NSHA Antimicrobial Stewardship Program
Beta-lactam allergy assessment and management

○ **Do not avoid all beta-lactams** in patients reporting penicillin allergies.
  - Penicillin allergy is **over reported** and cross-allergy between penicillins and cephalosporins is **overestimated**.

○ Beta-lactams include all penicillins (i.e. penicillin, ampicillin, amoxicillin, cloxacillin, piperacillin, etc.) including those combined with beta-lactamase inhibitors (amoxicillin/clavulanate, piperacillin/tazobactam), cephalosporins, and carbapenems.

○ The incidence of a true IgE mediated hypersensitivity reaction to a beta-lactam is
  - 1 to 5 per 10,000 treatment courses for penicillins
  - 0.1 to 100 per 100,000 for cephalosporins
  - Individuals with IgE mediated allergies are 3 times more likely to have de novo allergies to unrelated medications.

○ Patients with a history suggestive of a serious or life-threatening non-IgE mediated reaction to **ANY** beta-lactam (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, hemolytic anemia, interstitial nephritis, hepatitis, serum sickness), should **AVOID** all beta-lactams.

○ Penicillin, amoxicillin and 1st generation cephalosporins are safe, effective, and inexpensive antibiotics.
  - Unnecessarily avoiding of their use can result in therapy that is
    - less effective
    - more toxic
    - associated with greater risk of developing antibiotic resistant microorganisms
    - more costly

○ Since many people mistakenly attribute an adverse drug reaction to an allergy, it is important to clarify whether a reaction is
  - an IgE mediated hypersensitivity reaction
  - a non-IgE mediated hypersensitivity reaction
    - non-serious reaction
    - serious or life threatening
      - e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms, erythema multiforme
  - a non-hypersensitivity drug related adverse effect (e.g. GI complications, headache, yeast infections, isolated itch).
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Onset</th>
<th>Symptoms</th>
<th>Management options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgE mediated</td>
<td>Usually &lt;1 hour (max 72 hours)</td>
<td>Anaphylaxis, urticaria, angioedema, laryngeal edema, wheeze, hypotension</td>
<td>Do not give same drug again. Choose a cephalosporin with a different side chain. Do not give another penicillin if culprit was a penicillin.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-IgE mediated¹</td>
<td>&gt; 72 hours</td>
<td>Non-serious² Contact dermatitis, pruritic maculopapular eruption</td>
<td>Not a contraindication to using a beta-lactam. Consider provocation challenge or an antibiotic with a different side chain.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-hypersensitivity</td>
<td>Anytime</td>
<td>Gastrointestinal symptoms, flushing during infusion, headache, yeast infection, isolated itch</td>
<td>Not a contraindication to using a beta-lactam</td>
</tr>
</tbody>
</table>

¹ Skin testing has no role in the diagnosis of non-IgE mediated reactions.
² > 90% of rashes occurring after people take penicillin (amoxicillin) are mild non-IgE reactions. Rashes occur in up to 7% of people.
³ Serious or life threatening non-IgE mediated hypersensitivity reactions are rare with beta-lactams. They include Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, hemolytic anemia, interstitial nephritis, hepatitis, serum sickness

**Provocation challenge**

- Give 10% of therapeutic dose under observation;
- 30 minutes later, give remaining 90% of therapeutic dose;
- Observe for 1 hour after last dose
- Cross-reactivity risk between penicillin and cephalosporins is low.
  - For IgE-mediated allergies, the cross reaction between penicillin and cephalosporins is mediated by similarities of the specific chemical side chains of penicillin and cephalosporins, rather than the beta-lactam ring. See Table 2
  - Beta-lactams with different side chains may be considered in those with a history of an IgE-mediated reaction
  - This consideration is based on theoretical risk and studies using this approach are not yet available.
- If unable to rule in or rule out an IgE mediated allergy, referral to an allergist is recommended.
Table 2: Side chain similarities among beta-lactams. Cross reactivity potential indicated by “X”

<table>
<thead>
<tr>
<th></th>
<th>Penicillin</th>
<th>Amoxicillin</th>
<th>Ampicillin</th>
<th>Cloxacillin</th>
<th>Piperacillin</th>
<th>Cephalexin</th>
<th>Cefazolin</th>
<th>Cefadroxil</th>
<th>Cefoxitin</th>
<th>Cefuroxime</th>
<th>Cefprozil</th>
<th>Cefaclor</th>
<th>Cefotaxime</th>
<th>Ceftriaxone</th>
<th>Cefixime</th>
<th>Ceftazidime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>X</td>
<td>X X</td>
<td>X</td>
<td>X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Piperacillin</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefoxitin</td>
<td></td>
<td></td>
<td></td>
<td>X X</td>
<td>X X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefprozil</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefaclor</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefixime</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td>X X</td>
<td>X X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

X: Risk of IgE mediated cross reaction, use alternative
Cefazolin for surgical prophylaxis in patients with a beta-lactam allergy

Cefazolin is the drug of choice for surgical prophylaxis
- Cefazolin is more effective than alternatives like clindamycin and vancomycin for reducing surgical site infections
- Cefazolin is a safe medication with less toxicities than clindamycin and vancomycin
- Cefazolin can be administered quickly prior to incision

Can patients with a beta-lactam allergy receive cefazolin safely?
- Cefazolin has a unique side chain. Since side chain similarities are responsible for IgE-mediated (anaphylaxis) cross-reactions, cefazolin does not cross-react with other beta-lactams.
- Cefazolin for surgical prophylaxis is given in a monitored preoperative setting
- Cefazolin should be avoided if
  - history suggestive of a serious or life-threatening non-IgE mediated reaction to beta-lactams (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, hemolytic anemia, interstitial nephritis, hepatitis, serum sickness)
  - anaphylaxis to cefazolin specifically
Surgical prophylaxis for patients with beta-lactam allergy

Beta-lactam allergy?
penicillin, amoxicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, cloxacinil, cephalosporins, carbapenems

Individuals with anaphylaxis to penicillin are more likely than non-allergic patients to develop anaphylaxis to any unrelated compounds

No

Non Cefazolin beta-lactam allergy

Serious / life-threatening non-IgE reaction:
SJS/TEN, AGEP, DRESS, serum sickness, nephritis, hepatitis

Give Cefazolin 2g

Serious / life-threatening non-IgE reaction:
Onset within 1-72 hours
-urticaria
-angioedema
-stridor
-bronchoconstriction
-hypotension
-anaphylaxis

Use vancomycin 15mg/kg infused prior to incision & outpatient allergy consult

Yes

Cefazolin allergy

Serious / life-threatening non-IgE reaction:
SJS/TEN, AGEP, DRESS, serum sickness, nephritis, hepatitis

Maculopapular rash / morbilliform rash

Graduated challenge or Alternative

Intolerance:
-diarrhea
-nausea
-vomiting
-headache

Give Cefazolin 2g

Nova Scotia Health Authority
Antimicrobial Stewardship Program

SJS: Stevens-Johnson syndrome, TEN: Toxic epidermal necrolysis, AGEP: acute generalized exanthematous pustulosis, DRESS: drug rash with eosinophilia and systemic symptoms