

Management of Penicillin and Beta-Lactam Allergy

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, September 2017)

Key Points

- Beta-lactams are generally safe; allergic and adverse drug reactions are over diagnosed and **over reported**
- Nonpruritic, nonurticarial rashes occur in up to 10% of patients receiving penicillins. These rashes are usually not allergic and are not a contraindication to the use of a different beta-lactam
- The frequently cited risk of 8 to 10% cross-reactivity between penicillins and cephalosporins is an overestimate based on studies from the 1970's that are now considered flawed
- Expect new intolerances (i.e. any allergy or adverse reaction reported in a drug allergy field) to be reported after 0.5 to 4% of all antimicrobial courses depending on the gender and specific antimicrobial. Expect a higher incidence of new intolerances in patients with three or more prior medication intolerances¹
- For type-1 immediate hypersensitivity reactions (IgE-mediated), cross-reactivity among penicillins (table 1) is expected due to similar core structure and/or major/minor antigenic determinants, use not recommended without desensitization
- For type-1 immediate hypersensitivity reactions, cross-reactivity between penicillins (table 1) and cephalosporins is due to similarities in the side chains; risk of cross-reactivity will only be significant between penicillins and cephalosporins with similar side chains
- Only type-1 immediate hypersensitivity to a penicillin manifesting as anaphylaxis, bronchospasm, angioedema, hypotension, urticaria or pruritic rash warrant the avoidance of cephalosporins with similar side chains and other penicillins
- Patients with type-1 immediate hypersensitivity to a penicillin may be safely given cephalosporins with side chains unrelated to the offending agent (**See figure 1 & 2 below**)
 - For example, ceFAZolin does not share a side chain with any beta-lactam and is not expected to cross react with other agents
- Cross-reactivity between cephalosporins is low due to the heterogeneity between side chains; therefore, a patient with a cephalosporin allergy may be prescribed another cephalosporin with a dissimilar side chain
- Cross-reactivity between penicillins and carbapenems is low. Carbapenems would be a reasonable option when antibiotics are required in patients with type-1 immediate hypersensitivity reaction to penicillins
- Patients with reported Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, immune hepatitis, hemolytic anemia, serum sickness or interstitial nephritis secondary to beta-lactam use should avoid beta-lactams and not receive beta-lactam skin testing, re-challenging or desensitization
- Penicillin skin tests can be used to predict penicillin sensitivity and have a 97-99% negative predictive value
- Any patient with possibility of type-1 immediate hypersensitivity to a beta-lactam should be referred for allergy confirmation

Management of the Beta-Lactam Allergy (Figure 1 & Figure 2)^{1,2,3,4}

1. Avoid the unnecessary use of antimicrobials, particularly in the setting of viral infections.
2. Complete a thorough investigation of the patient's allergies, including, but not limited to: the specific drug the patient received, a detailed description of the reaction, temporal relationship of the onset of the reaction with respect to when the drug was given, concomitant drugs received when the reaction occurred, the time elapsed since the reaction occurred and tolerability of any structurally related compounds. If the patient:
 - a. reports **intolerance** (e.g. nausea, vomiting, diarrhea, headache) – likely **not allergic**, attempt beta-lactam therapy
 - b. has a documented **severe non-IgE mediated** hypersensitivity reaction to a beta-lactam (e.g. interstitial nephritis, immune hepatitis, hemolytic anemia, serum sickness, severe cutaneous reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), etc...) – **avoid all beta-lactam antibiotics** including their use for allergy testing, desensitization and re-challenge.
 - Treatment options include non-beta-lactam antibiotics
 - c. has a documented **severe type-1 immediate (IgE-mediated)** hypersensitivity reaction to a penicillin (e.g. anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritis) – avoid other penicillins and cephalosporins with similar side chain, unless patient undergoes desensitization.
 - Treatment options include cephalosporins with dissimilar side chains or carbapenems or non-beta-lactam antibiotics – Note: ceFAZolin **does not** share a side chain with any beta-lactam agent.
 - d. has a documented **severe type-1 immediate (Ige-mediated)** hypersensitivity reaction to a cephalosporin (e.g. anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritis) – avoid cephalosporins with similar side chains and penicillins with similar side chains (see figure 2) unless desensitization is performed.
 - Treatment options include penicillins with dissimilar side chains, cephalosporins with dissimilar side chains, carbapenems or non-beta-lactam antibiotics.

Figure 1: Management Diagram

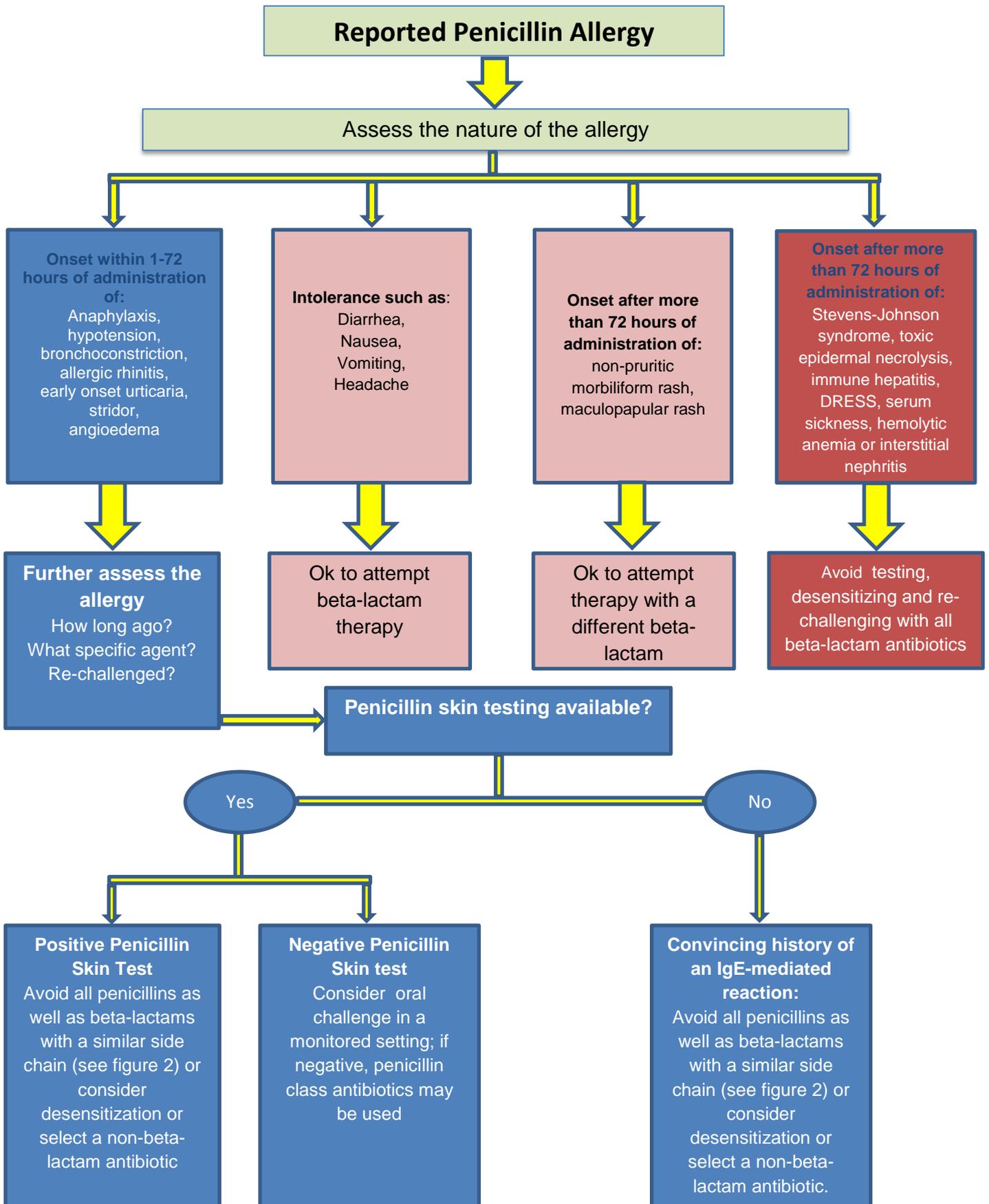


Figure 2: Matrix of Beta-Lactam Cross Allergy (based on similar core and/or side chains) ^{5,6,7,8,9}:

Each ‘*’ in the matrix indicates side-chain and/or major/minor antigenic similarity between two antibiotics. For type-1 immediate hypersensitivity there is a risk of cross-allergenicity between pairs due to similar side-chains and/or major/minor antigenic determinants, use NOT recommended without desensitization.

For example: a patient allergic to amoxicillin would likely manifest a reaction to ampicillin, cloxacillin, piperacillin, ticarcillin, cefadroxil, cephalixin, cefaclor and cefprozil but NOT to ceFAZolin, cefuroxime or ceFTRIAXone, etc.

		Beta-lactam cross-allergy																							
		penicillin	amoxicillin	ampicillin	cloxacillin	piperacillin	ticarcillin	cefadroxil	ceFAZolin	cephalexin	cephalothin	cefaclor	cefprozil	cefuroxime	cefOXitin	cefixime	cefotaxime	cefTAZidime	ceFTRIAXone	cefepime	meropenem	imipenem	ertapenem	aztreonam	
PENICILLINS	penicillin	*	*	*	*	*	*				*				*										
	amoxicillin	*	*	*	*	*	*	*		*		*	*												
	ampicillin	*	*	*	*	*	*	*		*		*	*												
	cloxacillin	*	*	*	*	*	*																		
	piperacillin	*	*	*	*	*	*																		
	ticarcillin	*	*	*	*	*	*																		
1ST GENERATION CEPHALOSPORIN	cefadroxil		*	*				*		*		*	*												
	ceFAZolin							*		*		*	*												
	cephalexin		*	*				*		*		*	*												
	cephalothin	*									*				*		*								
2ND GENERATION CEPHALOSPORIN	cefaclor		*	*				*		*		*	*												
	cefprozil		*	*				*		*		*	*												
	cefuroxime												*	*											
	cefOXitin	*									*			*	*										
3RD GENERATION CEPHALOSPORIN	cefixime														*										
	cefotaxime									*						*		*		*					
	cefTAZidime																*	*	*					*	
	ceFTRIAXone																*	*	*	*					
4TH GEN CEPH	cefepime															*	*	*	*	*					
CARBAPENEMS	meropenem																			*	*	*	*	*	
	imipenem																			*	*	*	*	*	
	ertapenem																			*	*	*	*	*	
Monobactam	aztreonam																*							*	

*Please note that the Matrix of Beta-Lactam Cross Allergy should only be used to evaluate the risk of cross-reactivity in patients with **type 1 immediate (IgE-mediated)** hypersensitivity reactions to a beta-lactam (e.g. anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritis). Please refer to figure 1 for all other types of reactions.

Therapeutic Review

Beta-lactam antibiotics are the most commonly prescribed class of antimicrobials and include penicillins, cephalosporins, carbapenems and monobactams (table 1).⁹ Due to similarities in their beta-lactam ring structure it has been widely accepted that penicillins, cephalosporins and carbapenems have significant cross-reactivity with other classes of beta-lactams.^{5,9,10,11} Historically it has been reported that approximately 10% of patients allergic to penicillins are also allergic to cephalosporins and up to 50% cross-reactivity has been reported between penicillins and carbapenems.^{4,5,9,10,11} Therefore, it has been commonly recommended that patients with a severe allergic reaction to one class of beta-lactam antibiotic should not receive any beta-lactam antibiotic.⁹ This historic over-estimation of cross-sensitivity between classes of beta-lactams is inaccurate and based on flawed methodologies.¹²

Studies have shown that physicians are more likely to prescribe antimicrobials from other classes when patients have a documented penicillin or cephalosporin allergy.^{13,14} Non beta-lactam alternatives may be: less effective, more toxic, broader spectrum, more expensive and more likely to lead to infection or colonization with resistant organisms.^{4,13,15,16,17} The inaccurate documentation of a penicillin allergy can lead to undesirable patient outcomes. For example, one study showed that patients with a documented penicillin allergy at admission spend more time in hospital and are more likely to be exposed to antibiotics associated with *C.difficile* and vancomycin resistant *Enterococcus*.¹⁸ In addition they had increased prevalence rates for infections secondary to *C.difficile*, vancomycin-resistant *Enterococcus* and methicillin-resistant *Staphylococcus aureus*.¹⁸ Another study showed that patients with an “allergy” label (to any antimicrobial) in their medical record were more likely to have longer hospital stays, to be admitted to an intensive care unit, to receive more than one antibiotic during their hospitalisation, and to die during hospitalisation.³⁶

Practice however is changing because allergies have been better defined and the role of the chemical structure on the likelihood of cross-reactivity is now better understood. Recent data shows that the rate of allergic cross-reactivity between penicillins and other beta-lactams is much lower than previous estimates.^{4,5,9,11}

Determining the nature of the patient's reaction is an important step in differentiating between an allergic reaction and an adverse drug reaction such as nausea, vomiting, diarrhea and headache.^{5,9} Immunologic reactions to medications are generally classified according to the Coombs and Gell classification of hypersensitivity reactions (see table 2).^{5,9} The onset and presentation of the reaction can be used to help classify the reaction and determine whether or not a beta-lactam antibiotic may be used (table 2).^{5,9} Type-1, immediate hypersensitivity reactions, are immunoglobulin (Ig) E-mediated reactions and are the only true allergic reactions where the potential risk of cross-reactivity between beta-lactams should be considered.^{5,9} Type-1 immediate hypersensitivity reactions usually occur within 1 hour of exposure and typically manifest as anaphylaxis, bronchospasm, angioedema, stridor, wheezing, hypotension, urticaria or a pruritic rash.⁵ The incidence of these reactions is very low.¹⁹ Nonurticarial and nonpruritic rashes are almost certainly not IgE-mediated.⁵

Penicillins

Penicillin is the most frequently reported drug allergy and is reported in 5-10% of the population.^{20,21,22} Studies have shown that between 80 and 95% or more of those patients reporting a penicillin allergy

do not in fact have true hypersensitivity reactions and the vast majority of these patients can tolerate beta-lactams.^{1,10,21,22,23,24,25}

The use of penicillins can be associated with a nonimmediate, nonpruritic, nonurticarial rash in up to 10% of patients that is unlikely to be IgE-mediated and most often idiopathic or T-cell mediated.^{5,26} While inconvenient, these reactions have not been associated with anaphylaxis and pose no risk of cross reactivity with other beta-lactams.²⁶ An example is the nonpruritic maculopapular rash commonly seen after the administration of ampicillin or amoxicillin to children suffering from infectious mononucleosis secondary to the Epstein-Barr virus.²⁷

Only a type-1 immediate (IgE-mediated) hypersensitivity reaction to a penicillin manifesting as: anaphylaxis, bronchospasm, angioedema, hypotension, urticaria or pruritic rash warrants the avoidance of other penicillins and cephalosporins with similar side chains.^{4,5,9,11} Cross-reactivity between penicillins (figure 2) may be due to shared common antigenic determinants based on similarities in their core ring structure that is common to all penicillins and/or the side chains that distinguish different penicillins from one another; therefore, cross-reactivity cannot be based on side chain similarities alone.

Currently, there is one Health Canada-approved standardized penicillin skin test. PRE-PEN contains the major antigenic determinant of penicillin and is used to rule out a type-1 immediate (IgE-mediated) penicillin allergy. Available literature suggests that the skin test using both major and minor antigenic determinants are roughly 50-60% predictive of penicillin hypersensitivity with a 97-99% negative predictive value.⁴ When penicillin skin testing is not available, the approach to penicillin allergic patients is based on their reaction history and the need for treatment with a penicillin.²⁸ While patients with a convincing reaction history are more likely to be allergic, those with vague histories cannot be discounted as they may also be penicillin allergic.²⁸ The time passed since the reaction is useful because 50-80% of penicillin allergic patients lose their sensitivity after 5 and 10 years respectively.^{2,29,30}

Skin testing, desensitization or re-challenge with a beta-lactam should not be performed in those patients with a history of Stevens-Johnson syndrome, toxic epidermal necrolysis, DRESS, serum sickness, immune hepatitis, hemolytic anemia or interstitial nephritis.⁵

Cephalosporins

Cephalosporin-induced skin reactions, described as urticarial, rash, exanthema and pruritus, occur in approximately 1 to 3% of patients.³¹

Early analysis of cephalosporin use in penicillin allergic patients was complicated by the uncritical evaluation of "allergic reaction".^{5,9,11} Any adverse reaction to cephalosporins was often classified as "allergic".^{5,9,11} This, accompanied with possible penicillin contamination in early cephalosporin production, resulted in overestimations of cross-sensitivity.^{5,9} In addition, penicillin allergic patients are more likely to have an allergy to any drug when compared to other patients.^{4,5,9,10,11} Investigations have shown that individuals with a penicillin allergy are three times more likely to develop new allergies to unrelated compounds, leading to further overestimations of cross-reactivity.^{5,9,10}

Cross-reactivity between penicillins and cephalosporins is due to similarities in side chains at the C-3 or C-7 position as shown in table 3 and not similarities in beta-lactam ring structure as previously speculated.^{4,5,9,11} The American Academy of Pediatrics states that the likelihood of a penicillin allergic

patient reacting to a cephalosporin with a different side chain is similar to that of a non-penicillin allergic patient.⁵ A prospective study with skin test or challenge dose confirmed penicillin allergy demonstrated a 0% cross-reactivity to ceFAZolin, cefuroxime and cefTRIAxone. None of these agents share a side chain with penicillin.³² Meanwhile the risk of cross-reactivity may be up to 40% between penicillins and cephalosporins with the similar R-group side chains.^{3,33} A retrospective population based analysis of 3.9 million patients revealed that there was no significant difference between the rates of anaphylaxis to a cephalosporin in patients with and without documented penicillin “allergy”. This study also highlighted that the practice of avoiding 1st and 2nd generation cephalosporins and using 3rd or 4th generation cephalosporins instead was associated with higher rates of *C. difficile* infection. The authors go on to say: “Warnings against the administration of cephalosporins to patients with unconfirmed penicillin allergy should be removed from electronic medical record systems. The public would be better served by warnings that the use of cephalosporins, particularly third- or higher generation parenteral cephalosporins, is associated with an increased risk of *C difficile* infection within 90 days.”³⁸

Cross-reactivity between cephalosporins is low because of the significant heterogeneity of the side chains at the C-3 and C-7 positions.^{9,34} Therefore, if a patient has a cephalosporin allergy, one can safely prescribe another cephalosporin that has dissimilar side chains at both C-3 and C-7 positions.³⁴ A prospective study evaluating the possibility of using alternative cephalosporins in patients with confirmed cephalosporin allergy demonstrated that cephalosporin allergies are not a class effect, and that patients with confirmed cephalosporin allergy can safely receive cephalosporins with dissimilar side chains.³⁷

CeFAZolin is not expected to cross react with any penicillin or cephalosporin as it does not share a side chain with any beta-lactam.^{4,34}

Carbapenems

Early studies evaluating the risk of cross-reactivity between penicillin and carbapenems found rates upwards of 47%. However, these studies had poor definitions of allergy and variable methods for determining allergy status.⁹ A more recent systematic review was completed to collect and combine all published data on pediatric and adult patients reported to have a clinical history of type-1 immediate hypersensitivity (IgE-mediated) to a penicillin and/or cephalosporin who were then given a carbapenem.³⁵ Within the study allergic reactions were classified as proven, suspected or possible IgE-mediated and non-IgE-mediated.³⁵ Overall, for patients with a history of proven, suspected or possible IgE-mediated reaction to a penicillin; 4.3% (36/838) had a suspected hypersensitivity reaction to a carbapenems but only 20 were compatible with an IgE-mediated reaction and only one was considered to be proven.³⁵ The authors concluded that carbapenems would be a reasonable option when antibiotics are required in patients with IgE-mediated reactions to penicillins.³⁵ They advise that clinicians proceed with caution by administering the first dose of carbapenem in a setting where anaphylaxis can be managed and to consider giving via a graduated challenge.³⁵ If at any stage the patient reacts then the options are to use a carbapenem desensitization protocol or switch to a non-beta-lactam antibiotic.³⁵

Desensitization

Desensitization, or temporary induction of drug tolerance, is used for patients with a documented or convincing history of type-1 immediate (IgE-mediated) beta-lactam allergy and/or positive skin test and a serious infection where non-cross-reacting alternatives are not appropriate.^{2,28} The goal of desensitization is to modify a patient's immune response to allow safe treatment with the allergenic drug.²⁸

Desensitization will not prevent non-IgE mediated reactions and should never be attempted in patients with reactions involving major organs or severe cutaneous reactions (e.g. interstitial nephritis, SJS, TEN, DRESS, etc.).²

Desensitization is performed by administering incremental doses of the allergenic drug.³ Usually the procedure is complete within hours and starts in the microgram range.²⁸ Dosages are usually doubled every 15 to 30 minutes until therapeutic doses are achieved.²⁸ When the desensitization process is complete, treatment with the select beta-lactam should be started immediately and must not be interrupted during the treatment course.^{2,28} Desensitization is usually lost within two days of cessation and must be repeated if the beta-lactam is required in the future.^{2,28}

Graduated Challenge

Graduated challenges are used when there is a low likelihood of drug allergy and differ from desensitization in that they do not alter the patient's underlying immune response to the drug in question.²⁸ Their purpose is to allow cautious administration in patients unlikely to be allergic when there is no intention to alter the patient's immune response.²⁸ If the graduated challenge is tolerated the patient is then considered not to be allergic and not at increased risk for future reactions.²⁸ Graduated challenges should never be performed in patients with reactions involving major organs or non-IgE mediated severe cutaneous reactions (e.g. interstitial nephritis, SJS, TEN, DRESS, etc...)²⁸

The starting dose of a graduated challenge is often higher than that used for desensitization and usually only involves 2 to 3 steps and completed within hours.²⁸ For a graduated challenge for an intravenous antibiotic, 1% of the full dose is administered, then 10 % of the full dose, then the full dose, separated by 30 minutes to 1 hour each and under careful observation.^{2,3} If at any point a reaction occurs the graduated challenge is stopped.

The decision to use a graduated challenge is based on the risk of cross-reactivity and the description and remoteness of the allergic reaction in question. Treatment options requiring desensitization or graduated challenge should be avoided in severe infections (ex. febrile neutropenia, sepsis, meningitis, etc.) where delays in appropriate drug therapy are associated with poor patient outcome, in these scenarios a non-beta lactam treatment option should be considered for empiric therapy.

Allergy assessment

Allergy evaluation and "de-labelling" is emerging as a new antimicrobial stewardship intervention. Recent IDSA guidelines recommend that antimicrobial stewardship programs promote allergy assessments and penicillin skin testing when appropriate, as these may enhance the use of first-line agents.³⁹ A multicenter prospective trial demonstrated that antimicrobial stewardship pharmacists performing beta-lactam allergy skin testing and graduated challenge at the point of care was

associated with greater use of preferred beta-lactam therapy without increasing the risk of adverse drug reactions.⁴⁰

Table 1: Classification of Beta-Lactams

Penicillins	Cephalosporins				Carbapenems	Monobactam
	First Generation	Second Generation	Third Generation	Fourth Generation		
penicillin ampicillin amoxicillin cloxacillin piperacillin ticarcillin	cefadroxil ceFAZolin cephalexin	cefaclor cefOXitin cefprozil cefuroxime	cefTAZidime cefixime cefTRIAxone cefotaxime	cefepime	ertapenem imipenem meropenem	aztreonam

Table 2: Coombs and Gell Classification of Hypersensitivity Reactions^{4,5,31,38,41,42,43,44}

Type	Mediator	Onset	Clinical Reaction	Comments
I - Immediate and Acute hypersensitivity	IgE antibodies	Less than 1hr (Rarely up to 72 hours)	Anaphylaxis, urticaria, angioedema, hypotension, bronchospasm, stridor, pruritis	Anaphylaxis: Penicillins 0.015 – 0.2% Cephalosporins 0.0001 – 0.1% Avoid the offending agent and side chain related agents (See Figure 2)
II – Delayed cytotoxic antibody-mediated hypersensitivity	IgG and IgM antibodies	Greater than 72 hours	Hemolytic anemia, thrombocytopenia, neutropenia	Drug specific, avoid the offending agent
III – Antibody complex-mediated hypersensitivity	IgG and IgM complexes	Greater than 72 hours	Serum sickness, glomerulonephritis, small vessel vasculitis, drug fever	Antibody-antigen complexes precipitate in tissues and potentially affect any end organ
IV – Delayed type hypersensitivity	T-Cells	Greater than 72 hours	Contact dermatitis, pustulosis	Incidence is low. Ex: Eosinophilia, bullous exanthems, severe exfoliative dermatoses (ex. SJS/TEN), interstitial nephritis, immune hepatitis and some morbilliform or maculopapular rashes
Idiopathic Reactions	Unknown	Usually greater than 72 hours	Maculopapular or morbilliform rashes	1 – 4% of patients receiving beta-lactams Not a contraindication to future use of beta-lactam antibiotics

*Anaphylaxis: defined as serious hypersensitivity reaction that is rapid in onset and may cause death, typically involving the skin, mucosal tissue or both and either respiratory compromise (e.g. dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) or reduced blood pressure or the associated symptoms and signs of end-organ dysfunction.

Table 3: Beta-Lactam Groups with Similar Side-Chains

Similar C-7 Side Chain (Cross Reactions between agents within one group is possible)			Similar C-3 Side Chain (Cross reactions between agents within one group is possible)						
Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
penicillin cefOXitin	amoxicillin ampicillin cefactor cephalexin cefadroxil cefprozil	cefepime cefotaxime cefTRIAxone	cefadroxil cephalexin		cefotaxime cephalothin		cefuroxime cefOXitin	cefixime	cefTAZidime aztreonam
<p>Note:</p> <ul style="list-style-type: none"> • CeFAZolin does not share a side chain with any beta-lactam and is not expected to cross react with other agents • Amoxicillin, ampicillin, penicillin, cloxacillin, piperacillin and ticarcillin share common major allergic determinants based on similarities in their core structure and/or side chains; therefore, cross-reactivity cannot be based on side chain similarities alone 									

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