Beta-Lactam Associated Allergic Reactions

Definitions

Drug Allergy	Adverse drug reaction that results from a specific immunologic response to a medication.
Anaphylaxis	Acute, life threatening allergic reaction which may involve skin, gastrointestinal, respiratory and cardiovascular symptoms.
Dermatologic reaction	Most commonly reported adverse drug events (e.g. morbiliform or maculopapular rashes)
Pseudoallergic reaction	Idiosyncratic adverse drug reactions with signs and symptoms that mimic immunologic drug allergies, but in which immunologic mechanisms have not been demonstrated.
Adverse reactions	Any undesirable, or unintended effect caused by a medication. Often described as a drug allergy, but of non-immunologic etiology. Includes pseudoallergic and "allergic type" reactions and can include itching, nausea, diarrhea, constipation, headache, and/or hypotension.

Background

- Beta-lactams are the preferred therapy for many infections
- Approximately 10% of people report a penicillin allergy
  - 85-90% of these patients **do not** have a true allergy
  - Many of the reported reactions did not represent true penicillin allergy or their true IgE-mediated penicillin allergy has waned over time

Beta-lactam Cross-reactivity

- Related to side chain structure, rather than beta-lactam ring
- Cross-reactivity between **penicillins** and **cephalosporins** is thought to be much lower than previously reported
  - Cross-reactivity with first-generation cephalosporins reported to be 0.5%
  - Cross-reactivity with second and third generation cephalosporins thought to be even less
- Cross-reactivity between **penicillins** and **carbapenems** thought to be lower compared to cephalosporins
- Cross-reactivity between **cephalosporins**
  - Related to side chains (C-3 and C-7)
  - Risk considered low due to more prevalent differences in side chains
  - If allergy identified, consideration can be given to use of an alternative cephalosporin with a different side chain

***Table 1**. Classification of beta-lactam antibiotics*

Penicillins	Cephalosporins	Carbapenems
Penicillin G, Penicillin VK, Amoxicillin, Ampicillin, Cloxacillin, Piperacillin	Cefazolin, Cephalexin, Cefadroxil, Cefaclor, Cefuroxime, Cefoxitin, Ceftriaxone, Cefotaxime, Cefixime, Ceftazidime, Cefepime	Ertapenem, Meropenem, Imipenem

! Amoxicillin or ampicillin can cause mild delayed skin rashes that are often caused by an interaction between the amino-penicillin and a viral infection (e.g. infectious mononucleosis caused by Epstein-Barr Virus, or cytomegalovirus). These are **not true "allergic" reactions** and therefore it is not necessary to avoid use of other beta-lactam antibiotics.

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***Table 2**. Beta-lactam allergic reactions*

Reaction/Complications	Immune Response Classification	Onset	Recommendations Regarding Beta-Lactam Antibiotics
Non-allergic Adverse Reactions Nausea/vomiting Diarrhea Headache	Idiopathic	Variable	No change in therapy required
"Allergic Type" - Delayed Mild Rash Mild to moderate rash without fever, involvement of internal organs or mucous membranes, or need for hospitalization	Idiopathic	Varies	Use beta-lactam from a different group with a different side chain (see **Table 3**)
"Allergic" - "Immediate" Hypersensitivity Reaction Systemic **anaphylaxis** (bronchospasm, hypotension, angioedema) Hives (urticaria), Pruritus	Type I or IgE mediated	Minutes to hours	Avoid **all beta-lactams** and consider Infectious Disease consult regarding selection of antimicrobial therapy
Delayed Hypersensitivity Reactions Drug–induced Hypersensitivity Syndrome or drug rash with eosinophilia and systemic symptoms (DRESS): Rash with fever and/or with involvement of internal organs, or mucous membranes Stevens-Johnson Syndrome Toxic Epidermal Necrolysis Morbilliform eruptions	Type IV - T cell mediated	Days to weeks Upon re-challenge, symptoms usually re-occur within 24 hours	Avoid **all beta-lactams** and consider Infectious Disease consult regarding selection of antimicrobial therapy
Cytotoxic or Cytolytic Reaction Hemolytic anemia Cytopenia Nephritis	Type II - Antibody (usually IgG) mediated cell destruction	Days to weeks High doses	Depends on severity of reaction *Expert consultation recommended*
Immune Complex Serum-sickness-like reaction Drug fever	Type III - Immune complex deposition and complement activation	7 to 21 days after initiation of drug	
Pseudoallergic reactions Urticaria Hypotension Wheezing Flushing	Idiosyncratic	Variable, usually within hours	Depends on reaction *Expert consultation recommended*

***Table 3**. Beta-lactam C-3 and C-7 side chain grouping*

Similar C-7 side chain. Cross reactions between agents within one group are possible.			**Similar C-3 side chain. Cross reactions between agents within one group are possible.**					
Group 1	**Group 2**	**Group 3**	**Group 1**	**Group 2**	**Group 3**	**Group 4**	**Group 5**	**Group 6**
Penicillin Cephalothin Cefoxitin	Amoxicillin Ampicillin Cefaclor Cephalexin Cefadroxil	Cefepime Cefotaxime Ceftriaxone	Cefadroxil Cephalexin	Cefotetan	Cefotaxime Cephalothin		Cefuroxime Cefoxitin	Ceftazidime

Adapted from Lagace-Weins P, Rubenstein E. Adverse reactions to beta-lactam antimicrobials. Expert Opin Drug Saf. 2012 May;11(3):381-99