Antibiotic Drug Allergy: Evaluation and Special Considerations

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Objectives

- Review the mechanism and manifestations of hypersensitivity reactions to antibiotics
- Recognize the incidence of penicillin allergy labels compared with true allergy
- Apply testing approaches for patients with reported drug allergy based on risk stratification
- Understand cross-reactivity between major antibiotic classes
- Discuss the implications of drug allergy in surgical, pregnant and immunocompromised patients and considerations for de-labeling in these special populations

Adverse Drug Reactions (ADRs)

Type A (Predictable) Reactions
≈ 80% of all ADRs

Related to known pharmacological action of the drug

- **Overdose**
- **Side effects**
- **Secondary effects**
- **Drug interactions**

Type B (Unpredictable) Reactions
≈ 20% of all ADRs

Unrelated to the pharmacologic action of the drug
Occur is susceptible individuals

- **Drug intolerance**
- **Nonallergic reactions with immune manifestations**
- **Hypersensitivity reactions (immunologically mediated, known as drug allergy)**

Middleton's Allergy: Principles and Practice, 9th edition
American Academy of Allergy, Asthma, and Immunology Teaching Slides (2024)

Hypersensitivity Reactions - *Types*

TYPE I	IgE-Mediated (Immediate)	Allergen binds to **IgE antibodies** on mast cells and basophils → release of vasoactive mediators (histamine, leukotrienes, etc.) *- e.g. urticaria, angioedema, respiratory distress → anaphylaxis*	**30 – 120 min (Out to 6 hrs)**
TYPE II	Cytotoxic	Antigen or hapten binds to **IgG or IgM antibodies** → cell or tissue injury *- e.g. hemolytic anemia, thrombocytopenia, neutropenia*	**>72 hrs to weeks**
TYPE III	Immune Complex	Antigen-antibody **complexes** form and get deposited in blood vessels or tissues → activate complement system and/or neutrophil recruitment *- e.g. serum sickness*	**>72 hrs to weeks**
TYPE IV	Cell-Mediated (Delayed)	Antigens caused activation of **T lymphocytes** → release of cytokines and recruitment of effector cells (macrophages, eosinophils, neutrophils) *- e.g. morbilliform eruption, Stevens-Johnson Syndrome*	**>72 hrs to weeks**

Gell and Coombs ed. Clinical Aspects of Immunology. Oxford, England: Blackwell; 1963: 317-37.
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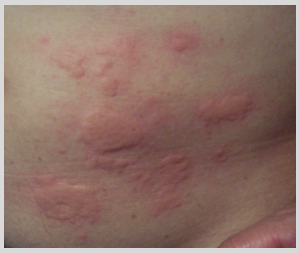
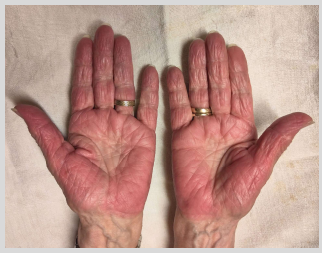
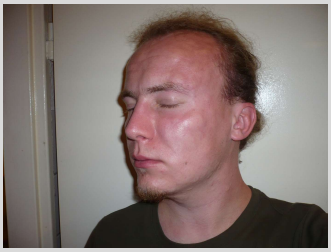
Immediate IgE-Mediated Reactions

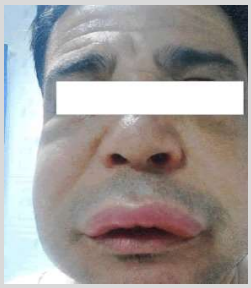


Urticaria, erythematous, raised pruritic lesions, with each lesion lasting <24 hours



Palmar erythema, pruritus





Angioedema of the face/lips

Bronchospasm

Anaphylaxis

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Photos courtesy of Wikimedia: Enochlau (photo 1); Jmarchn (photo 2); Ravn (photo 3); Boussetta N1, Military Hospital of Tunis (photo 4)

Delayed Hypersensitivity Reactions

- **Morbilliform drug eruption (MDE)** (e.g. benign exanthem)
- **Severe Cutaneous Adverse Reactions (SCARs):**
  - Acute generalized exanthematous pustulosis (AGEP)
  - Drug reaction with eosinophilia and systemic symptoms (DRESS)
  - Stevens-Johnson syndrome (STS)/toxic epidermal necrolysis (TEN)
- **Other**
  - Fixed drug eruption
  - Generalized bullous fixed drug eruption
  - Serum sickness and serum sickness-like reactions
  - Non-cutaneous organ-specific reactions (e.g. drug-induced liver injury (DILI), immune-mediated nephritis, cytopenias)

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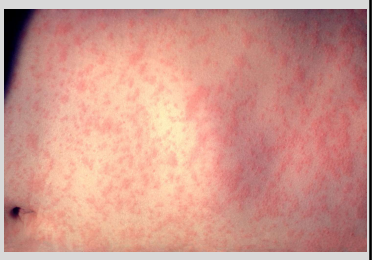
Morbilliform Drug Eruption (MDE)

Etiology	Presentation	Timing	Management
Most common = ~90% of all drug rashes Also known as benign exanthems or maculopapular exanthema Cross-reactivity is unknown	Usually benign erythema with macules/papules typically on the trunk, may extend to extremities Itching may be present May be associated with peripheral blood eosinophilia and/or fever Trunk; may extend to extremities, sparing the face	**Type IV Reaction** **Onset** >72 hours (up to 10 days) **Resolution** Can last days to weeks (2–14 days) *May not recur on subsequent exposures*	Symptomatic treatment Mild reactions: • Rechallenge • Consider "treat through" with close monitoring • Pre-medication



Mauri-Hellweg D, J Immunol 1996;157:1071-9.
Padovan E, Eur J Immunol 1996;26:42-8.
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Photo Courtesy of Wikimedia - CDC/Dr. Heinz F. Eichenwald

SCAR: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Etiology	Presentation	Timing	Treatment
Also called drug-induced hypersensitivity syndrome (DIHS) Multiple drugs implicated • High-risk include anticonvulsants, allopurinol, antimicrobials (e.g. sulfonamides, vancomycin), and antituberculosis agents Potentially life-threatening (mortality ≤10%)	Extensive, long-lasting papulopustular rash (>50% body surface area) Systemic symptoms: fever, lymphadenopathy, hematologic abnormalities (e.g. eosinophilia, neutrophilia) and organ involvement (e.g. hepatitis, nephritis)	**Type IV Reaction** **Onset** 2-6 weeks **Resolution** 6-9 weeks Most patients fully recover	**PROMPT recognition and withdrawal** of offending agent and supportive care Assess the severity and prognosis with RegiSCAR **AVOID re-challenge** AVOID chemically related drugs • Possible genetic involvement, associations with HLA polymorphism for certain medications in high-risk ethnic groups (e.g. A32:01 with vancomycin in European populations)

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SCAR: Acute Generalized Exanthematous Pustulosis (AGEP)

Etiology	Presentation	Timing	Management
Drug-induced 90% of the time - Most often antibiotics (e.g. aminopenicillins, cephalosporins, macrolides, quinolones, and tetracyclines) - Antimalarials - Antifungals Infections: viral (e.g. Parvovirus B19, CMV), Mycoplasma, parasitic	Multiple small, sterile pustules on erythematous skin; fever; leukocytosis with neutrophilia Diagnosis based on presentation, histology (spongiform sub-corneal and/or intraepidermal pustules, often-eosinophils in the pustules) and rapid resolution after stopping the drug	**Type IV Reaction** **Onset** Hours to days (average – 3 days) **Resolution** Spontaneously in one to two weeks after drug discontinuation	Identify and stop causative drug Assess the severity and prognosis with AGEP Validation Score Supportive care if needed for symptomatic relief **Re-challenge can cause relapse** • AVOID implicated drug

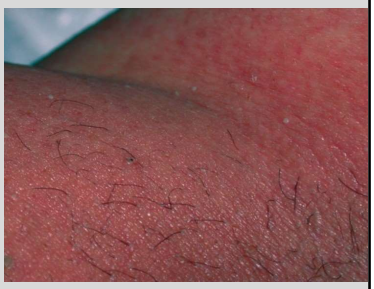

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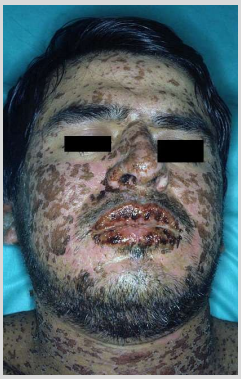
Photo Courtesy of Wikimedia – Fastily Clone

SCAR: Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Etiology	Presentation	Timing	Treatment
0.4-1.2 cases/million/year Causes: • Drug-induced (80-95% of cases), most common: allopurinol, antiepileptics, NSAIDs, antibiotics, nevirapine; immune check point inhibitors • Infection (HIV, mycoplasma, herpes simplex virus), idiopathic Risk factors: genetic factors, autoimmune diseases, and malignancy **Mortality** 5-40%	Onset with ill-defined erythematous macules and atypical target lesions, that progress to **extensive necrosis and detachment of the epidermis** Mucous membrane involved in >90% of patients *(oral, ocular – 80%, urogenital; may have GI/bronchial)* Diagnosis: clinical and histologic findings are supportive	**Type IV Reaction** **Onset** 4-28 days, Rare >8 wks **Resolution** Weeks to months	**PROMPT recognition and withdrawal** of offending agent and supportive care Assess the severity and prognosis with SCORTEN Consider transferring to a specialized center (burn unit) with supportive care Consider adjunctive therapy (cyclosporine, etanercept; routine use of steroids is not recommended) **AVOID re-challenge** even with chemically related drugs



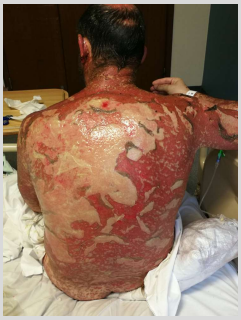


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Photo Courtesy of Wikimedia – DermNet, Thomas Habif (photo 1); Jay2Base (photo 2)

Evaluation - *History*

MEDICATION Exact drug, dose and route	**CONDITION** Coincident infections and illnesses	**OTHER MEDS** Co-administered meds/OTCs at that time	**EXPOSURE** Repeated reaction to the same drug, prior to OR since reaction	***When available, a detailed history of the drug reaction significantly simplifies risk stratification and management***
REACTION Symptoms, photos, records, laboratories	**LATENCY** How long ago did the reaction occur	**ONSET / DURATION** Doses/days into the course; duration of symptoms	**TREATMENT** Need for emergency room, hospitalization, epinephrine, etc.	

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Evaluation – *Testing*

- Skin testing can help identify **a culprit agent** that is essential for appropriate drug avoidance
- Testing can also identify medications safe for drug challenge to delabel a drug allergy
- **Types of drug testing:**
  - Prick and intradermal skin testing - for suspected IgE-mediated drug reactions
  - Patch and delayed intradermal skin test reading –for delayed reactions
- Currently, there are no commercially available drug-specific laboratory tests to aid in diagnosis of drug allergy, except HLA-B*57:01 for Abacavir hypersensitivity
- Drug specific IgE testing is **NOT** helpful (i.e. penicillin)

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Evaluation - *Skin Testing*

- **Immediate skin testing** is used for possible IgE-mediated reactions
  - No role for skin testing in SJS/TEN, acute interstitial nephritis, hemolytic anemia
- Skin testing for drug allergy is only validated for **penicillin allergy**
  - Established non-irritating concentrations are used for the other drugs
- Concomitant medications can interfere with skin testing, avoid prior to skin testing:
  - Stop ≥5-7 days prior to testing – long-acting antihistamines (cetirizine, fexofenadine, loratadine, etc.)
  - Stop ≥48 hours – short-acting antihistamines (diphenhydramine)
  - Stop ≥24 hours - histamine H2-receptor antagonists (cimetidine, famotidine)
  - May ask patients to hold or decrease the dose of beta-blockers for high risk patients
  - *Tricyclic antidepressants and some antipsychotics may also interfere with test results*
- Results are available immediately (<1 hour) for IgE mediated reactions
- Following negative skin test results, the absence of allergy **should be confirmed with a drug challenge (when possible)**

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Evaluation - *Skin Testing Process*

Useful only to rule out **Type I hypersensitivity, performed** in steps (skin prick and intradermal testing)

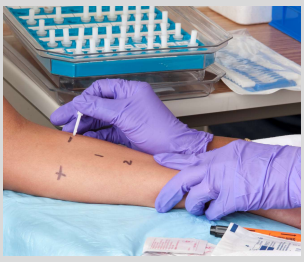
Step 1: **Skin prick test**, measured at 15 min
Histamine control, saline control and active drug
Positive is wheal >3 mm and flare >5 mm of neg control

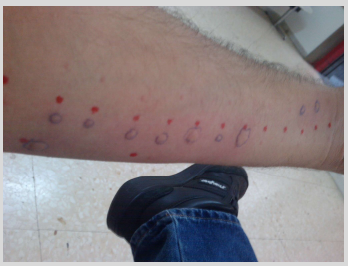
→

Step 2 (if Negative): **Intradermal test** in duplicates, measured at 20 min

→

Step 3 (if Negative Testing): **Drug challenge** (when possible) followed by observation





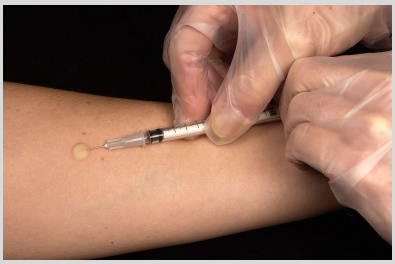


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Photo Courtesy of Wikimedia: National Institutes of Health (photo 1); Ismael Olea (photo 2); CDC/NIH, Greg Knobloch Photo 3)

Evaluation - *Drug Challenge*

- Procedure whereby drug is administered to determine tolerance, referred to as “test dose” or "drug provocation test"
- When a drug challenge is not preceded by skin testing, it is called a **"direct challenge”**
- Indicated for **low-risk patients** who are unlikely to be allergic or after negative skin testing
- NOT for life-threatening SCAR reactions such as SJS/TEN, DRESS, and exfoliative dermatitis
- **Protocols:**
  - *Direct challenge (without prior skin testing)*
    - *Full dose, observe ≥ 60 min*
    - *Graded challenge: 10-25% of the dose, observe for 30 minutes; if no reaction – administer the remainder of the dose, observe 60 minutes to 2 hours*

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Evaluation – *Choosing the Appropriate Diagnostic Test*

Direct Drug Challenge

OR

Skin Tests

- Risk stratify based on reaction phenotype
- **Skin testing** is of value for patients with a history of **drug-induced anaphylaxis** or a recent reaction suspected to be IgE-mediated
  - Negative skin testing, should be followed by a diagnostic drug challenge
- **Direct drug challenge** is offered for low-risk patients with **benign non-anaphylactic reactions**
  - *Serum sickness like reaction (SSLR) are no longer a contraindication to challenges and can be considered, after taking into consideration remoteness of the reaction, importance of the drug and likelihood that the reaction was drug-related*
- Role for **shared decision making** in diagnostic testing and management

American Academy of Allergy, Asthma, and Immunology Teaching Slides (2024)

Khan DA, et al. J Allergy Clin Immunol 2022;150(6):1333-93.

Evaluation – *Delayed Drug Testing*

Delayed Intradermal Testing (dIDT) and Patch Testing (PT)

- Delayed drug testing is suggested for delayed drug HSRs where the pretest probability is high (e.g. DRESS), but the implicated agent is uncertain
- For well-phenotyped Type IV delayed T-cell mechanism (e.g. AGEP, DRESS)
- dIDT and/or PT maybe useful as adjunctive tests to support drug causality

- **Limitations**
  - Lack of FDA-approved reagents for testing, standardized methods and information on concentrations for testing
  - Sensitivity, specificity, positive- and negative-predictive values are not able to be reliably calculated

American Academy of Allergy, Asthma, and Immunology Teaching Slides (2024)

Phillips, et al. J Allergy Clin Immunol 2019

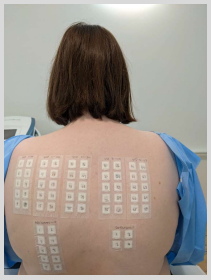
Khan DA, et al. J Allergy Clin Immunol 2022;150(6):1333-93.

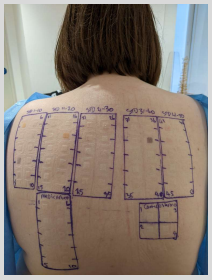
Evaluation – *Role for Patch Testing After SCARs*

- Perform: > 6 wks after reaction and > 4 wks after discontinuation of systemic steroids
- Drug concentrations for testing: 1-10% for powder, 10-30% for product itself
- **A negative test does not exclude causality**
- Sensitivity varies based on clinical setting, causal drug, drug concentrations used, and reaction phenotype

Clinical Scenario	Sensitivity of Patch Testing
AGEP	**58-64%**
DRESS	**32-80%**
SJS/TEN	**9-24%**
Antiepileptics, contrast media, beta-lactams, tetrazepam and pristinamycin	**Increase the sensitivity (Carbamazepine: 50%)**
Allopurinol or its active metabolite	**Do not provide clinical utility**

Placement **Reading**





Copaescu A et al. Front Pharmacol. 2021
Barbaud, et al. Br J Dermatol. 2013
Lezmi, et al. Pediatr Allergy Immunol. 2017
Romano J, et al. Allergy Clin Immunol Pract. 2014
Khan DA, et al. J Allergy Clin Immunol 2022;150(6):1333-93

American Academy of Allergy, Asthma, and Immunology Teaching Slides (2024)
Photos Courtesy of Wikimedia: Smirkybec

Updates in Drug Allergy (from the latest allergy/immunology practice parameters)

- Many patients with a history of an allergy to piperacillin/tazobactam (Zosyn) may be selectively allergic to piperacillin/tazobactam and can tolerate other beta-lactam antibiotics
- Administer carbapenems without prior testing in patients with other beta-lactam allergies

Updates in Drug Allergy (from the latest allergy/immunology practice parameters)

- 2-step aspirin challenge (not desensitization) for patients with a history of non-aspirin exacerbated respiratory disease aspirin allergy in acute need of aspirin for cardiovascular disease

Updates in Drug Allergy (from the latest allergy/immunology practice parameters)

- Non-IgE chemotherapy, monoclonal antibodies, or biologic reactions be treated with slowed infusion rate, graded dose escalation, and/or premedications without desensitization

Updates in Drug Allergy (from the latest allergy/immunology practice parameters)

- Excipient allergy is very rare but may be considered in patients with anaphylaxis to ≥2 structurally unrelated products that share a common excipient

Penicillin Allergy - *Background*

10% of the population reports a penicillin allergy, but
<1% of the whole population is truly allergic

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Penicillin Allergy – *Why the "Allergy Label" Matters*

Penicillin allergy delabeling is important because **unverified penicillin allergy labels lead to:**

- **worse patient outcomes**
- **increased antimicrobial resistance**
- **higher healthcare costs**

- Patients labeled as penicillin allergic are more likely to receive second-line, broad-spectrum antibiotics, which are associated with increased treatment toxicity, longer hospital stays, and higher mortality.
- These alternative antibiotics also drive antimicrobial resistance, including increased rates of methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus*, and *Clostridioides difficile* infection.
- The economic burden is substantial, with penicillin allergy labels contributing to increased healthcare costs through both direct treatment expenses and prolonged hospitalizations.

Blumenthal KG et al. Reaction risk to direct penicillin challenges: a systematic review and meta-analysis. JAMA Internal Medicine. 2024;184;(11):1374-1383.
Copaescu AM 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.
Shenoy ES et al. JAMA. Evaluation and Management of Penicillin Allergy: A Review. 2019;321;(2):188-199.

Penicillin Allergy – *Proactive Delabeling*

American Academy of Allergy, Asthma, and Immunology (AAAAI) Drug Allergy Practice Parameter Recommends

A **proactive effort should be made to delabel** patients with reported penicillin allergy

After appropriate history and evaluation, including a **negative drug challenge, penicillin allergy label should be removed**

Delabeling a Drug Allergy

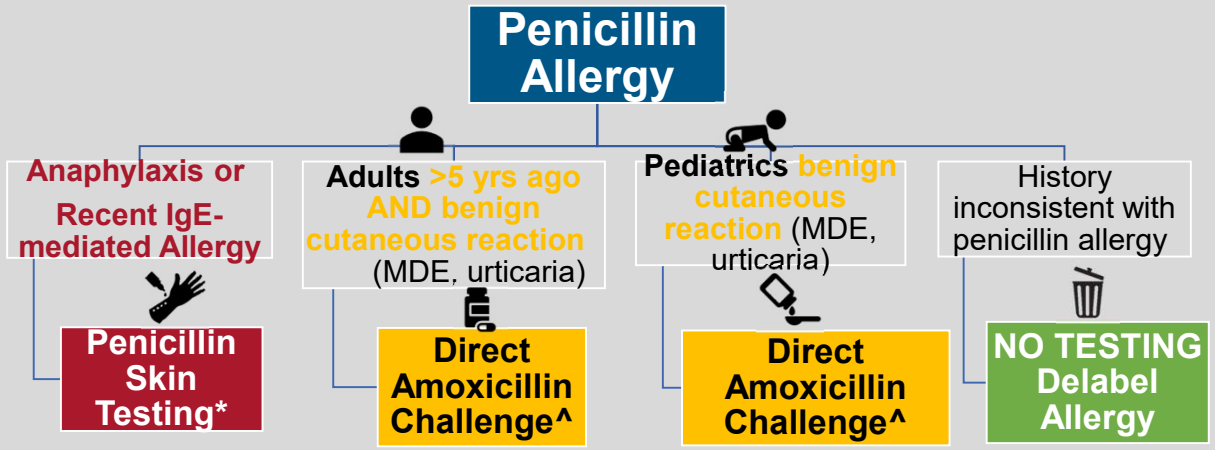
1. **Add comments** to the allergy about the allergy history
2. **Delete** the allergy entry
3. Select the **reason for deletion** and **add detailed comments about why you are deleting the allergy**
4. **Educate the patient and** provide **instructions** on clinic discharge
   Consider communicating to outside providers and pharmacy and/or providing a wallet card to patients

American Academy of Allergy, Asthma, and Immunology Teaching Slides (2024)

Khan DA, et al. J Allergy Clin Immunol 2022;150(6):1333-93.

Penicillin Allergy – *Summary of Recommendations*

- **Risk stratification** based on reaction phenotype and shared decision making:



Abbreviations: MDE – Morbilliform drug eruption
*If penicillin is required in patients with positive skin tests an induction of drug tolerance procedure should be performed
^Challenge with therapeutic dose of a penicillin-class antibiotic, followed by 1 hour observation is a gold standard for drug allergy

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Adapted from Khan DA, et al. J Allergy Clin Immunol 2022;150(6):1333-93.

Penicillin Allergy – *PEN-FAST Clinical Decision Tool*

This clinical decision rule can:
- Provide a quick and easy risk assessment for patients with reported penicillin allergies
- Has internal and external validation
- A negative predictive value of 96%

	PEN	**Pen**icillin allergy reported by patient
+2	F	**F**ive years or less since reaction
+2	A OR S	**A**naphylaxis or **A**ngioedema OR **S**evere cutaneous adverse reaction (SCAR)*
+1	T	**T**reatment required for reaction (or unknown)

Points	Risk of a Positive Penicillin Skin Test	
0	Very Low	< 1%
1-2	Low	5%
3	Moderate	20%
4-5	High	50%

***History of SCAR is a contraindication for a re-challenge, even with a "low-risk" PEN-FAST score of 2**

American Academy of Allergy, Asthma, and Immunology Teaching Slides (2024)
Trubiano, et al. JAMA Intern Med. 2020;180(5):745-752.

AAAAI Position Statement


FULL TEXT ARTICLE
Penicillin Allergy Evaluation Should Be Performed Proactively in Patients with a Penicillin Allergy Label
Article in Press: Accepted Manuscript
Journal of Allergy and Clinical Immunology: In Practice, Copyright © 2023

- A penicillin allergy evaluation accurately identifies approximately 9 of 10 patients who, despite reporting a history of "penicillin allergy," can receive penicillins without allergic reaction
- **Efforts to delabel can and should be performed by all clinicians,** especially for those patients with low-risk histories, not limited to those from Allergy and Immunology
- For those clinicians not comfortable performing delabeling procedures, referral to Allergy and Immunology is an appropriate alternative
- **The AAAAI encourages widespread and routine penicillin allergy evaluations, which are integral for successful antibiotic stewardship**

American Academy of Allergy, Asthma, and Immunology Teaching Slides (2024)
Journal of Allergy and Clinical Immunology: In Practice, 2023-12-01; 11(12): 626-3628

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Specific Antibiotic Allergies

Penicillin may be the most common…

But it is not the only antibiotic allergy you'll see on a patient's chart

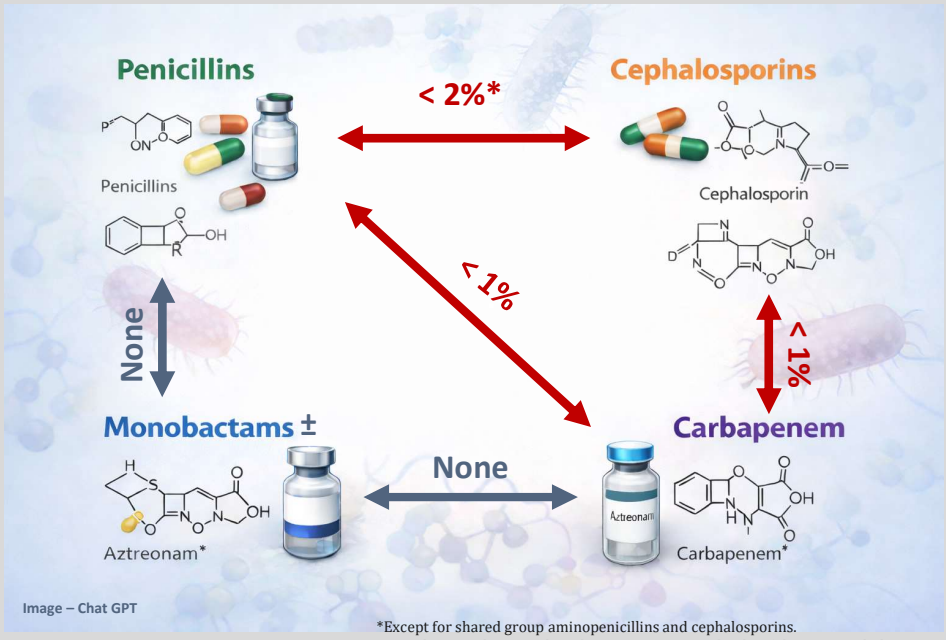
- Cephalosporins and other beta-lactams
- Sulfonamides
- Macrolides
- Aminoglycosides
- Tetracyclines
- Clindamycin
- Vancomycin

β-Lactam antibiotic allergy

- Penicillin remains most commonly reported (**10-15%** of the population)
- Cephalosporin allergy – around **1-2%** of population
- Others even more rare
- Principles of history/ identification of allergy is the same but **cross-reactivity** helps to determine which can be safely used

J Allergy Clin Immunol Pract. 2019 Sep-Oct;7(7):2105-2114.

β-Lactam Cross-Reactivity



*Except for shared group aminopenicillins and cephalosporins.
±Monobactams have no shared cross-reactivity with other β-lactams, with the exception for aztreonam and ceftazidime, which share an identical R1.

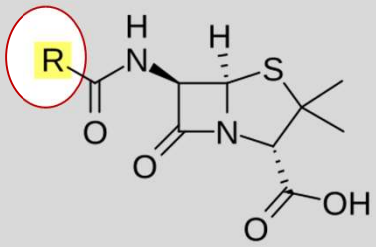
Lancet. 2018 Dec 14;393(10167):183–198.

β-Lactam Cross-Reactivity

R^1 side chains predict cross-reactivity across penicillin and cephalosporins

Not the beta lactam ring

Penicillin Core Structure



Cephalosporin Core Structure

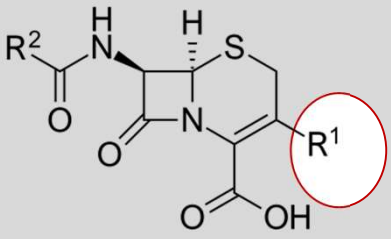


Image source: Wikicommons

Cross-reactive cephalosporin and aminopenicillins based on R1 side chains

	Cefazolin	Cefaclor	Cefadroxil	Cefepime	Cefotaxime	Cefoxitin	Cefprozil	Ceftazidime	Ceftriaxone	Cephalexin	Amoxicillin	Ampicillin
Cefazolin												
Cefaclor										X		X
Cefadroxil							X			X	X	
Cefepime					X				X			
Cefotaxime				X					X			
Cefoxitin												
Cefprozil			X								X	
Ceftazidime												
Ceftriaxone				X	X							
Cephalexin		X	X									X
Amoxicillin			X				X					
Ampicillin		X								X		

Banerjee et al. J Allergy Clin Immunol Pract Feb 2023;11(2): 356-368

Beta-Lactam Allergies – *Risk Stratification and Definitive Testing*

	Drug to be Administered	History of a Penicillin Allergy/Hypersensitivity	History of Cephalosporin Allergy/Hypersensitivity
Nonanaphylactic Benign Cutaneous Reaction (>5 Years Ago)	Penicillin Derivative	**Amoxicillin drug challenge**	**Administer penicillin normally (no testing is needed)**
	Cephalosporin Derivative	**Administer cephalosporin normally (no testing is needed)**	*Structurally Similar* **Cephalosporin skin testing** (when available) followed by cephalosporin drug challenge **OR** **Cephalosporin drug challenge** only in low risk patients
			Structurally Dissimilar **Cephalosporin drug challenge**
Anaphylactic Reaction OR Recent Ig-E Mediated Reaction (<5 years Ago)	Penicillin Derivative	**Penicillin skin testing** followed by amoxicillin drug challenge	**Penicillin skin testing** followed by amoxicillin drug challenge **OR** **Cephalosporin skin testing** (when available)
	Cephalosporin Derivative	*Structurally Similar* **Penicillin skin testing** followed by amoxicillin drug challenge and **Administer cephalosporin normally**	**Cephalosporin skin testing** (when available) followed by cephalosporin drug challenge
		Structurally Dissimilar **Administer cephalosporin normally (no testing is needed)**	

Image from American Academy of Allergy, Asthma, and Immunology Teaching Slides (2024)
Adapted from Khan DA, et al. J Allergy Clin Immunol 2022;150(6):1333-93.

Sulfonamide Antibiotics

Sulfonamide antibiotics are the second most commonly listed antibiotic allergy (after beta-lactams)

Image soure: Pixabay

Sulfonamide Cross-Reactivity

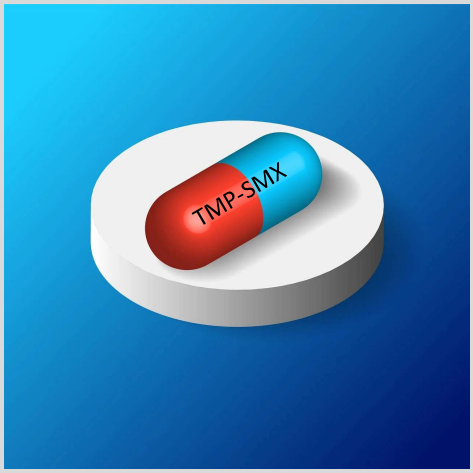
- Trimethoprim-sulfamethoxazole is the most common sulfonamide antibiotic
- There is **not** clinically significant immunologic-mediated cross-reactivity between **sulfonamide antibiotics** and **non-antibiotic sulfonamides*, i.e:**
  - Furosemide
  - Glipizide
  - Celecoxib
  - Hydrochlorothiazide
  - Acetazolamide

***Sulfasalazine** is an exception – when interacts with gut flora releases sulfapyridine which does cross-react

- Other medications commonly confused with but do not cross-react with sulfonamides:
  - Dapsone (sulf**one** not sulfonamide)
  - Sulf**ites** (e.g. food addititves)
  - Sulf**ur**
  - Sulf**ate** (e.g. albuterol sulfate)

Sulfonamide Antibiotic Allergy - Testing

- No definitive skin testing
- Oral challenge with trimethoprim-sulfamethoxazole is gold standard*
  - > 5 years since reaction → 1 step
  - Within 5 years → 2 step
- If negative, de-label



*Reactions consistent with SCAR (severe cutaneous reaction) → AVOID, do not rechallenge

Khan DA, et al. J Allergy Clin Immunol 2022;150(6):1333-93

Other antibiotic classes

- Fluoroquinolones
  - Delayed morbilliform reactions common (2-3%)
  - Recurrence when re-challenged < 5%
  - Some may be non-IgE mediated (i.e. ciprofloxacin)
- Macrolides
  - Less common; benign delayed exanthem in <1%
  - True allergy even more rare

Khan DA, et al. J Allergy Clin Immunol 2022;150(6):1333-93.

Banerji, et al. J Allergy Clin Immunol Pract Feb 2023;11(2): 356-368.

Reactions may not always be "allergy" and can be amenable to pre-medication

- Vancomycin "Red Man Syndrome"
- Infusion Reactions
- Non-specific mast cell degranulation via MRGPRX2

(Mas-related G protein-coupled receptor X2)

Examples: Ciprofloxacin, Vancomycin, Opioids, NMBDAs

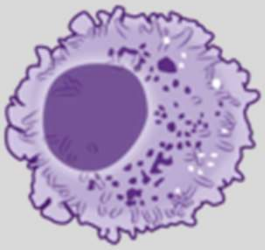


Image source: WikiCommons (courtesy NIAID)

Key Take-Aways:

Regardless of the specific antibiotic, history is critical to risk stratification

Penicillin is the only antibiotic with validated skin testing, but current practice parameters support direct oral challenge for other antibiotics especially with low risk-history

Knowledge of cross-reactivity can guide alternative antibiotic selection when allergy is likely/ suspected

Antibiotic Allergy considerations in Special Populations

- Surgical Patients
- Pregnant Patients
- Immune compromise

Surgical Prophylaxis

- Timely administration of antibiotics help reduce surgical site infections
- Cefazolin is the agent of choice in most surgical cases in the U.S.

Penicillin allergy on a patient's chart often results in choosing second line agents instead of the cephalosporin

Surg Infect 2013; 14:73–156.

Penicillin allergy leads to second-choice antibiotics

- Blumenthal et al. (2018) looked at 8385 patients who underwent 9004 procedures
  - Hip/ Knee arthroplasty
  - Hysterectomy
  - Colon surgery
  - Coronary artery bypass grafting
- 922 (11%) reported a penicillin allergy
- They received:
  - Less cefazolin
  - More Clindamycin, Vancomycin, Gentamicin

Patients with penicillin allergy had **50%** increased odds of surgical site infection

Clin Infect Dis. 2018 Feb 1; 66(3): 329–336.

We know that penicillin-allergic patients tolerate cefazolin

- Penicillin allergy often leads to a “flag” in electronic records for any beta lactams including cephalosporins like cefazolin
- Cefazolin has **no shared side chains** with penicillin or cephalosporins used in the U.S

Khan DA, et al. J Allergy Clin Immunol 2022;150(6):1333-93

	Cefazolin	Cefaclor	Cefadroxil	Cefepime	Cefotaxime	Cefoxitin	Cefprozil	Ceftazidime	Ceftriaxone	Cephalexin	Amoxicillin	Ampicillin
Cefazolin												
Cefaclor										X		X
Cefadroxil							X			X	X	
Cefepime					X				X			
Cefotaxime				X					X			
Cefoxitin												
Cefprozil			X								X	
Ceftazidime												
Ceftriaxone				X	X							
Cephalexin		X	X									X
Amoxicillin			X				X					
Ampicillin		X								X		

Special Populations – Pregnancy

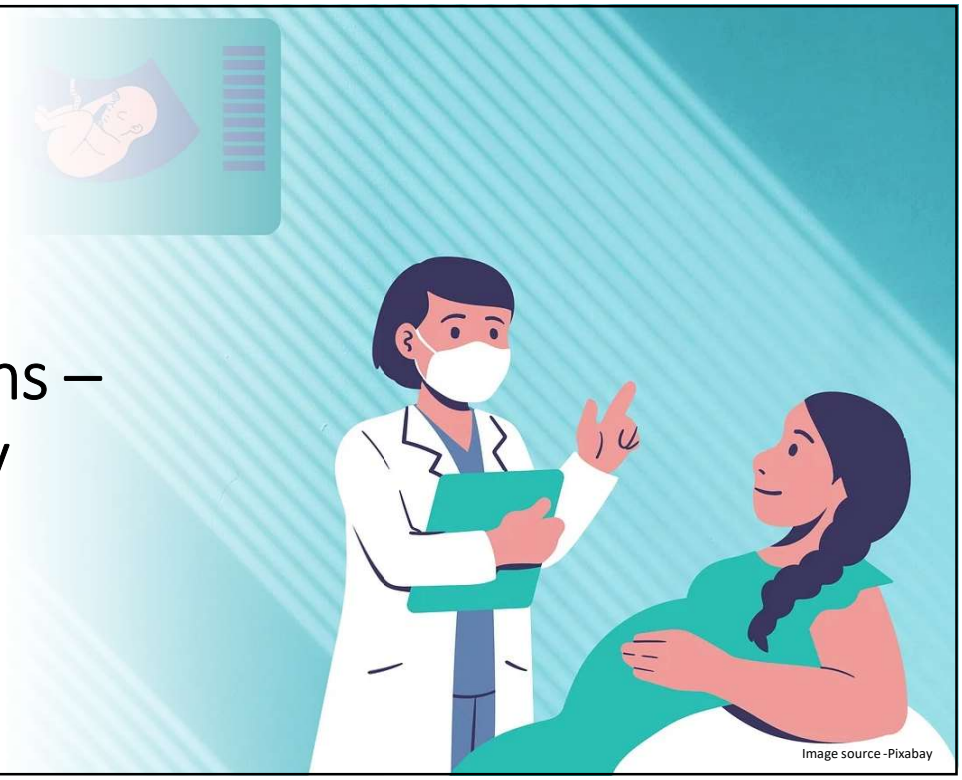


Image source -Pixabay

Penicillin Allergy in Pregnancy

8%
- Pregnant women who report penicillin allergy
  - *90% of these are not allergic*

1/3
- Women have GBS colonization during pregnancy

Penicillin
- Treatment of choice for intra-partum prophylaxis for GBS
- Only effective treatment for syphilis during pregnancy

Iammatteo, Solensky. JACI: IP 2021 Mar;9(3):1347-1348

Penicillin Allergy in Pregnancy

Pregnant patients with reported penicillin allergy have:

- Use of broader-spectrum antibiotics for GBS prophylaxis
- Use of non-preferred, non-beta lactam antibiotics for surgical site prophylaxis (C-section), PROM
- Higher rates of surgical site infection, endometriosis

Iammatteo, Solensky. JACI: IP 2021 Mar;9(3):1347-1348

Penicillin Allergy Testing is Safe in Pregnancy

Study Author & Year	Number of Patients Tested	Adverse Outcomes
Macy et al, 2006	56	Two delayed-onset rashes associated with intrapartum PCN use of 47 patients who received PCN
Philipson, 2007	27	None
Kuder et al, 2020	46	None
Desravines et al, 2021	46	Two experienced systemic reactions with oral challenge consistent with anaphylaxis and received epinephrine with no long-term effect to fetus
Wolfson et al, 2021	220	One with immediate non-urticarial rash and 2 with delayed rash after oral challenge
Kwah et al, 2022	117	None
Patel et al, 2022	133	One patient had immediate nausea and itching with penicillin intrapartum without objective data and was re-labeled
Tsao et al, 2024	149	One case of immediate rash after oral challenge and 1 case of delayed rash after oral challenge

Penicillin Allergy Testing is Safe in Pregnancy

Study Author & Year	Number of Patients Tested	Adverse Outcomes
Zhang et al, 2021	65	None
Mak et al, 2022	235	Four cases of delayed rashes classified as benign reported
Nair et al, 2024	251	One case of delayed rash reported
Stephen et al, 2024	46	None
Wong et al, 2024	276	Two cases of mild cutaneous reactions and 1 case of transient abdominal discomfort were reported
Godfrey et al, 2025	267	Three cases of reactions during oral challenge, two subjects with mild rash, on subject developed rash, swelling and vomiting shortly after leaving the clinic
Patrawala et al, 2025	143	No adverse outcomes from testing or reactions reported

Special Populations – Immune Suppression/ Immune Compromise

- Antibiotic prophylaxis is indicated for a variety of conditions to prevent opportunistic infections such as *Pneumocystis jirovecii pneumonia (PJP)* including:
  - HIV
  - Transplant
  - Malignancy
  - Lymphopenia
  - Inborn error of immunity
- Antibiotic use in general may be higher due to increased infection risk

Antibiotic Allergy Testing Improves Outcomes

IMPROVES 1ST LINE ANTIBIOTIC USE

DECREASES COST

PROVIDES CLARITY OF "TRUE" VS "SELF-REPORTED" ALLERGY

J Antimicrob Chemother. 2018 Jul 27;73(11):3209–3211.
Transpl Infect Dis. 2022 Oct;24(5):e13885.
Allergy . 2025 Nov;80(11):3140-3150

"Sulfa Allergy" impedes use of TMP-SMX as first line prophylaxis

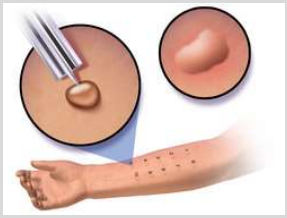
- Trimethoprim-sulfamethoxazole (TMP-SMX) is more efficacious and cost-effective than alternatives for immunosuppressed patients
- Many patients with low-risk history may be de-labeled
  - De-labeling allergy via TMP-SMX challenge pre-transplant showed cost savings of **$254 to $2,910** per patient in post-transplant compared to alternatives
- Those with IgE-mediated allergy may have option for desensitization
- Still need caution with non-IgE mediated/ severe cutaneous reactions

World Allergy Organ J. 2024 Jan 3;17(1):100856.

Transpl Infect Dis. 2022 Oct;24(5):e13885.

To summarize…

Clarifying Antibiotic Allergy Labels is Important!



- Skin testing and oral challenge are useful tools, but **history is the most important**
- The majority of listed medication "allergies" can be de-labeled based on clinical history
- Consider subspecialist evaluation for confirmatory testing when the history is unclear or suggestive of allergy
- Talk with your patients about *why* clarifying antibiotic allergies is important for their health

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