

Of all the drugs on the market, beta-lactams (and penicillin in particular) seem to be most implicated in allergic reactions. However, such allergy is over-reported.

Clinical Pearls

1. Delayed rashes caused by penicillin, **if after first few doses/days & no itchiness/hives**, are not typically indicative of a true IgE-mediated allergy. A beta-lactam, such as a cephalosporin, can usually be given.
2. When possible, refer patients with uncertain penicillin allergy for **skin testing**. Skin testing is especially helpful when the allergy history is unclear, when the reaction took place >10 years ago, or when the reaction occurred days rather than hours after taking the antibiotic.
3. When the risk of true penicillin allergy is low, **a graded challenge** using a cephalosporin with a dissimilar side-chain is appropriate.

Definitions

- **Beta-lactams**: group of antibiotics with a distinctive beta-lactam ring; includes penicillins, cephalosporins, and carbapenems. Allergy may occur to either the beta-lactam ring (in which case a patient is allergic to all beta-lactams) or to the unique side chain (in which case the allergy is only to specific agents).
- **IgE**: immunoglobulin type E antibody. After encountering a specific allergen, IgE antibodies can trigger an immune response.¹⁰
- **"True" IgE-mediated allergy**: potentially life-threatening reaction; also known as a type-1 immediate hypersensitivity reaction. Symptoms are described below in "Management of Penicillin Allergy". Anaphylaxis describes the most severe form of reaction.¹¹
- **Graded challenge**: some variation in approaches, but often a small dose of a potential allergen (e.g. 10% of the full dose) is given, followed by the full dose 1 hour later.⁷ {NOTE: **in the in-patient setting**, inappropriate consideration of penicillin allergy resulting in use of vancomycin or clindamycin may create suboptimal outcomes. Often a beta-lactam can be used. Take advantage of the inpatient status to confirm/monitor as necessary.}
- **Desensitization**: similar to the graded challenge, but at a slower pace (e.g. starting at 1/10,000th of the full dose). A sample protocol for an oral desensitization is here: www.cdc.gov/std/tg2015/pen-allergy.htm and an intravenous approach may be found in the **Online Extras** .
- **Penicillin skin-testing**: pricking the skin with a minute quantity of penicillin; if a localized reaction not observed, an IgE-mediated allergy is unlikely.⁵

How likely is a beta-lactam allergy?

10,000	In a given group of 10,000 patients:
1,000	⇒ will report they have a penicillin allergy, ¹
<100	⇒ will have a true IgE-mediated penicillin allergy, ²
1 to 3	⇒ will have cephalosporin cross-reactivity, ³
1	⇒ will have anaphylaxis when given penicillin. ⁴

Table 1: Factors that decrease the likelihood of a true IgE-mediated allergy

- **Skin test is negative**: this provides a 97-99% certainty that the patient is not allergic.⁵
- **Age**: **80% of patients** with a reaction that occurred **>10 years ago** will no longer be allergic to penicillin.¹
- **Administration**: reactions reported from oral administration are less likely to be true allergies.
- **Symptoms**: see below for how IgE-mediated symptoms differ from other beta-lactam reactions.
- **Timing**: **if reaction occurred after days to weeks of taking antibiotic, it is unlikely to be IgE-mediated.**¹¹

Management of Penicillin Allergy

After a reaction to penicillin, can a beta-lactam be prescribed in the future? The answer requires accurate differentiation between three types of beta-lactam adverse reactions.

Penicillin Adverse Event	Serious Penicillin Adverse Event	True IgE-Mediated Penicillin Allergy
e.g. rash, GI upset, headache. A diffuse rash, which is not itchy, occurs in ≤10% of patients taking penicillin, usually after 2-5 days of therapy, and may last several weeks. ¹² These reactions are <u>not</u> IgE-mediated.	e.g. Stevens-Johnson syndrome, interstitial nephritis, hemolytic anemia, serum sickness*. These reactions usually occur >72hrs after beta-lactam dose. ¹¹ They are <u>not</u> IgE-mediated.	At minimum, presents as an itchy rash or hives. More severe symptoms include angioedema, hypotension, or bronchospasm. These reactions can be life-threatening and usually occur <1hr after taking a beta-lactam dose. ⁹⁻¹¹ Anaphylaxis describes the most severe form of reaction.
<ul style="list-style-type: none"> • An uncomplicated rash, a headache, or GI upset is not IgE-mediated, and so a cephalosporin or different penicillin may be prescribed. • Amoxicillin has a high risk of rash when given during some viral infections, such as infectious mononucleosis (e.g. Epstein-Barr virus, cytomegalovirus); however this is <u>not</u> an allergy.⁸ 	<ul style="list-style-type: none"> • All beta-lactams are contraindicated. Prescribe an alternative agent. • Skin testing, desensitization, and graded challenges are all potentially harmful and not recommended.⁸ 	<ol style="list-style-type: none"> 1. Skin test if possible, especially if reaction was many years ago. If the skin test result is negative, cephalosporins may be given safely & penicillins may be given with minimal risk.^{AAAA/ACAAI (D)} Consider administering the first dose via graded challenge if previous severe reaction. If the skin test result is positive, OR skin testing is unavailable, a cephalosporin graded challenge may be appropriate if patient factors described in Table 1 point away from IgE-mediated. A cephalosporin with a dissimilar side chain is preferred (see below).¹²⁻¹⁵ 2. Otherwise, prescribe an alternative agent. 3. If no good alternative agents, initiate a cephalosporin desensitization procedure.
Similar side chains (Canada):		
penicillin VK and cefoxitin amoxicillin, ampicillin, cefadroxil, cephalixin, cefaclor, and cefprozil cefepime, ceftriaxone, and cefotaxime cefuroxime and cefoxitin ceftazidime and aztreonam Of note: cefazolin has a unique side chain dissimilar to all other beta-lactams		

Additional Information:

- **Cephalosporin allergy management**: similar to penicillins, but less studied.
 - 1 GI upset, headache, or rash (without hives/itch) are not signs of true IgE-mediated allergy and a beta-lactam may be prescribed;
 - 2 Serious adverse events (e.g. Stevens-Johnson syndrome, interstitial nephritis, hemolytic anemia, serum sickness) are contraindications to any beta-lactam;
 - 3 If allergy is likely IgE-mediated, skin test (if possible) using a cephalosporin with a different side chain than the cephalosporin that previously reacted. **If no reaction**, give a graded challenge; **if reaction, or if skin testing not available**, use an alternative agent (or desensitization).¹²⁻¹⁵
- **Skin tests in Saskatchewan are available via referral** (currently <6 month waiting list²⁰¹⁷). Encouraged for all with questionable allergies. Cost to patient: ~\$20.
- **Cross-sensitivity data**: Cephalosporin and penicillin cross-sensitivity rate was at first thought to be up to 10%; however this was due to penicillin contamination in cephalosporin products and the true rate is likely 1-3%.^{3,7} Evidence suggests that carbapenems have a ~1% cross-reactivity with penicillins, and are appropriate in penicillin allergies any time a cephalosporin could be prescribed.¹⁶ Aztreonam does not typically have cross-reactivity with penicillins, and so can be prescribed safely even in patients with a history of true IgE-mediated penicillin allergy.²

***Serum sickness reactions:** These are more common than the other serious reactions listed. Generally, these occur after 7-10 days of therapy and relate to immune complexes of IgG. Symptoms include urticarial vasculitis, renal dysfunction and joint pain. Skin testing is not helpful. Challenges and desensitization are contraindicated.

Desensitization template¹⁷

The goal of desensitization is to gradually increase the rate of antibiotic such that immune response is altered, and temporary tolerance is conferred. A 12-step protocol is commonly used, starting with a very low concentration of antibiotic (e.g. 1/50,000) and gradually increasing to target dose every 15 minutes.

Obtain patient consent prior to protocol start. Throughout the protocol, take vitals every 15 minutes (q30 minutes during last step). At conclusion of protocol, observe patient carefully for 30 minutes - then can give full therapeutic dose at usual schedule.

If patient has a severe reaction during protocol (e.g. hypotension, throat swelling, bronchospasm), stop the infusion and treat with **epinephrine** 0.3mg IM, **diphenhydramine** 50mg IV and **methylprednisolone** 50mg IV, 2 puffs of inhaled **salbutamol** 100mcg (if bronchospasm), and IV fluids.

Step 1	1/50,000 th	of usual dose given over 15 minutes
Step 2	1/20,000 th	of usual dose given over 15 minutes
Step 3	1/10,000 th	of usual dose given over 15 minutes
Step 4	1/5,000 th	of usual dose given over 15 minutes
Step 5	1/2,000 th	of usual dose given over 15 minutes
Step 6	1/1,000 th	of usual dose given over 15 minutes
Step 7	1/500 th	of usual dose given over 15 minutes
Step 8	1/250 th	of usual dose given over 15 minutes
Step 9	1/100 th	of usual dose given over 15 minutes
Step 10	1/50 th	of usual dose given over 15 minutes
Step 11	1/25 th	of usual dose given over 15 minutes
Step 12	~90%	of usual dose given slowly over ~3 hours

Sample Desensitization Protocol for Ceftriaxone (adapted with permission from the Saskatoon Health Region)1. Prepare Solutions **One**, **Two**, and **Three**

			Total mg per bag	Amount of bag infused
Solution One	250 mL of	0.08 mg/mL	20mg	9.25 mL*
Solution Two	250 mL of	0.8 mg/mL	200mg	18.75 mL*
Solution Three	250 mL of	8 mg/mL	2000mg	248 mL

* Discard unused portions of the minibag

2. Infuse Solutions as follows:

Dose Number	Solution Number	Infusion Rate (mL/hr)	Time	Volume Infused	Dose Administered	Cumulative Dose
Step 1	Solution One	2	15 minutes	0.5 mL	0.04 mg	0.04 mg
Step 2		5	15 minutes	1.25 mL	0.1 mg	0.14 mg
Step 3		10	15 minutes	2.5 mL	0.2 mg	0.34 mg
Step 4		20	15 minutes	5 mL	0.4 mg	0.74 mg
Step 5	Solution Two	5	15 minutes	1.25 mL	1 mg	1.74 mg
Step 6		10	15 minutes	2.5 mL	2 mg	3.74 mg
Step 7		20	15 minutes	5 mL	4 mg	7.74 mg
Step 8		40	15 minutes	10 mL	8 mg	15.74 mg
Step 9	Solution Three	10	15 minutes	2.5 mL	20 mg	35.74 mg
Step 10		20	15 minutes	5 mL	40 mg	75.74 mg
Step 11		40	15 minutes	10 mL	80 mg	155.74 mg
Step 12		80	175 minutes	230.5 mL	1844 mg	2000 mg

Total time = 338 minutes = 5 hours 38 minutes

1. CDC. Get Smart Fact Sheet: is it really a penicillin allergy? <https://www.cdc.gov/getsmart/week/downloads/getsmart-penicillin-factsheet.pdf> (Accessed March 15, 2017).
2. Joint Task Force on Practice Parameters representing the 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
3. American Academy of Allergy Asthma & Immunology. Cephalosporin administration to patients with a history of penicillin allergy. www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/Cephalosporin-administration-2009.pdf. (Accessed March 15, 2017).
4. Allergic reactions to long-term benzathine penicillin prophylaxis for rheumatic fever. International Rheumatic Fever Study Group. *Lancet*. 1991 Jun 1;337(8753):1308-10.
5. Forrest DM, Schellenberg R, Thien VV, et al. Introduction of a practice guideline for penicillin skin testing improves the appropriateness of antibiotic therapy. *Clin Infect Dis* 2001;32:1685-90.
6. DiPiro JT. Allergic and pseudoallergic drug reactions. *Pharmacotherapy: A Pathophysiologic Approach*. 7th ed. DiPiro JT, Talbert RL, Yee GC, et al, eds. New York, NY: McGraw-Hill; 2008;1447-1482
7. Solensky R, Banerji A, Bloomberg GR, et al. Cephalosporin administration to patients with a history of penicillin allergy. May 1, 2009. <http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/Cephalosporin-administration-2009.pdf> (Accessed March 15, 2017).
8. 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;285:2498-505.
9. Rochester Regional Health. Penicillin skin testing. February 2016. <https://www.rochesterregional.org/-/media/files/air/penicillinbrochure.pdf?la=en> (Accessed March 15, 2017).
10. Gonzalez-Estrada A, Radojicic C. Penicillin allergy: a practical guide for clinicians. *Cleve Clin J Med* 2015;82:295-300.
11. Spacek LA, Adkinson NF. Johns Hopkins Medicine. Johns Hopkins antibiotic (abx) guide: beta-lactam allergy. January 2014. https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540622/all/Beta_lactam_allergy (Accessed March 15, 2017).
12. Macy E and Ngor E. Recommendations for the Management of Beta-Lactam Intolerance. *Clinic Rev Allerg Immunol* 2014; 47:46-55
13. Blondel-Hill and Fryters. B-Lactam Allergy. *Bugs and Drugs: An antimicrobial/infectious disease reference*. 2012:87-90.
14. PL Detailed-document, Allergic Cross-reactivity Among Beta-lactam Antibiotics: An Update. *Pharmacist's Letter/Prescriber's Letter*. October 2013
15. Terico AT and Gallagher JC. Beta-lactam allergy and cross-reactivity. *J Pharm Pract*. 2014 Dec;27(6):530-44.
16. Romano A, Viola M, Gueant-Rodriguez RM, et al. Imipenem in patients with immediate hypersensitivity to penicillins. *N Engl J Med* 2006;354:2835-7. Solensky R, Banerji A, Bloomberg GR, et al. Cephalosporin administration to patients with a history of penicillin allergy. May 1, 2009.
17. Brennan PJ, Bouza TR, Hsu FI, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allerg Clin Immunol* 2009; 124:1259.