Managing Beta-Lactam Allergies

Approximately 10% of the population reports having an allergy to a penicillin or other beta-lactam antibiotic.[1] However, about 90% of these patients are able to safely tolerate penicillins when re-exposed.[2-7] Guidelines recommend taking steps to proactively delabel penicillin allergy.[8] This can help avoid the use of second-line antibiotics, which may be less effective, more expensive, more toxic, or have a broader spectrum of activity than necessary (which may contribute to antibiotic resistance).[3,4,9,10] Conducting a thorough allergy history is sometimes enough to determine a falsely labeled allergy. It can also help determine which patients can complete desensitization or challenge, or who should undergo skin testing to rule out IgE-mediated antibiotic allergies.[5-7] In patients with a proven penicillin allergy, it is important to know which antibiotics can be safe alternatives. The chart below answers common questions about beta-lactam allergies, cross-reactivity, treatment options, and offers tips for evaluating allergy history with a review of desensitization and challenge protocols.

Clinical Question	Suggested Approach/Pertinent Information

What are the different types of hypersensitivity reactions?	**Immediate/Accelerated Reactions (type I)**: mediated by IgE antibodies.[4]
	• **Immediate**: typically occur within one hour (but could be up to six hours) of medication dose.[1]
	• **Accelerated**: typically occur within one to 72 hours of medication dose.[1]
	• Signs and symptoms could include anaphylaxis, angioedema, drop in blood pressure, itchy rash, hives, swelling of the larynx, and wheezing. Patients may also have GI symptoms (e.g., nausea, vomiting, diarrhea) when the med was administered orally.[1,4]
	Late/Delayed Reactions (type II, III, IV, and idiopathic): non-IgE-mediated reactions
	• **Type II (cytotoxic)**: mediated by IgG or IgM antibodies; onset is hours to days.[4,12]
	  ○ Signs and symptoms include hemolytic anemia, interstitial nephritis, and thrombocytopenia.[1]
	• **Type III (immune complex)**: mediated by IgG and IgM immune complexes, onset is 7 to 21 days.[4,12]
	  ○ Typically presents as serum sickness (rash, joint pain, itching, swollen lymph nodes).[4]
	• **Type IV (cell-mediated)**: delayed reaction with an onset of days to weeks.[4,12]
	  ○ Can present as contact dermatitis, Stevens-Johnson syndrome.[1,12]
	• **Idiopathic Reactions**: Mediated through unknown mechanisms.[13]
	  ○ Typically present as a maculopapular or morbilliform rash.[13]
	  ○ Example is the rash after use of ampicillin or amoxicillin in patients with a viral infection (e.g., Epstein-Barr, cytomegalovirus).[13] Risk appears to be highest in patients who receive ampicillin.[13,14]
	  ○ Patients who develop this rash are likely to be able to tolerate penicillins in the future.[13-15]

Clinical Question	Suggested Approach/Pertinent Information
How should a penicillin allergy be assessed?	• Obtain a thorough allergy history to assess likelihood of a true allergy and to gauge severity.[35] • See our resource for more tips on *Investigating Possible Drug Allergy or Sensitivity*. Consider using a validated clinical decision rule (e.g., PEN-FAST) to identify low-risk penicillin allergies.[16] • Examples of questions to ask the patient include:[13,15] o Please describe the reaction. How was the reaction managed? o How old were you when the reaction occurred? o When did the reaction occur? After the first dose? After the tenth dose? o How was the penicillin administered? Orally? Intravenously? o What other medications were you taking at that time? o When the penicillin was stopped, what happened? o Have you since taken a penicillin (e.g., amoxicillin), cephalosporin (e.g., cephalexin), carbapenem, or monobactam? If yes, what happened? • Document the antibiotic given and its indication, reaction symptoms and their onset, treatment of the reaction, and how long ago the reaction occurred.[4,5,17] • IgE-mediated reaction risk diminishes over time. After ten years, at least 80% do not react and risk may be as low as 1% to 2%.[5,18] • Guidelines recommend delabeling patients with histories that are not consistent with a penicillin allergy (e.g., headache, family history of a penicillin allergy), without the need for allergy testing.[8] o Single treatment-dose challenge with observation can be used for patients who are reluctant (even after counseling) to remove their penicillin allergy from their medical record.[8] • Reactions can occur in patients with viral infections who are on antibiotics (e.g., a rash in a patient with mononucleosis taking amoxicillin). Be careful that these are not mislabeled as allergic reactions.[9,19] These reactions do not indicate a true allergy to the med.[9,19] • Be alert to patients who report being allergic to multiple meds, to try to separate adverse drug reactions and allergic reactions. In general, patients with a penicillin allergy are three times more likely to have an adverse effect to an unrelated drug.[4]

Clinical Question	Suggested Approach/Pertinent Information
How can antibiotic allergic reaction risk be stratified?	• Guidelines place an emphasis on risk stratification based on reaction phenotype.[8] • Consider the reaction symptoms and their severity to help determine the likelihood of true allergy and the risk for subsequent reactions:[5] o **High risk**: anaphylaxis, within minutes to hours of exposure, is IgE-mediated (type I).[5,17,21] ▪ signs and symptoms of anaphylaxis typically affect two or more organ systems and may involve:[5,17] • skin and/or mucosa (angioedema, flushing, and/or hives). • respiratory tract (shortness of breath, stridor, and/or wheezing). • gastrointestinal tract (persistent diarrhea and/or vomiting). • circulatory (hypotension and/or syncope); note isolated hypotension may also indicate anaphylaxis. ▪ positive skin testing, recurrent and/or recent reactions (less than one year ago), or reaction to two or more meds in the same class.[5,21] These reactions are more likely to be IgE-mediated (type 1).[21] • Patients with reactions within the previous three months have a 20% to 50% chance of reacting again upon re-exposure to the med.[3] ▪ **Severe, delayed reactions**: organ involvement (e.g., hepatitis), serum sickness, Stevens-Johnson syndrome, and other reactions occurring several days into therapy.[4,5] • Re-exposure to the med is **contraindicated** with these reactions.[4,22,23] • These late-onset reactions are not IgE-mediated.[3,4] o **Moderate risk**: isolated hives or an IgE-mediated feature (e.g., abdominal pain, or wheezing. o **Low risk**: isolated GI symptoms, headache, mild rash, or itching.
Which beta-lactams have similar R-group side chains?	• Cross-reactivity among beta-lactams is primarily driven by R-group side chains. • Reported cross-reactivity rates vary and range from about 16% to 40% between penicillins and cephalosporins with **identical R-group side chains**.[36] • Cephalosporins with **low R-group side chain similarity** to penicillins (e.g., cefazolin, cefuroxime, and the third-, fourth-, and fifth-generation cephalosporins) have a low risk of cross reactivity with penicillins.[36] • Beta-lactams with identical R-group side chains include:[8,33,36] o amoxicillin, cefadroxil, and cefprozil. o ampicillin, cefaclor, and cephalexin. o aztreonam, ceftazidime, and cefiderocol. • The following cephalosporins share similar R-group side chains:[8,33,41] o cefuroxime and cefoxitin. o ceftriaxone, cefotaxime, cefpodoxime, cefditoren, and cefepime. o cephalexin, cefaclor, and cefadroxil. • Many charts are available online with more information on R-group cross-reactivity (e.g., https://adsp.nm.org/allergy-resources.html).

Clinical Question	Suggested Approach/Pertinent Information
How/when can a patient reporting a penicillin allergy be treated with a penicillin?	• **Low-risk patients**[a] may be appropriate for a direct challenge.[3,5,8] • **Moderate-risk patients**[a] may be appropriate for skin testing if available, or can consider a drug challenge.[3,5] • **High-risk patients,**[a] when the culprit med is required therapy: use desensitization (note that if a patient has a negative skin test, desensitization is not needed).[3,5,24] • Avoid penicillins, including penicillin skin testing, in patients who have a history of **severe NON-IgE-mediated reactions to penicillin, such as type II, III, or IV reactions** (e.g., Stevens-Johnson syndrome, interstitial nephritis, hemolytic anemia).[5,26,31,32] • Patients who have allergic reactions to **piperacillin/tazobactam** may tolerate other penicillins.[8] o Specific piperacillin/tazobactam skin testing may be helpful in these patients when amoxicillin and penicillin skin testing is negative.[8]
What is the likelihood that a penicillin-allergic patient will react to a cephalosporin?	• Data show that between 1% and 4% of patients with a penicillin allergy will have a true allergy to a cephalosporin, much lower than previously suggested.[5,33] More specifically, cross-reactivity with cephalosporins is: o about 0.1% if penicillin reaction was mild or without skin test-confirmed penicillin allergy. o about 2% for patients with a positive penicillin skin test. • Cross-reactivity is primarily driven by R1-group side chains, rather than to the beta-lactam structure itself.[2,8,20] • Historically, cephalosporins were contraindicated in patients with a penicillin allergy. Older studies suggested cross-reactivity between penicillins and cephalosporins was as high as 50%.[35] o Some experts hypothesize that early cephalosporins (pre-1980) may have been contaminated with trace amounts of benzylpenicillin.[33]
Can a patient reporting a penicillin allergy be treated with a cephalosporin?	• Generally, any cephalosporin can be given to patients with a nonanaphylactic history.[3,31,32,37] • For patients with an anaphylactic reaction to penicillin, a non-cross-reactive cephalosporin can be given without prior testing (see above section on similar R-group side chains).[8] • Avoid cephalosporins in patients who have a history of **severe NON-IgE-mediated reactions to penicillin** (e.g., serum sickness, Stevens-Johnson, interstitial nephritis, hemolytic anemia).[31,32]
Can a patient reporting a penicillin or cephalosporin allergy be treated with a carbapenem?	• Cross-reactivity of type I IgE-mediated reactions between penicillins and carbapenems is very low.[36,38-40] • Guidelines suggest that patients with either a penicillin or cephalosporin allergy (even if it was anaphylactic) can be given a carbapenem without testing or precautions.[8] • As with all beta-lactams, carbapenems must be avoided in patients who have a history of **severe NON-IgE-mediated reactions to penicillin** (e.g., serum sickness, Stevens-Johnson, interstitial nephritis, hemolytic anemia).[31,32]

Clinical Question	Suggested Approach/Pertinent Information
Can a patient allergic to penicillin or cephalosporins be treated with aztreonam?	• Aztreonam (a monocyclic beta-lactam) can be administered to patients with allergies to penicillin or cephalosporins (except ceftazidime or cefiderocol) without prior testing.[8,43] o There is potential cross-reactivity with **aztreonam and ceftazidime or cefiderocol**, due to an identical R-group side chain.[8,33,40,44] o Use caution with aztreonam in cystic fibrosis when patients have hypersensitivities to beta-lactam antibiotics.[40,45] Potentially due to exposure to high-dose repetitive antibiotics, these patients can have high rates of beta-lactam hypersensitivity and may have higher rates of cross-reactivity with aztreonam.[45]
What treatment considerations are important for patients reporting a CEPHALOSPORIN allergy?	• Treatments for patients reporting a cephalosporin allergy may be chosen based on R-group side-chain similarities.[8] o Patients with an immediate or accelerated allergy to a cephalosporin should **not** receive a cephalosporin (or aztreonam) with the **same R-group side chain** without cephalosporin skin testing and desensitization to that drug.[8] o A cephalosporin with a **different R-group side chain** may be able to be used safely. • Direct challenge is suggested with cephalosporins with dissimilar side chains in patients with non-anaphylactic cephalosporin allergy.[8] ▪ The use of cephalosporin skin testing, following by either desensitization or drug challenge, is suggested before a parenteral cephalosporin is administered if there is a history of anaphylaxis.[8]
What treatment considerations are important for patients who report a CARBAPENEM allergy?	• Patients with type I reactions to one carbapenem should avoid the use of other carbapenems due to lack of data on cross-reactivity.[46] o Can consider desensitization, if a carbapenem is truly needed (e.g., extended spectrum beta-lactamase producing organisms).[32] • **Low-risk[a] patients** can usually be given a penicillin or cephalosporin.[32] • **Moderate-risk patients** can be given a penicillin or cephalosporin after a direct or graded challenge.[32] • **High-risk[a] patients** can be given a penicillin or a cephalosporin after desensitization.[32]
When are desensitization or drug challenges considered?	• Desensitization and drug challenge are contraindicated for types II, III, IV, and idiopathic reactions (those with organ involvement).[4,20,47] • A **graded drug challenge** may be favored over skin testing in patients with a higher risk for true allergy (e.g., a severe reaction within the previous five years).[4,5,22,24] • **Graded** or **direct drug challenge** are used for patients with a history of non-life-threatening reactions, when there is a low clinical probability of a true drug allergy.[8,49] o **direct challenge (also called one-step)** may be preferred for most patients.[3,8] o patients with multiple drug allergies or significant anxiety may prefer a **graded challenge**.[8] • Be aware that allergists can differ on when to use graded vs direct challenge.[6,7,29,34,37,50-52]

Clinical Question	Suggested Approach/Pertinent Information

What are direct and graded drug challenges?	• For a **direct (one-step) challenge** the antibiotic is given, then the patient is monitored for 30 to 60 minutes.[4,5,47]
	  o For example, for a penicillin allergy, give amoxicillin 250 to 500 mg and observe for one hour.[4,5,47]
	• **A graded challenge** serves as a test dose for gauging allergic reaction risk while minimizing chances for provoking a severe response.[5,8,22]
	  o can be performed by trained clinicians. Close vital sign monitoring and quick access to meds for treating anaphylactic reactions are required.[5]
	  o typically, involves two to three escalating doses, starting with a small percentage of the total dose and building up to the full dose.[5,8,22]
	  ▪ IV: 1% of the dose is given, then 10%, then the full dose. Doses are given 30 to 60 minutes apart.
	  • Use of a smaller initial dose may help offset the potentially higher allergic reaction risk associated with IV administration.
	  ▪ Orally: 10% to 25% of the dose is followed by the full dose 20 to 30 minutes later.[8]
	  o Patient should be monitored for signs of reaction after each dose and have rescue meds readily available.[4,51]
	• Graded challenge procedures vary but generally involve giving two to three rapidly escalating step-wise doses.[5,48] The patient is then monitored for signs of a reaction and if none occurs, treatment proceeds with the full dose.[5,48]
	  o For example, for an oral graded challenge for cephalexin:[48]
	  ▪ Prepare doses using cephalexin oral suspension 250 mg/5 mL.
	  ▪ Give 1/10th of the therapeutic dose (e.g., 50 mg [1 mL] for a target dose of 500 mg).
	  ▪ Observe the patient for 30 minutes.
	  ▪ If there are no signs of an allergic reaction, give the full dose (e.g., 500 mg [10 mL]).
	  ▪ Observe the patient for signs of a reaction for an additional 60 minutes.
	• Patients who don't react during a drug challenge are deemed non-allergic to the med and their medical records should be updated accodingly.[3,15]
	• Patients who develop an acute allergic reaction during a drug challenge should undergo desensitization if the medication is deemed necessary for treatment.[3]
	• A patient-blinded placebo may be administered before starting a graded challenge. This may help reduce the risk of false positive reactions being mistaken as true allergies.[48] This approach is suggested for patients with low-risk reactions (e.g., subjective symptoms) or with multiple reported allergies.[8,48]

Clinical Question	Suggested Approach/Pertinent Information

What is desensitization?	• **Desensitization** temporarily induces tolerance to the culprit antibiotic for a needed treatment course.[15,23,24]
	  ▪ It is reserved for patients at high risk of life-threatening reactions (e.g., history of anaphylaxis).[15]
	  o Desensitization is preferred for patients with compromised cardiac or respiratory status and during pregnancy.[5,22]
	• Due to the risk of serious allergic reaction, desensitization should be performed under supervision of an allergist or specialist, in an ICU or other specialized care area with continuous vital sign monitoring, including rescue meds.[5,15,17,23]
	  o Informed consent must be completed prior to initiation of desensitization.
	• Continuous dose escalations (often 12 or more) are given to increase blood levels of the med without triggering an immune response.[4,15,23,47]
	• Institutions should develop desensitization protocols which standardize the dose escalations given to achieve tolerance of the full dose.[3,5]
	• Published desensitization protocols are available for beta-lactams, carbapenems, sulfonamides, tobramycin, and vancomycin.[3,17,26,47,53-57]

How often does desensitization or graded challenge need to be repeated?	• **Desensitization** induces **temporary** tolerance that lasts only as long as the med is taken continuously.[3,8,21,23]
	  o When the antibiotic treatment is held or discontinued, tolerance is lost and the desensitization procedure must be repeated/restarted if the patient requires further therapy.[3,21]
	  o Educate patients to contact the prescriber for advice on how to proceed if one or more doses are missed. Tolerance is generally maintained through two to five half-lives of the antibiotic.[3]
	  o Lack of allergic response following desensitization does NOT indicate a change in the patient's allergy status.[15]
	  ▪ Ensure patients understand that they are **still allergic** to the med and that desensitization will likely need to be repeated for future treatment courses.[5]
	• Patients who don't have a reaction during **direct or graded challenge** should be considered nonallergic.[5]
	  o Be sure to update allergy info in the patient's medical records to reflect their true allergy status.[5]
	  o Tell patients that they are no longer allergic to the med and that it is safe for them to receive if needed.[5,48]

Clinical Question	Suggested Approach/Pertinent Information
When is allergy skin testing warranted?	• Drug challenge is typically preferred over allergy skin testing (especially in patients with non-anaphylactic reactions or with a history of non-severe cutaneous reactions).[8] • Skin testing is of most value in patients with a history of anaphylaxis or a recent suspected IgE-mediated reaction (e.g., immediate onset urticaria).[8] • Skin testing is suggested for patients with anaphylactic cephalosporin allergy (rare), in addition to drug challenge, prior to administration of penicillin therapy.[8] • Skin testing may permit the preferred beta-lactam antibiotic to be used in a patient who may have had an IgE-mediated reaction, when alternatives are less desirable, as when treating:[5,17,21,24] o methicillin-sensitive *Staph aureus* (MSSA) bacteremia with nafcillin rather than vancomycin.[5,24] o uncomplicated gonorrhea with ceftriaxone instead of broader-spectrum antibiotics.[5,25] o syphilis with penicillin during pregnancy rather than an a less effective alternative.[5,26] • Suggest consideration of delayed intradermal test and/or patch tests to identify culprit drugs when a patient has had a delayed reaction and the offending med is uncertain.[8]
How is skin testing done? *Continued…*	• Skin testing must be done in a controlled setting with close monitoring, including rescue meds (epinephrine, etc).[5] • Medications with antihistamine activity may interfere with skin test interpretation.[22] o Most of these meds should be stopped for at least two to three days before skin testing, but some require longer (e.g., loratadine should be held for at least one week prior).[22] • Skin testing can be performed by specially trained pharmacists, nurses, or physicians.[19,26] o Follow state laws, policies, and procedures for test administration. o To locate an allergist for testing, go to: http://acaai.org/locate-an-allergist. o Use billing code 95018 for percutaneous (scratch, puncture, prick) and intracutaneous/intradermal tests.[11] o Use billing code 95076 (first 120 minutes) and 95079 (for each additional hour) for oral challenge tests.[11] • Skin testing may involve the following:[4,5,22,24] o **Skin prick test** with one or more determinants, a positive control (histamine), and a negative control (saline).[27] ▪ Penicillin: major and minor determinants are *Pre-Pen* and a penicillin (e.g., Penicillin G), respectively.[27] ▪ Other antibiotics: determinant is a nonirritating antibiotic concentration (a 10- to 1,000-fold dilution from full-strength concentration).[22,28] Nonirritating concentrations have been determined for cephalosporins, clindamycin, levofloxacin, macrolides, sulfamethoxazole/trimethoprim, tobramycin, and vancomycin.[22,28] ▪ The patient is observed for 15 minutes, then results are interpreted by measuring any wheals that form. o If the skin prick results are negative or indeterminant, an **intradermal test** may be done with the same determinant(s) and controls. ▪ The patient is observed for 15 minutes, then results are interpreted as with the skin prick test.

Clinical Question	Suggested Approach/Pertinent Information
Skin testing, continued	○ If the intradermal test is negative, the patient may be given a **direct oral challenge** of the med (e.g., amoxicillin) and observed for one hour. ▪ Note that penicillin skin testing is **not recommended** prior to a direct oral challenge of amoxicillin in low-risk (e.g., benign cutaneous reactions) pediatric patients.[8] • **Negative** skin test results may indicate a low chance of a severe allergic reaction, depending on the med tested.[4,17] ○ Only 3% of patients with negative penicillin skin testing will react upon re-exposure to the med.[3,4,17] ○ The predictive value of negative skin testing is less clear for other antibiotics.[3,17,22] • **Positive** skin test results suggest true IgE-mediated allergy to the tested med.[17,29] However, false positives limit its usefulness, since a positive result reflects only a 50% chance of severe reaction upon re-exposure.[24]
How should allergy information be updated in patient profiles?	• Ensure accurate documentation of allergies. ○ This helps ensure effective electronic allergy screenings.[58] ○ Document the exact medication, not a medication class when updating allergies.[58] ○ Add information about which medications the patient has tolerated or any allergy testing/challenges done. ○ Educate patients about their allergies to help keep inaccuracies from being re-added. • Inaccurate allergies could mean exposing patients to less effective, more expensive, more toxic, or unnecessarily broad coverage antibiotics.[58] ○ False penicillin allergy labels can lead to longer hospital stays and increased risk of serious infections.[42] • Allergy information can be updated at any time, but admission and discharge are perfect opportunities to ensure allergy information is current.

Abbreviations: GI = gastrointestinal; IV = intravenous.

a. **Risk of a true IgE-mediated reaction**:[5]
   - **low-risk**: isolated GI symptoms, headache, mild rash, or itching.
   - **moderate-risk**: isolated hives, abdominal pain, or wheezing.
   - **high-risk**: anaphylaxis, positive skin test, recurrent and/or recent reactions (less than one year ago).

b. Note that product labeling for ceftolozane/tazobactam (*Zerbaxa*), a fifth-generation cephalosporin, lists **serious** beta-lactam allergy as a contraindication to use.[30,34]

References

1. Spacek LA. Johns Hopkins Medicine. Johns Hopkins antibiotic ABX guide: beta-lactam allergy. December 11, 2022. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540622/all/Beta_lactam_allergy. (Accessed March 29, 2023).
2. Ledford DK. Cephalosporin administration with a penicillin allergy history. February 2, 2016. https://www.aaaai.org/allergist-resources/ask-the-expert/answers/old-ask-the-experts/cephalosporin-penicillin. (Accessed March 28, 2023).
3. Macy E, Romano A, Khan D. Practical Management of Antibiotic Hypersensitivity in 2017. J Allergy Clin Immunol Pract. 2017 May-Jun;5(3):577-586.
4. Gonzalez-Estrada A, Radojicic C. Penicillin allergy: A practical guide for clinicians. Cleve Clin J Med. 2015 May;82(5):295-300.
5. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019 Jan 15;321(2):188-199.
6. Blumenthal KG, Wickner PG, Hurwitz S, et al. Tackling inpatient penicillin allergies: Assessing tools for antimicrobial stewardship. J Allergy Clin Immunol. 2017 Jul;140(1):154-161.e6.
7. Mill C, Primeau MN, Medoff E, et al. Assessing the Diagnostic Properties of a Graded Oral Provocation Challenge for the Diagnosis of Immediate and Nonimmediate Reactions to Amoxicillin in Children. JAMA Pediatr. 2016 Jun 6;170(6):e160033.
8. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.
9. Jeffres MN, Narayanan PP, Shuster JE, Schramm GE. Consequences of avoiding β-lactams in patients with β-lactam allergies. J Allergy Clin Immunol. 2016 Apr;137(4):1148-1153.
10. Rochester Regional Health. Penicillin skin testing. February 2016. https://www.rochesterregional.org/-/media/files/air/penicillinbrochure.pdf?la=en. (Accessed March 29, 2023).
11. American Academy of Allergy, Asthma, & Immunology. Review 2023 CMS values for commonly used allergy/immunology codes. November 2022. https://www.aaaai.org/Aaaai/media/Media-Library-PDFs/About/Advocacy/2023-Allergy-RVU-values-as-of-November-2022-Edited.pdf. (Accessed April 21, 2023).
12. Marwa K, Kondamudi NP. Type IV hypersensitivity reaction. Updated March 6, 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing: 2023 Jan-.
13. Salkind AR, Cuddy PG, Foxworth JW. The rational clinical examination. Is this patient allergic to penicillin? An evidence-based analysis of the likelihood of penicillin allergy. JAMA. 2001 May 16;285(19):2498-505.
14. Ikediobi NI, Tyring SK. Cutaneous manifestations of Epstein-Barr virus infection. Dermatol Clin. 2002 Apr;20(2):283-9.
15. Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010 Oct;105(4):259-273.
16. Trubiano JA, Vogrin S, Chua KYL, et al. Development and Validation of a Penicillin Allergy Clinical Decision Rule. JAMA Intern Med. 2020 May 1;180(5):745-752.
17. Lieberman P, Nicklas RA, Randolph C, et al. Anaphylaxis--a practice parameter update 2015. Ann Allergy Asthma Immunol. 2015 Nov;115(5):341-84.
18. CDC. Antibiotic prescribing and use: evaluation and diagnosis of penicillin allergy for healthcare professionals. October 31, 2017. https://www.cdc.gov/antibiotic-use/community/for-hcp/Penicillin-Allergy.html. (Accessed March 28, 2023).
19. Wall GC, Peters L, Leaders CB, Wille JA. Pharmacist-managed service providing penicillin allergy skin tests. Am J Health Syst Pharm. 2004 Jun 15;61(12):1271-5.
20. Pichichero ME. A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. Pediatrics. 2005 Apr;115(4):1048-57.
21. Wheatley LM, Plaut M, Schwaninger JM, et al. Report from the National Institute of Allergy and Infectious Diseases workshop on drug allergy. J Allergy Clin Immunol. 2015 Aug;136(2):262-71.e2.
22. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. Ann Allergy Asthma Immunol. 2008 Mar;100(3 Suppl 3):S1-148.
23. Liu A, Fanning L, Chong H, et al. Desensitization regimens for drug allergy: state of the art in the 21st century. Clin Exp Allergy. 2011 Dec;41(12):1679-89.
24. Unger NR, Gauthier TP, Cheung LW. Penicillin skin testing: potential implications for antimicrobial stewardship. Pharmacotherapy. 2013 Aug;33(8):856-67.
25. CDC. Gonorrhea treatment and care. December 1, 2022. https://www.cdc.gov/std/gonorrhea/treatment.htm. (Accessed April 13, 2023).
26. CDC. Sexually transmitted infections treatment guidelines, 2021: managing persons who have a history of penicillin allergy. September 21,2022. https://www.cdc.gov/std/treatment-guidelines/penicillin-allergy.htm. (Accessed March 28, 2023).
27. PRE-PEN. Implementing penicillin allergy skin testing. https://www.penallergytest.com/implementing-penicillin-allergy-skin-testing/. (Accessed April 13, 2023).
28. Empedrad R, Darter AL, Earl HS, Gruchalla RS. Nonirritating intradermal skin test concentrations for commonly prescribed antibiotics. J Allergy Clin Immunol. 2003 Sep;112(3):629-30.

29. Kuruvilla M, Thomas J. Direct oral amoxicillin challenge without antecedent penicillin skin testing in low-risk patients. Ann Allergy Asthma Immunol. 2018 Nov;121(5):627-628.
30. Product information for Zerbaxa. Merck Sharp & Dohme. Rahway, NJ 07065. May 2022.
31. Blumenthal KG, Shenoy ES, Wolfson AR, et al. Addressing Inpatient Beta-Lactam Allergies: A Multihospital Implementation. J Allergy Clin Immunol Pract. 2017 May-Jun;5(3):616-625.e7.
32. University of Wisconsin Health. Treatment of patients with reported allergies to beta-lactam antibiotics – adult – inpatient clinical practice guideline. September 2016. https://www.uwhealth.org/cckm/cpg/infection-and-isolation/Treatment-of-Patients-with-Reported-Allergies-to-Beta-Lactam-Antibiotics---Adult---Inpatient-16.09.20.pdf. (Accessed March 28, 2023).
33. Chaudhry SB, Veve MP, Wagner JL. Cephalosporins: A Focus on Side Chains and β-Lactam Cross-Reactivity. Pharmacy (Basel). 2019 Jul 29;7(3):103.
34. Product monograph for Zerbaxa. Merck Canada. Kirkland, QC H9H 4M7. October 2020.
35. Daulat S, Solensky R, Earl HS, et al. Safety of cephalosporin administration to patients with histories of penicillin allergy. J Allergy Clin Immunol. 2004 Jun;113(6):1220-2.
36. Picard M, Robitaille G, Karam F, et al. Cross-Reactivity to Cephalosporins and Carbapenems in Penicillin-Allergic Patients: Two Systematic Reviews and Meta-Analyses. J Allergy Clin Immunol Pract. 2019 Nov-Dec;7(8):2722-2738.e5.
37. Macy E, Blumenthal KG. Are Cephalosporins Safe for Use in Penicillin Allergy without Prior Allergy Evaluation? J Allergy Clin Immunol Pract. 2018 Jan-Feb;6(1):82-89.
38. Saxon A, Adelman DC, Patel A, et al. Imipenem cross-reactivity with penicillin in humans. J Allergy Clin Immunol. 1988 Aug;82(2):213-7.
39. Romano A, Viola M, Gueant-Rodriguez RM, et al. Imipenem in patients with immediate hypersensitivity to penicillins. N Engl J Med. 2006 Jun 29;354(26):2835-7.
40. Frumin J, Gallagher JC. Allergic cross-sensitivity between penicillin, carbapenem, and monobactam antibiotics: what are the chances? Ann Pharmacother. 2009 Feb;43(2):304-15.
41. Chaudhry SB, Veve MP, Wagner JL. Cephalosporins: A Focus on Side Chains and β-Lactam Cross-Reactivity. Pharmacy (Basel). 2019 Jul 29;7(3):103.
42. 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 Mar;133(3):790-6.
43. Clinical Pharmacology powered by ClinicalKey. Tampa (FL): Elsevier. 2023. http://www.clinicalkey.com. (Accessed April 13, 2023).
44. Robinson JL, Hameed T, Carr S. Practical aspects of choosing an antibiotic for patients with a reported allergy to an antibiotic. Clin Infect Dis. 2002 Jul 1;35(1):26-31.
45. Moss RB. Sensitization to aztreonam and cross-reactivity with other beta-lactam antibiotics in high-risk patients with cystic fibrosis. J Allergy Clin Immunol. 1991 Jan;87(1 Pt 1):78-88.
46. Noguerado-Mellado B, Pinto Fernandez C, Pineda-Pineda R, et al. Cross-reactivity between carbapenems: two case reports. J Allergy Clin Immunol Pract. 2014 Nov-Dec;2(6):816-7.
47. Castells M. Rapid desensitization for hypersensitivity reactions to medications. Immunol Allergy Clin North Am. 2009 Aug;29(3):585-606.
48. Iammatteo M, Ferastraoaru D, Koransky R, et al. Identifying Allergic Drug Reactions Through Placebo-Controlled Graded Challenges. J Allergy Clin Immunol Pract. 2017 May-Jun;5(3):711-717.e2.
49. Iammatteo M, Alvarez Arango S, Ferastraoaru D, et al. Safety and Outcomes of Oral Graded Challenges to Amoxicillin without Prior Skin Testing. J Allergy Clin Immunol Pract. 2019 Jan;7(1):236-243.
50. Gaeta F, Valluzzi RL, Alonzi C, et al. Tolerability of aztreonam and carbapenems in patients with IgE-mediated hypersensitivity to penicillins. J Allergy Clin Immunol. 2015 Apr;135(4):972-976.
51. Kelso JM. Provocation Challenges to Evaluate Amoxicillin Allergy in Children. JAMA Pediatr. 2016 Jun 6;170(6):e160282.
52. Wall GC, Nayima VA, Neumeister KM. Assessment of hypersensitivity reactions in patients receiving carbapenem antibiotics who report a history of penicillin allergy. J Chemother. 2014 Jun;26(3):150-3.
53. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for Pneumocystis Carinii pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. J Infect Dis. 2001 Oct 15;184(8):992-7.
54. Gorman SK, Zed PJ, Dhingra VK, Ronco JJ. Rapid imipenem/cilastatin desensitization for multidrug-resistant Acinetobacter pneumonia. Ann Pharmacother. 2003 Apr;37(4):513-6.
55. Wilson DL, Owens RC Jr, Zuckerman JB. Successful meropenem desensitization in a patient with cystic fibrosis. Ann Pharmacother. 2003 Oct;37(10):1424-8.
56. Spigarelli MG, Hurwitz ME, Nasr SZ. Hypersensitivity to inhaled TOBI following reaction to gentamicin. Pediatr Pulmonol. 2002 Apr;33(4):311-4.
57. Wazny LD, Daghigh B. Desensitization protocols for vancomycin hypersensitivity. Ann Pharmacother. 2001 Nov;35(11):1458-64.
58. Shands at the University of Florida. Drug & Therapy Bulletin: the importance of accurate drug allergy information. May 2010. http://professionals.ufhealth.org/files/2011/11/0510-drugs-therapy-bulletin.pdf. (Accessed March 28, 2023).

Cite this document as follows: **Clinical Resource,** ***Managing Beta-Lactam Allergies. Pharmacist's Letter/Pharmacy Technician's Letter/Prescriber's Letter.*** **May 2023. [390503]**