



## Penicillin and Cephalosporin Antibiotic Allergy Screening and Treatment Guidance

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*This guideline has been designed to assist the clinician in the management of patients with penicillin and cephalosporin antibiotic allergy. It is not intended to replace clinical judgment where individual patient characteristics may require modification of these recommendations.*

### I. PURPOSE:

To provide guidance to clinicians on how to classify risk and manage patients with a suspected or known allergic reaction to penicillin (PCN) or cephalosporin antibiotics.

### II. BACKGROUND:

Penicillin and other beta-lactam antibiotics remain first-line therapy for many infections. Compared with beta-lactams, use of non-beta-lactam antibiotics has been associated with inferior clinical outcomes including worse treatment outcomes and higher risk of adverse drug effects,<sup>1,2</sup> but beta-lactams are sometimes avoided because of a suspected or questionable history of an allergy to a penicillin or cephalosporin. In a study by Salkind, et al.<sup>3</sup> only 10-20% who report an allergic reaction to penicillin actually were skin test positive for immediate-type hypersensitivity. Cross reactivity (Table 3, 4) has also been explored across the beta-lactam classes and while they do share a beta-lactam ring, cephalosporin side chains can be significantly different. Given the potential for treatment failure with substituted agents, unnecessary collateral activity, toxicity and/or higher costs, clinical staff should carefully interview patients and review the online and paper Medical Record for patients with a listed beta-lactam allergy for treatment decisions and for precise documentation in the Medical Record.

### III. PROCEDURE:

- 1.) If an allergy flag appears, start by researching the type of allergy documented via cPOE/OMR. Allergy alerts require investigation by the prescriber, the pharmacist and the RN. Up to 10% of patients report a history of penicillin allergy, but after complete evaluation, up to 90% of them are able to tolerate penicillins.<sup>4</sup>
- 2.) The prescriber should always interview the patient or health care proxy to confirm and/or obtain details regarding allergies is responsible for documenting these in cPOE or WebOMR. Ask about:
  - The specific drug and route of administration.
  - What were the specific details of the type and severity of reaction? It is most relevant to distinguish immediate-type hypersensitivity, e.g., urticaria (hives), angioedema, laryngeal edema, wheezing, hypotension, etc., and other potentially life-threatening allergies from other types of reactions including adverse reactions from drug side-effects. See Table 1 for details of types of allergic reactions.
  - Timing of allergic reaction (minutes, hours or days later) after taking the antibiotic?
  - When did this reaction occur? This is important because often temporally remote allergies will resolve.
  - How was the reaction treated? Did it require epinephrine or urgent care?
  - Since the reaction, has the patient received and tolerated medications in the same therapeutic class or related classes, e.g., if allergic to ampicillin have they tolerated cephalexin?
- 3.) As appropriate, the prescriber can write the order and specify the rationale for bypassing the allergy.
- 4.) The pharmacist receiving the order should :
  - Review the rationale for bypassing the allergy alert, and if on the patient care unit, reinvestigate with the patient and/or with the prescriber or RN. If unable to get to the patient care unit (evenings, overnight, weekends), contact the RN and prescriber to review the override.



- Grade the reaction as mild, moderate or severe according to the categories listed. If there is a significant possibility of a severe allergy or direct reaction in any category (e.g., same class), investigate options as shown in Figure 1 below and review with the prescriber.
- Update cPOE or WebOMR allergies and use the Pharmacy system to log an intervention to document the evaluation of the allergy, the review of any recent rechallenge with the agent or a similar agent and actions taken to clarify, change therapy or pursue desensitization.

Allergic reactions can be classified by the Gel-Coombs classification, an important consideration for the approach to drug challenge, cross reactivity decision making, desensitization attempts or drug class avoidance.

**Table 1: Gel-Coombs Types of Allergic Reactions<sup>5,6</sup>**

Types of Allergic Reactions		Description of Reaction
<b>Immediate/accelerated (usually within 1-72 hrs after exposure)</b>		
Type I	IgE mediated	<b>Most severe:</b> anaphylaxis: refractory hypotension or 2 systems involved <b>Severe:</b> angioedema, laryngeal edema, hypotension, wheezing <b>Moderate:</b> hives/urticaria, swelling <b>Mild:</b> pruritic rash
<b>Late onset (often &gt;72 hrs after exposure)</b>		
Type II	IgM mediated/ cytotoxic	Hemolytic anemia, thrombocytopenia, neutropenia
Type III	Immune Complex	Serum sickness, glomerulonephritis, vasculitis <sup>7</sup>
Type IV	Cell mediated	<b>Mild:</b> contact dermatitis, delayed hypersensitivity <b>Severe:</b> interstitial nephritis, erythema multiforme, Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Drug Rash Eosinophilia Systemic Symptoms Syndrome (DRESS)

**Table 2: Alternative Non-Beta-Lactam Antibiotic: not all inclusive and susceptibility data should be carefully reviewed in addition to the institutional antibiogram, the type and severity of infection.**

Pathogen	Alternative agents for consideration
Gram positive: e.g. Staphylococci, Streptococci, Enterococci	<ol style="list-style-type: none"> <li>1. Vancomycin</li> <li>2. Linezolid (Pna) / Daptomycin (BSI)</li> <li>3. Bactrim/Tetracycline (UTI, SSTI) – Staph only</li> <li>4. Levofloxacin (CAP)</li> <li>5. Tigecycline (IAI, Pna)</li> <li>6. Nitrofurantoin (UTI)</li> </ol>
Gram-negative rods (non- <i>Pseudomonas</i> )	<ol style="list-style-type: none"> <li>1. Ciprofloxacin (UTI, IAI, Pna, SSTI)</li> <li>2. Gentamicin/Tobramycin (BSI, Pna)</li> <li>3. Bactrim (UTI)</li> </ol>
<i>Pseudomonas</i> spp.	<ol style="list-style-type: none"> <li>1. Tobramycin (BSI, Pna)</li> <li>2. Aztreonam (UTI)</li> <li>3. Ciprofloxacin (UTI, SSTI, IAI)</li> </ol>
<b>Pna=pneumonia, BSI=bloodstream infection, UTI=urinary tract infection, SSTI=skin soft tissue infection CAP=community-acquired pneumonia, IAI=intra-abdominal infection</b>	



Figure 1: Algorithmic Approach to Penicillin/Cephalosporin Allergies

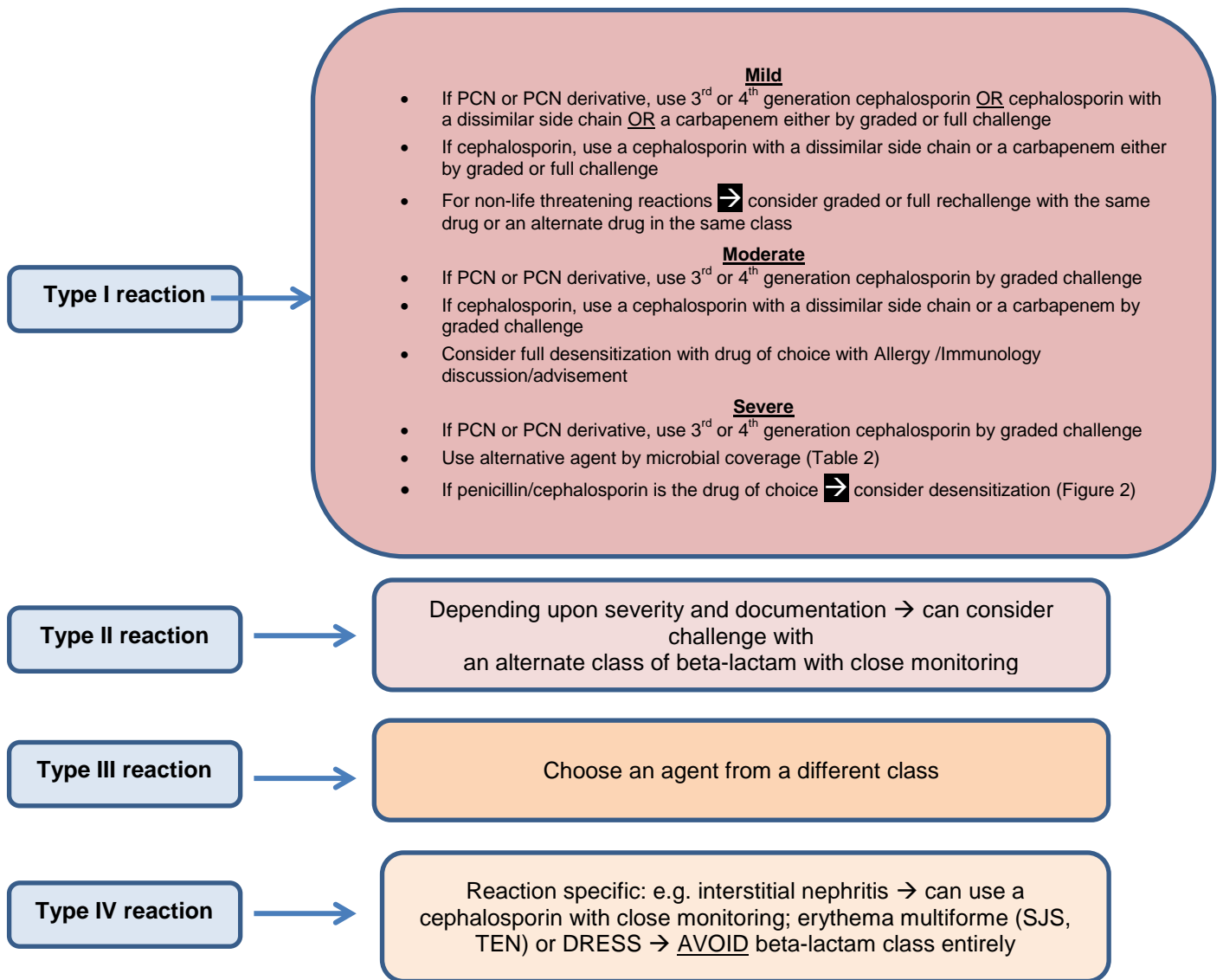




Figure 2: Graded Challenge versus Desensitization<sup>6,8</sup>

**Graded Challenge (i.e., using a test dose)**

Administer a fraction of the intended dose (~5-10%) (see BIDMC preprogrammed standards below) of the antibiotic with the goal of assessing if the patient has immediate-type hypersensitivity. All entries have been populated in the computerized Provider Order Entry System. Observe for at least 30 minutes post dose, and if no adverse reaction administer the full dose as scheduled. A separate order is required for the maintenance dosing.

**Desensitization (i.e., invoking drug tolerance)**

Formal procedure in which very small doses are given with a progressive escalation of dose over 6–12 h. Tolerance is not permanent and only maintained for as long as the drug is continued. This process is utilized ONLY in patients with a moderate or severe type I allergic reaction and has no effect on the incidence of non-IgE mediated reactions (type II-IV).

Refer to BIDMC guidelines regarding [Antibiotic Desensitization](#)

**Fixed doses for graded challenge**

Antibiotic	Dose
Ampicillin Cefazolin Ceftazidime Ceftriaxone Cefepime Meropenem Nafcillin	100 mg
Piperacillin Tazobactam	450 mg
Ampicillin Sulbactam	300 mg
Penicillin	300,000 units



**Table 3: Cross Reactivity Data<sup>9-24</sup>**

Antimicrobial Agent	BIDMC Formulary Examples	% Cross Reactivity with Patients Reporting Penicillin Allergies (range)
1 <sup>st</sup> generation cephalosporins	Cephalexin	1-2% for penicillin May be higher if amox/amp allergy
	Cefazolin	0.1-6%
2 <sup>nd</sup> generation cephalosporins	no formulary 2 <sup>nd</sup> generation cephalosporin for general use	-0.8 to 2%
3 <sup>rd</sup> generation cephalosporins	Cefpodoxime, Ceftazidime <sup>^</sup> , Ceftriaxone	-0.8 to 2%
4 <sup>th</sup> generation cephalosporins	Cefepime	0.5-3%
Monobactams	Aztreonam <sup>^</sup>	1-3%
Carbapenems	Meropenem	0.1-10%

<sup>^</sup>Note that ceftazidime and aztreonam have similar side chains so a reaction to one precludes use of the other.

**Table 4: Matrix of Penicillin and Cephalosporins on BIDMC Formulary with Similar Side Chain Structures<sup>25</sup>**

	PCN	Amoxicillin	Ampicillin	Cephalexin (1 <sup>st</sup> )	Cefoxitin (2 <sup>nd</sup> )	Ceftazidime (3 <sup>rd</sup> )	Ceftriaxone (3 <sup>rd</sup> )	Cefpodoxime (3 <sup>rd</sup> )	Cefepime (4 <sup>th</sup> )
PCN					◇				
Amoxicillin			◇	◇					
Ampicillin		◇		◇					
Cephalexin		◇	◇						
Cefoxitin	◇								
Ceftazidime									
Ceftriaxone								◇	◇
Cefpodoxime							◇		◇
Cefepime							◇	◇	

◇ = share similar side chains      PCN = penicillin

Note: Cefazolin is notably missing from the table above as it has a 7-position side chain dissimilar to any other cephalosporin.



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