Management of Penicillin and Beta-Lactam Allergy – Executive Summary

(NB Provincial Health Authorities Anti-Infective Stewardship Committee, February 2016)

Key Points

- Beta-lactams are generally safe; allergic and adverse drug reactions are over diagnosed and 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 intolerances.[1]
- 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
   a. Patient reports intolerance (e.g. nausea, vomiting, diarrhea, headache) – likely not allergic, attempt beta-lactam therapy
   b. Patient 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. Patient has a documented severe type-1 immediate 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. Patient has a documented severe type-1 immediate 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

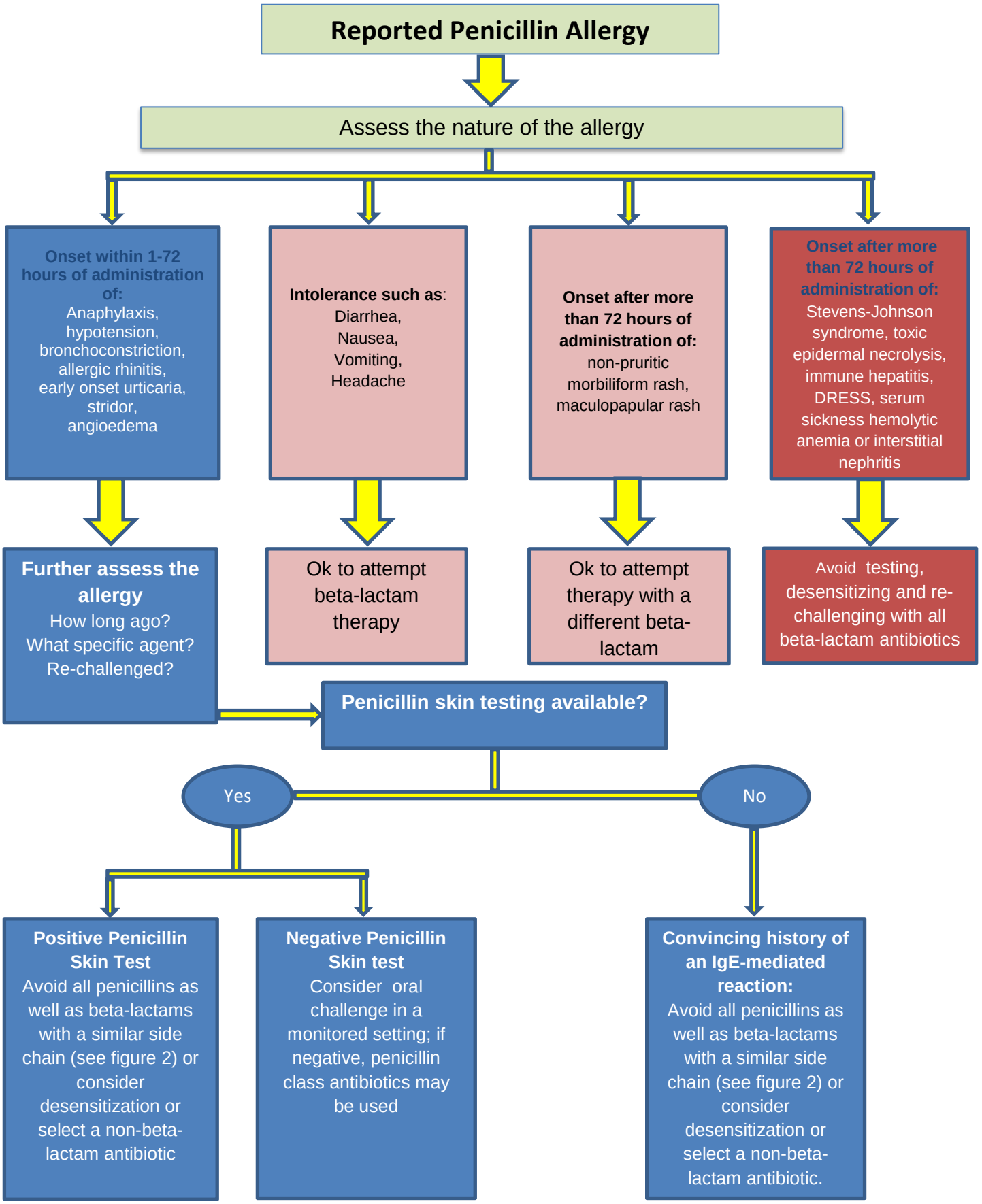

Figure 2: Matrix of Beta-Lactam Cross Allergy (based on similar core and/or side chain structures) [5, 6, 7, 8, 9]

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, cephalexin, cefaclor and cefprozil but NOT to ceFAZolin, cefuroxime or cefTRIAXone, etc.

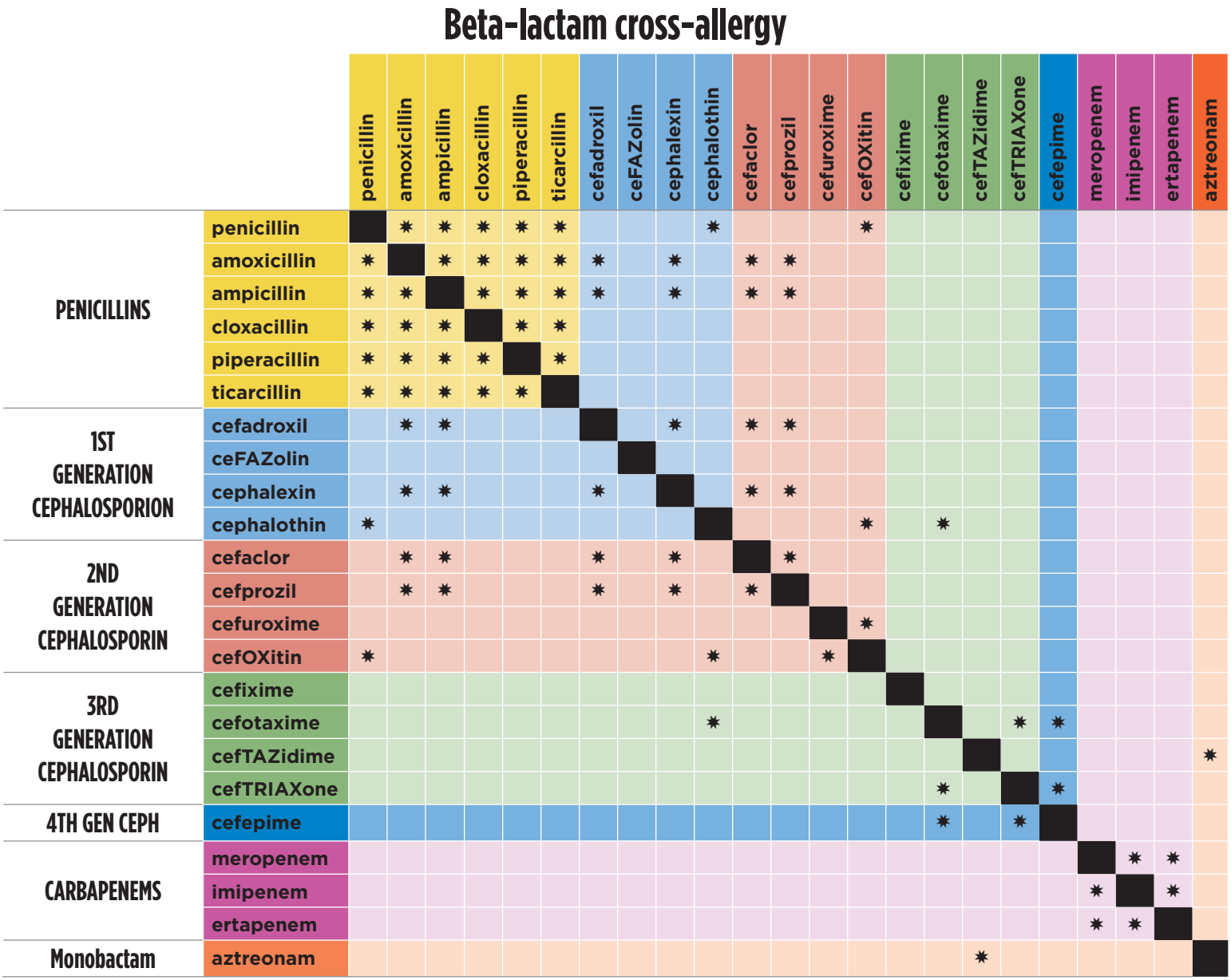

Table 1: Coombs and Gell Classification of Hypersensitivity Reactions[4,5]

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 0.01-0.05% 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 2: Detailed Allergy History

Questions	
When did the reaction take place?	How old was the patient at the time of the reaction?
Does the patient recall the reaction? If not, who informed them of the reaction?	Does the patient remember which medication?
What was the medication prescribed for?	What was the route of administration?
How long after starting the medication did the reaction begin?	What were the characteristics of the reaction?
Did the patient seek medical care due to the reaction?	Was the medication discontinued? If so, what happened after it was discontinued?
Did the patient have any other ongoing medical problem at the time of the reaction?	What other medications was the patient taking? Why and when were they prescribed?
Has the patient taken any similar medications before or after the reaction? If so, what was the result?	Has the patient ever experienced this reaction without intake of the suspected medication?

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