BACK TO

BASICS

BETA-LACTAM ALLERGIES

Objectives

- Review spectrum of allergies and adverse drug reactions (ADRs) related to beta-lactam antibiotics
- Review proper collection and documentation of allergy history
- Discuss strategies in selecting alternative options

Background

- Approximately 10% of people report a penicillin allergy
  - 85-90% of these patients **do not** have a true allergy
- Beta-lactams are the preferred therapy for many infections
- *Macfadden et al. 2016:* 1/3 of patients with a reported beta-lactam allergy did not receive it for indications where it was *preferred therapy*
  - *Potential Implications: Greater adverse events, broader spectrum of activity (more resistance), higher cost, less effective*

Allergy History Collection

Allergic Reactions

Reported allergy

Allergy History

Agent – Identify specific offending beta-lactam

Reaction Details – What was the nature of the reaction?

Allergy History

- **Timing/Onset**
  - When did it occur (as a child, more than 10, 20, etc. years ago)?
  - Time to onset of reaction (minutes, hours, days)?

Timing can affect willingness to re-challenge

- **Management**
  - Self-resolved after stopping?
  - Additional medications needed?
  - Family physician/Walk-in clinic visit?
  - Hospitalization?

Allergy History

- **Timing/Onset**
  - When did it occur (as a child, more than 10, 20, etc. years ago)?
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Timing can affect willingness to re-challenge

- **Management**
  - Self-resolved after stopping?
  - Additional medications needed?
  - Family physician/Walk-in clinic visit?
  - Hospitalization?

80% of penicillin-allergic patients lose their sensitivity after 10 years

Ann Allergy Asthma Immunol. 2010 Oct;105(4):259-273.

Allergy History

- Timing/Onset
  - When did it occur (as a child, more than 10, 20, etc. years ago)?
  - Time before reaction occurred (minutes, hours, days)?

- **Management**
  - Self-resolved after stopping?
  - Additional medications needed?
  - Family physician/Walk-in clinic visit?
  - Hospitalization?

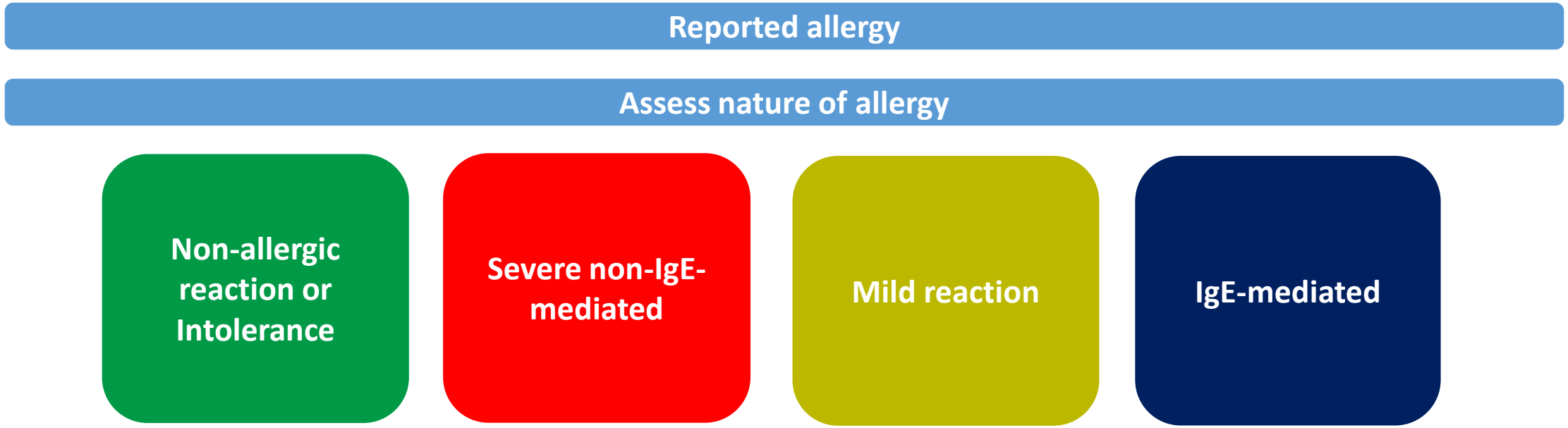
Estimates severity, which can affect our willingness to re-challenge

Allergy History

- **Collateral history**
  - Previous prescriptions for beta-lactams
    - Meditech Medication History
    - ConnectingOntario/ODB profile
    - BPMH/Medication Reconciliation
  - Community pharmacy/physician office
  - Family

Allergy Classification and Management

Types of Allergic Reactions



Managing Beta-Lactam Allergic Reactions

Non-allergic reaction or Intolerance

- *Listed on profile, but denies*
- *Family member allergic*
- *Has previously tolerated the reported antibiotic*
- *Nausea/vomiting/diarrhea or any other intolerance*

Use any beta-lactam therapy
REMOVE documentation of allergy

Managing Beta-Lactam Allergic Reactions

Severe non-IgE-mediated

- *Stevens-Johnson syndrome*
- *Toxic epidermal necrosis*
- *Drug-rash eosinophilia*
- *Systemic symptoms (DRESS) syndrome*
- *Hemolytic anemia*
- *Drug-induced vasculitis*
- *Serum sickness*

Avoid beta-lactam therapy
Avoid desensitization/challenge

Managing Beta-Lactam Allergic Reactions

Mild reactions

- *Itching (without rash)*
- *Maculopapular rash/eruption*
- *Unknown remote reaction (>10 years ago) without recollection of:*
  - *ER visit/Hospitalization*
  - *Life-threatening reaction*

Treat with any cephalosporin

OR

Use amoxicillin test dose

Managing Beta-Lactam Allergic Reactions

IgE-mediated
Non-severe

Isolated hives/urticaria

Non-cross reactive cephalosporin

Managing Beta-Lactam Allergic Reactions

IgE-mediated

- *Anaphylaxis (hypotension, respiratory failure, cardiac arrest > 10 years ago)*
- *Angioedema*
- *Wheezing*
- *Laryngeal edema*
- *Extensive hives/urticaria*

Test dose of non-cross reactive cephalosporin

OR

Full dose non-cross reactive cephalosporin in 'monitored setting' (in-patient ward/ER)

OR

Non-beta lactam agent

Managing Beta-Lactam Allergic Reactions

IgE-mediated

History of near fatal anaphylaxis within last 10 years

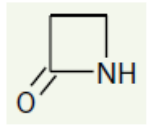
Non-beta lactam agent

Cross-Reactivity

Beta-lactam Cross-Reactivity

Basic structures

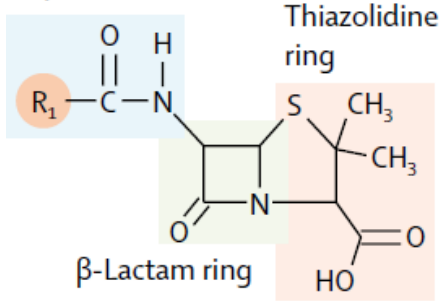
β-Lactam ring



Penicillin structure

Acyl side chain

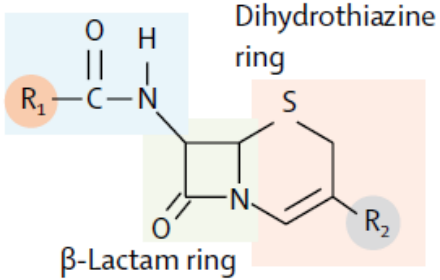
Thiazolidine ring



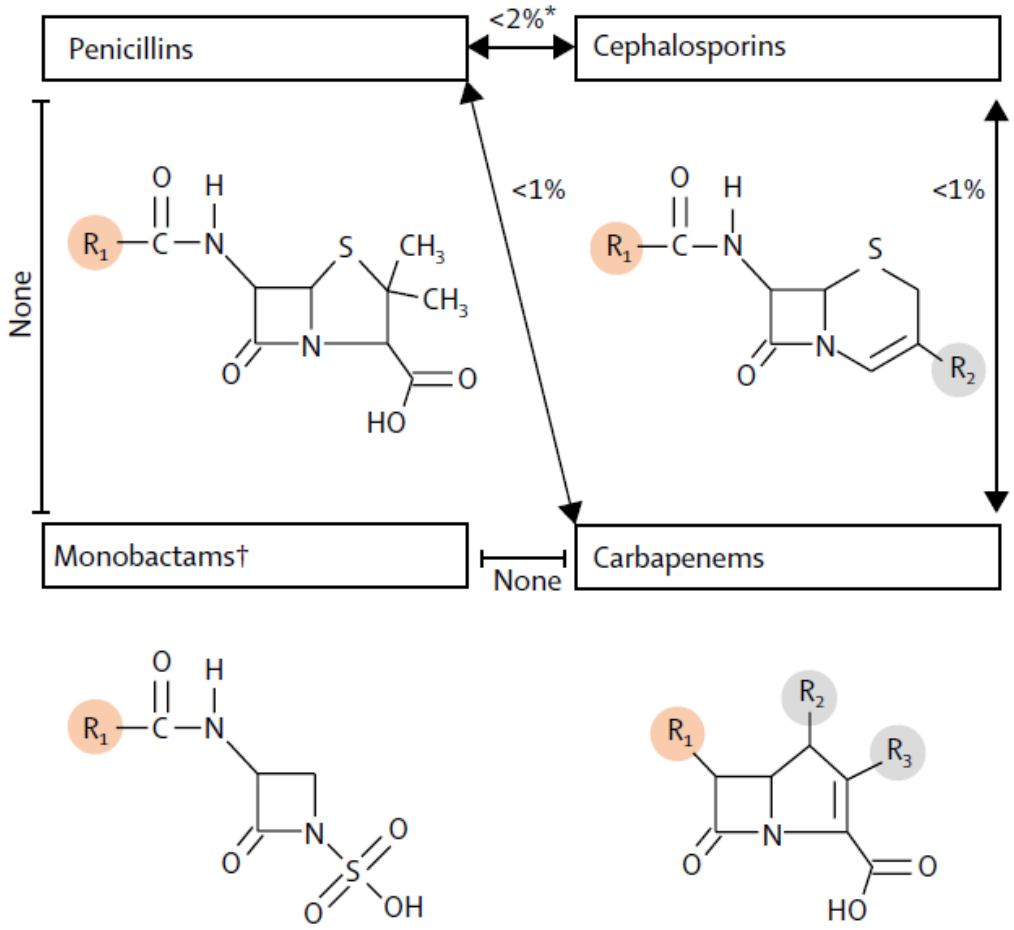
Cephalosporin structure

Acyl side chain

Dihydrothiazine ring



β-Lactam structures and rates of cross-reactivity



Clinically relevant cross-reactivity

Similar side-chains penicillins (R1):

- Penicillin VK and penicillin G

Shared side-chains, penicillins, and cephalosporins (R1):

- Amoxicillin‡ and cefadoxil, cefprozil, cefatrizine
- Ampicillin‡ and cefaclor, cephalexin, cephradine, cephaloglycin

Shared side-chains cephalosporins (R1):

- Cefadroxil, cefprozil, cefatrizine
- Cefaclor, cephalexin, cephradine, cephaloglycin
- Cefepime, ceftriaxone, cefotaxime, cefpodoxime, ceftizoxime
- Ceftazidime and aztreonam

No shared side-chains, penicillins, and cephalosporins (R1):

- Cefazolin

Lancet 2019; 393: 183–98

Beta-lactam Cross-Reactivity

Penicillins and cephalosporins

- 1st generation: 0.5%
- 2nd and 3rd generation: Less than 0.5%

Between cephalosporins

- Related to side chains (C-3 and C-7)
- Consideration can be given to use of a cephalosporin with a different side chain

***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

A Note on Cefazolin

- Does not appear on previous table
  - Unique side chain
- Thought to be a selective allergy
- Avoid if the reaction is a severe non-IgE-mediated reaction

Severe non-IgE-mediated

- *Stevens-Johnson syndrome*
- *Toxic epidermal necrosis*
- *Drug-rash eosinophilia*
- *Systemic symptoms (DRESS) syndrome*
- *Hemolytic anemia*
- *Drug-induced vasculitis*
- *Serum sickness*

Beta-lactam Challenges

Beta-lactam Allergy Skin Test (BLAST)

- **Who** Patients with history of IgE reaction
- **What** Bedside skin testing
  - 98% sensitive
  - Minimal risk of allergic reaction if negative result
- **Why** Beta-lactam therapy is clinically superior
- **When** *Coming soon!*

Oral Beta-lactam Challenges

- **Who** Patients with history of non-severe/mild allergic reaction OR patients with negative BLAST results
- **What** 10 – 50% of full dose, followed by remainder of dose after 60 minutes (*ongoing monitoring*)
- **Why** Beta-lactam therapy is clinically superior
- **When** Happening now

Oral Beta-lactam Challenges

- **How**

Penicillin allergy with mild or unknown reaction (>10 years & without features of IgE or immediate hypersensitivity)

- 250 mg or 500 mg amoxicillin “challenge”

Nursing: Observe x 60 minutes (q15min) & document any reaction

JAMA. 2019;321(2):188-199

Oral Beta-lactam Challenges

How

Re-constitute amoxicillin liquid to provide initial 10% dose

Drug & Dose	Amoxicillin Any Dose	Clavulin® 875/125 mg	Clavulin® 500/125 mg*
10% Test Dose	Amoxicillin Liquid		
Give remainder if no reaction in 1 h	Amoxicillin Liquid	Clavulin® 875/125 mg tab	Clavulin® 500/125 mg tab

* Entire challenge can be done with Clavulin 500/125mg liquid

Cases

CASE 1

TW - 64 yo F

Indication for therapy:

Biliary sepsis with underlying cholangiocarcinoma

Allergy History:

Amoxicillin - Facial/eye swelling (Many years ago), *reported by patient*

MRP asking for input on empiric antibiotic management

Managing Beta-Lactam Allergic Reactions

Reported penicillin allergy

Assess nature of allergy

IgE-mediated

Anaphylaxis (hypotension, respiratory failure, cardiac arrest > 10 years ago)
Angioedema
Wheezing
Laryngeal edema
Extensive Hives/urticaria

Depends: **Avoid beta-lactam or consider BLAST/oral challenge**

- Test dose of non-cross reactive cephalosporin
- Full dose non-cross reactive cephalosporin in closely monitored setting (i.e. ICU)
- Non-beta lactam agent

If penicillin/1st or 2nd generation cephalosporin required
→ BLAST followed by oral challenge

CASE 1

TW - 64 yo F

Indication for therapy:

Biliary sepsis with underlying cholangiocarcinoma

Allergy History:

Amoxicillin - Facial/eye swelling (Many years ago), *reported by patient*

Recommended Plan:

- Give 3rd generation cephalosporin

AND

- Recommend BLAST to assess for oral step down to amoxicillin/clavulanate **OR** non-beta lactam option

CASE 2

JB - 48 yo M

Indication for therapy:

Aspiration pneumonia

Allergy History:

Cloxacillin – Full body rash (1994), *reported by patient's mother*

MRP asking for input on empiric antibiotic management

Managing Beta-Lactam Allergic Reactions

Mild reactions

- *Itching (without rash)*
- *Maculopapular rash/eruption*
- *Unknown remote reaction (>10 years ago) without recollection of:*
  - *ER visit/Hospitalization*
  - *Life-threatening reaction*

Treat with any cephalosporin

OR

Use amoxicillin test dose

CASE 2

JB - 48 yo M

Indication for therapy:

Aspiration pneumonia

Allergy History:

Cloxacillin – Full body rash (1994), *reported by patient's mother*

Recommended Plan:

- Consider oral challenge with amoxicillin/clavulanate

OR

- Treat with 2nd generation cephalosporin (i.e. cefuroxime)

CASE 3

HP - 88 yo F

Indication for therapy:

Pan-sensitive *E. coli* bacteremia from a urinary source

Allergy History:

"Penicillin" – "Can't recall reaction. Happened a long, long time ago", *Reported by patient*

Current Antibiotic:

Ceftriaxone – Day 2

MRP asking for input for oral stepdown

Managing Beta-Lactam Allergic Reactions

Mild reactions

- *Itching (without rash)*
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Treat with any cephalosporin

OR

Use amoxicillin test dose

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HP - 88 yo F

Indication for therapy:

Pan-sensitive *E. coli* bacteremia from a urinary source

Allergy History:

"Penicillin" – "Can't recall reaction. Happened a long, long time ago", *Reported by patient*

Recommended Plan:

- Treat with any cephalosporin **AND** Suggest BLAST/outpatient allergy testing
  OR
- 250 mg oral amoxicillin challenge, followed by full dose amoxicillin

Role of Clinical Pharmacist

- Obtain and document thorough allergy history
  - Highlight specific agent, reaction, timing and management when possible
  - Investigate previous antibiotic usage (i.e. Meditech, ConnectingOntario, etc)

- Provide education in settings where reported reaction is not considered a true allergy (prescriber, allied health, patient/caregiver)

- De-labeling allergies when updated information becomes available
  - Remove from pharmacy & nursing allergy module
  - Document change in PCI and in the chart

Managing Beta-Lactam Allergic Reactions