challenge under observation if the skin test is negative.[e] Consider allergy/immunology referral.	Allergy/immunology referral or desensitization.

[a] No penicillin allergy testing should be performed on patients with possible penicillin-associated severe cutaneous adverse reaction, hemolytic anemia, organ-specific reaction, drug fever, or serum sickness. Patients with unstable or compromised hemodynamic or respiratory status and pregnant patients should never be considered low risk.

[b] IgE features classically include cutaneous symptoms, such as itching, flushing, urticaria, and angioedema, but also involve respiratory system (rhinitis, wheezing, shortness of breath, bronchospasm), cardiovascular system (arrhythmia, syncope, chest tightness), and gastrointestinal system (abdominal pain, nausea, vomiting, diarrhea) symptoms.

[c] The most severe IgE-mediated reaction is anaphylaxis (eFigure 1 in Supplement 1). Allergy/immunology consultation is advised.

[d] Considering patient comfort level with trying penicillin again and whether resources exist for observation.

[e] If skin testing is not possible, a graded amoxicillin challenge can be considered for medium-risk histories. A graded challenge often requires administration of a one-tenth to one-fourth full dose of the desired drug and a 30- to 60-minute period of monitoring followed by administration of a full dose of the desired drug and a final 30- to 60-minute period of monitoring (Toolkit C in Supplement 2).

(Shenoy et al. JAMA)

Points for discussion

- What symptom patterns and timing should prompt "this isn't allergy" confidently enough to skip testing entirely, rather than "let's test just to be safe"?
- How do you distinguish a known side effect (e.g., GI upset, common with many antibiotics) from a true hypersensitivity reaction when taking a history?
- How do you communicate a relabeling decision to a patient who has carried the label for years and may feel their symptom is being dismissed?

- What concrete documentation habits prevent the label from resurfacing at the next encounter or transition of care?
- Recognizing the label is often the easy part; making a correction stick in the chart is the harder, more practical skill.

Case 5: The "18 Allergies" Patient / Multi-Drug Intolerance

Narrative vignette

A patient presents with an extensive medication allergy list spanning every antibiotic class: penicillins, cephalosporins, macrolides, fluoroquinolones, and others each associated with a similar, vague description ("felt sick," "didn't feel right," "my body rejected it"). The patient is convinced they will react to anything given and approaches the visit with strong anticipatory anxiety about a new prescription.

Background literature & evidence

- Multiple drug allergy syndrome (MDAS) is defined as hypersensitivity reaction symptoms to more than 1 drug class, while multiple drug intolerance syndrome (MDIS) is defined as adverse drug reactions to more than 3 drug classes, incidence of MDIS and MDAS are rising. (PMID: 23245818) MDIS leads to use of alternative medications that often have worse side effects and increased healthcare expenditure. (PMID: 29574787)
- The nocebo effect is commonly implicated in adverse drug reaction reporting and occurs frequently in clinical practice, patients' negative expectations concerning their state of health creating a dilemma for treating physicians to differentiate between true drug allergies and somatization. (PMID: 29574787)
- A 5-year retrospective review of 229 patients undergoing single-blind, placebo-controlled graded drug challenges; found that reaction to drug and placebo was similar during the beta-lactam challenges (9.4% vs 8.2%; P =.9) and during nonsteroidal anti-inflammatory drug challenges (14% vs 7%, P =.5), respectively. Placebo-controlled challenges can, therefore, serve to minimize the rate of false-positive reactions and provide reassurance both to patients and to physicians. (PMID: 27888028)
- In 155 patients completing an amoxicillin challenge, 120 (77.4%) had no reaction at all, while 31 (20%) experienced a nonallergic reaction split evenly between placebo (16) and amoxicillin (15). Graded amoxicillin challenges without prior skin testing in this patient population with non-life-threatening historical reactions to penicillin were observed to be safe. (PMID: 29802906)

Points for discussion

- How do you introduce the concept that some challenge symptoms may be psychogenic/nocebo-driven, in a way that validates the patient's experience rather than sounding dismissive?

- What is a practical, time-efficient framework for triaging a long allergy list in a single visit, rather than trying to litigate all 18 entries?
- Which drug(s) on a list like this would you prioritize for challenge first, and why?

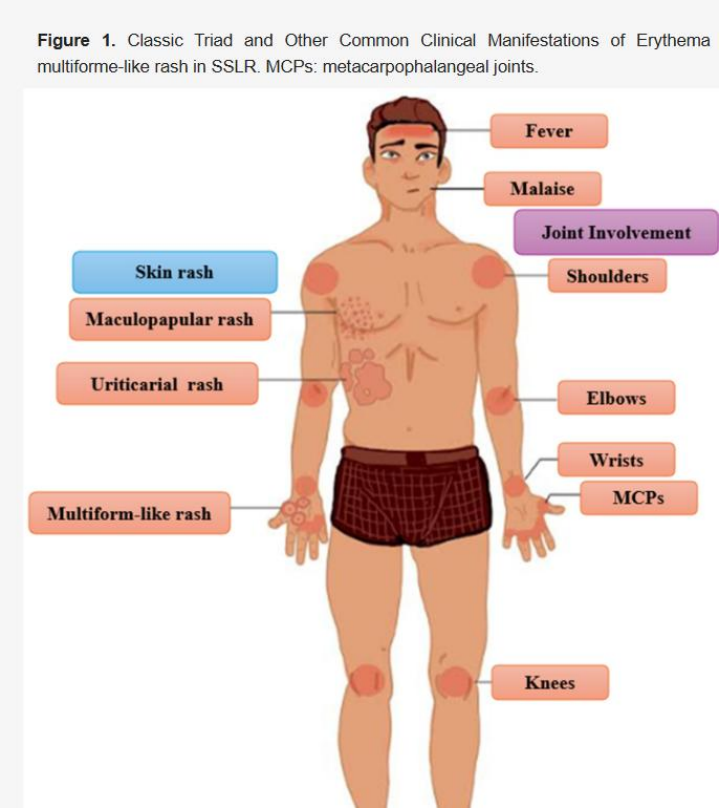
Case 6: Pediatric Serum Sickness-Like Reaction

Narrative vignette

A 3-year-old completed a course of amoxicillin (or cefaclor) for otitis media 10 days ago and now presents with an urticarial/morbilliform rash, joint pain and swelling affecting the wrists and knees, and a low-grade fever. Symptoms began a week after the drug started, well after the classic immediate-hypersensitivity window. The family was told at the time to avoid the drug permanently and the record reflects a lifelong "allergy" label. The parents now ask whether that avoidance is necessary long term.

Background literature & evidence

- Serum sickness-like reaction (SSLR) is a rare, delayed, non-IgE, non-immune-complex-mediated reaction most classically associated with cefaclor in young children, though amoxicillin and other beta-lactams, as well as sulfonamides, are also common triggers. Onset is typically 1-2 weeks after exposure, with a triad of rash, joint involvement, and fever, distinct in both timing and mechanism from immediate IgE-mediated penicillin allergy. (PMID: 41148776)

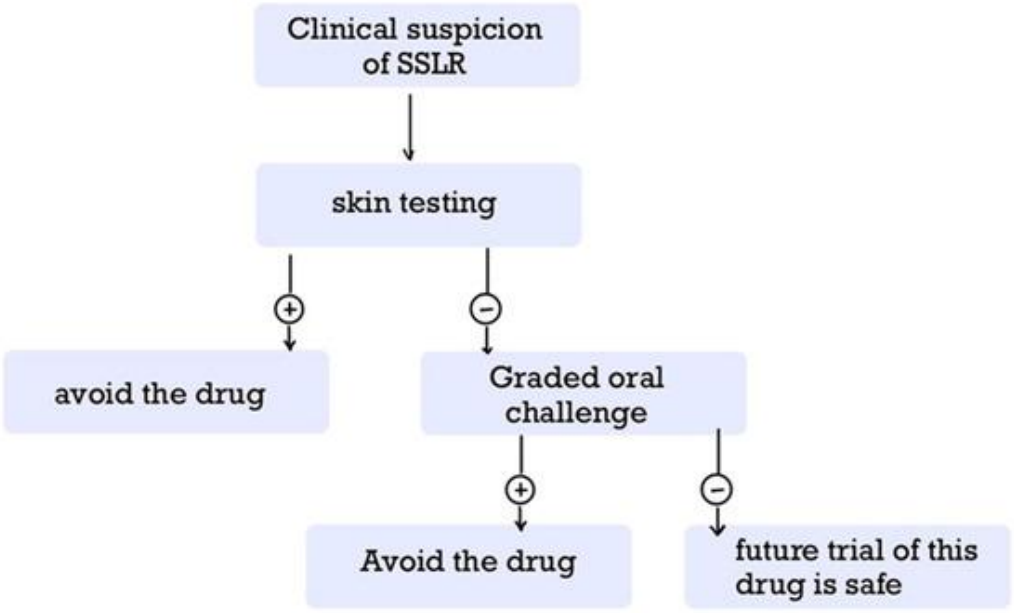


(Chatzigrigoriadis et al. Clinics and Practice)

- 2025 CME review directly addressing a central question, Serum Sickness–Like Reactions in Children-Is Lifelong Avoidance Indicated? examining whether the traditional teaching of lifelong avoidance after a pediatric SSLR is supported by the evidence, given the reaction's presumed non-IgE mechanism. The review mentions that for all patients with acute urticarial disorders challenge should be considered and that until the pathogenic pathways are clearly defined, the struggle with de-labeling is unavoidable. (PMID: 39978544)

- A systematic review with 444 patients cohort, antibiotics accounted for most cases overall (90.1%), driven by amoxicillin (71.8%) and cephalosporins (12.9%); most antibiotic-associated cases were prescribed for otitis media (53.2%) or URIs (20.5%). Antibiotics were significantly more likely to be the culprit in children than adults (97.3% vs. 27.3%, P<.01), while vaccines were implicated far more often in adults than children (43.1% vs. 0%, P<.01), inactivated influenza vaccine being the most common vaccine trigger. Mean time to symptom onset was similar across groups (~11–12 days). Of 353 patients with reported treatment, most received antihistamines (67.4%), corticosteroids (52.1%), and/or NSAIDs (43.3%); antihistamine and NSAID use were both significantly higher in children than adults (71.8% vs. 36.4% and 46.0% vs. 25.0%, respectively; P<.01/P=.01), while corticosteroid use was similar across groups (~52%). (PMID: 40032232)

- In a cohort of 156 children with prior serum sickness like reactions, who underwent formal antibiotic challenge, 148 (95%) passed. However, of 60 children later re-exposed to the culprit antibiotic clinically, 24 (40%) reacted again, including some who reacted to a different antibiotic than the original culprit, and some who reacted only after having previously tolerated a repeat course. Recurrence timing did not differ from the original reaction, and reactions occurred without the faster/predictable onset expected of classic immune-mediated (type III) serum sickness, suggesting it may represent a spectrum of infection-associated urticaria rather than true drug allergy. Families should be advised that a negative challenge does not guarantee future tolerance, and clinics should have a plan for re-evaluation if reactions recur. (PMID: 39855469)



(Chatzigrigoriadis et al. Clinics and Practice)

Points for discussion

- What distinguishes SSLR from a true IgE-mediated penicillin allergy in terms of timing, mechanism, and clinical features - and why does that distinction matter for future drug exposure?
- Given the newer literature questioning lifelong avoidance, how should a clinician counsel a family who was previously told to avoid the drug permanently?
- What would a reasonable re-exposure or referral pathway look like for a child with a history like this, and how does it differ from the direct-challenge pathways discussed in Cases 1 and 2?
- How do you balance newer evidence against a label that's already deeply embedded in the chart and in the family's understanding of their child's health?