

Beta-lactam Antibiotic Cross-Reactivity Chart Education

Beta-lactams are the first-line class of antibiotics for the treatment of many common infectious disease states, with penicillins, cephalosporins, carbapenems, and monobactams being the four major sub-classes. An allergy to penicillin is the most common drug allergy documented in medical records, with reported rates ranging from 6 to 25% of hospitalized patients with documented allergies,^{1,2} and 10% in the general population.^{3,4} However, literature suggests that in patients with a reported penicillin allergy, 99% do not have a true allergy and can safely tolerate beta-lactam antibiotics.⁴ Documented reactions for penicillins also vary, ranging from unknown childhood reactions to benign cutaneous reactions such as urticaria and maculopapular rash, to severe IgE-mediated anaphylactic reactions such as angioedema.^{5,6} Insufficient documentation and/or unclear historical information provided by patients contribute to the lack of clarity surrounding the details and timing of documented allergies. This often results in providers avoiding the beta-lactam class entirely or selecting agents such as carbapenems due to being perceived as safer options in the setting of a penicillin allergy.

Studies have shown that the use of non-beta-lactam agents in certain scenarios is associated with poor outcomes. Clinical failure rates are higher in patients with Gram-negative bloodstream infections receiving non-beta-lactam therapy,⁷ and patients with documented penicillin allergies have an increased risk of MRSA and *C. difficile* infection due to receiving non-beta-lactam antibiotics.⁸ Increased hospital length of stay and development of antimicrobial resistance are also associated with the utilization of non-beta-lactam agents,² and patients with reported penicillin allergies have a 50% increased odds of surgical site infection that is attributed to the utilization of second-line perioperative antibiotics.⁹

Documented allergies to cephalosporins are less commonly encountered. An estimated 1 to 3% of the population has a listed allergy to a cephalosporin,³ with studies demonstrating exceedingly low reported anaphylaxis rates of <0.0001% to 0.1%.^{10,11} Cross-reactivity amongst penicillins and cephalosporins and within the individual classes is primarily due to a specific structural component, the R1 side chain, rather than a class effect.^{12,13} Rates of cross-reactivity between beta-lactams with identical R1 side chains occurs in up to 38% of patients with immediate or anaphylactic hypersensitivity reactions but is lower for non-anaphylactic reactions.¹⁴ Among beta-lactams with dissimilar side chains, the reported rate of cross-reactivity drops to <2%. Overall, cross reactivity between cephalosporins and penicillins is significantly lower than historically reported rates of 10% and can be managed by consideration of structure.

There are many studies evaluating the clinical benefits of assessing patient allergies, optimizing allergy alerts for beta-lactams, and providing references for which beta-lactams are appropriate for use depending on their side chains. Collectively, these interventions have resulted in an increase in utilization of beta-lactams, a decrease in 30-day hospital readmissions,¹⁵ a decrease in *C. difficile* infections,¹⁶ and a decrease in clinical failure rate.⁵ Because of these successes, Baptist Health will employ similar tactics with an aim to optimize care for our patients with beta-lactam allergies.

An Epic update will go live that will suppress allergy cross-reactivity alerts between different classes of beta-lactam antibiotics if the reported reactions are “itching,” “rash,” and/or “unknown.” The chart below is a reference for which beta-lactams share similar side chains. This may be used to guide clinical decisions surrounding which antibiotics are appropriate to use in patients with specific beta-lactam allergies.

		Antibiotic Allergy																				
		Amoxicillin ± clavulanate	Ampicillin ± sulbactam	Aztreonam	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefepime	Cefotaxime	Cefoxitin	Cefpodoxime	Ceftaroline	Ceftazidime ± avibactam	Ceftolozane/tazobactam	Ceftriaxone	Cefuroxime	Cephalexin	Nafcillin	Penicillin G	Piperacillin/tazobactam	
Antibiotic Ordered	Amoxicillin or amoxicillin/clavulanate	Black	Red	Green	Yellow	Red	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Yellow	Green	Yellow	Green
	Ampicillin or ampicillin/sulbactam	Red	Black	Green	Red	Yellow	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Red	Green	Yellow	Green
	Aztreonam	Green	Green	Black	Green	Green	Green	Yellow	Yellow	Yellow	Green	Yellow	Yellow	Red	Yellow	Yellow	Green	Green	Green	Green	Green	Green
	Cefaclor	Yellow	Red	Green	Black	Yellow	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Red	Yellow	Yellow	Green
	Cefadroxil	Red	Yellow	Green	Yellow	Black	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Yellow	Green	Yellow	Green
	Cefazolin	Green	Green	Green	Green	Green	Black	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
	Cefdinir	Green	Green	Yellow	Green	Green	Green	Black	Yellow	Yellow	Green	Yellow	Yellow	Yellow	Yellow	Yellow	Green	Green	Green	Green	Green	Green
	Cefepime	Green	Green	Green	Green	Green	Green	Yellow	Black	Red	Green	Red	Yellow	Yellow	Yellow	Yellow	Red	Yellow	Green	Green	Green	Green
	Cefotaxime	Green	Green	Yellow	Green	Green	Green	Yellow	Red	Black	Yellow	Red	Yellow	Yellow	Yellow	Yellow	Red	Yellow	Green	Green	Green	Green
	Cefoxitin	Green	Green	Green	Green	Green	Green	Green	Green	Yellow	Black	Green	Green	Green	Green	Green	Green	Red	Green	Yellow	Green	Green
	Cefpodoxime	Green	Green	Yellow	Green	Green	Green	Yellow	Red	Red	Green	Black	Yellow	Yellow	Yellow	Yellow	Red	Yellow	Green	Green	Green	Green
	Ceftaroline	Green	Green	Yellow	Green	Green	Green	Yellow	Red	Red	Green	Yellow	Black	Yellow	Yellow	Yellow	Yellow	Yellow	Green	Green	Green	Green
	Ceftazidime or ceftazidime/avibactam	Green	Green	Red	Green	Green	Green	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Black	Red	Yellow	Green	Green	Green	Green	Green	Green
	Ceftolozane/tazobactam	Green	Green	Yellow	Green	Green	Green	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Black	Yellow	Green	Green	Green	Green	Green	Green
	Ceftriaxone	Green	Green	Yellow	Green	Green	Green	Yellow	Red	Red	Green	Red	Yellow	Yellow	Yellow	Yellow	Black	Yellow	Green	Green	Green	Green
	Cefuroxime	Green	Green	Green	Green	Green	Green	Yellow	Yellow	Red	Yellow	Yellow	Yellow	Yellow	Yellow	Yellow	Black	Yellow	Green	Green	Green	Green
	Cephalexin	Yellow	Red	Green	Red	Yellow	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Black	Green	Yellow	Yellow
	Nafcillin	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Black	Green	Green
	Penicillin G	Yellow	Yellow	Green	Yellow	Yellow	Green	Green	Green	Green	Green	Yellow	Green	Green	Green	Green	Green	Green	Yellow	Green	Black	Yellow
Piperacillin/tazobactam	Yellow	Yellow	Green	Yellow	Yellow	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Yellow	Green	Yellow	Black	
MAY USE	Expect <2% chance of cross-reactivity																					
USE WITH CAUTION	Intermediate or conflicting data—exercise clinical judgement <ul style="list-style-type: none"> • May consider utilizing agent if patient reaction is not a type-1 hypersensitivity reaction* • May consider switching agent to a “Green” agent, or other alternative agent if reaction is a type-1 hypersensitivity reaction* 																					
AVOID USE	Expect ~20% chance of cross-reactivity for rash, ~40% chance for Type 1 hypersensitivity reaction*																					

* Type 1 hypersensitivity reaction is defined as an immediate allergic reaction occurring within 15-30 minutes after receiving a dose of a beta-lactam antibiotic. Symptoms can consist of anaphylaxis (including angioedema), neurologic deficits (lightheadedness, weakness, loss of consciousness), respiratory complications (shortness of breath, wheezing, bronchospasm, stridor, hypoxia), and/or cardiovascular complications (hypotension, tachycardia).

KEY TAKEAWAYS

- Use of non-beta-lactam antibiotics is often associated with poor outcomes.
- Of patients with a documented penicillin allergy, 99% can tolerate beta-lactam antibiotics.
- Rates of anaphylaxis to cephalosporins range from <0.0001% to 0.1%.
- Cross-reactivity between penicillins and cephalosporins is due to similarities in R1 side chains, rather than a class effect.
- Reported rate of cross reactivity is <2% among beta-lactams with dissimilar side chains.
- Cefazolin has a unique side chain that does not share similarities with other beta-lactam antibiotics and therefore has no expected cross-reactivity.
- Due to dissimilar side chains, patients with a documented penicillin allergy usually tolerate ceftriaxone and cefepime.

References:

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