TITLE: PENICILLIN AND CEPHALOSPORIN ALLERGY EVALUATION AND MANAGEMENT

GUIDELINES:

Of the approximately 10-20% of hospitalized patients labeled as penicillin allergic, only 10% or less have a true IgE mediated (type-1) hypersensitivity.[1] These patients often receive second-line antibiotics (non-beta-lactams) that may be less effective, more toxic, broader in spectrum than necessary, and more expensive. Use of second-line agents is also correlated with a longer hospital length-of-stay, increased rate of adverse events such as *Clostridium difficile* infection, and increased mortality.[2] The correct labeling of penicillin allergy will facilitate the use of a preferred beta-lactam regimen, decrease the use of second-line antibiotics, and potentially decrease healthcare costs.

PURPOSE:

To assist clinicians in the evaluation and management of penicillin and cephalosporin (beta-lactam) allergies in patients who have an indication for a beta-lactam antimicrobial. Also to assist in clarifying and de-labeling patients of penicillin and cephalosporin allergies when they do not have a true allergy.

APPLICABILITY:

All centers

RESPONSIBILITY:

Joint Subcommittee on Anti-Infective Use

PROCEDURE:

I. ALLERGY ASSESSMENT

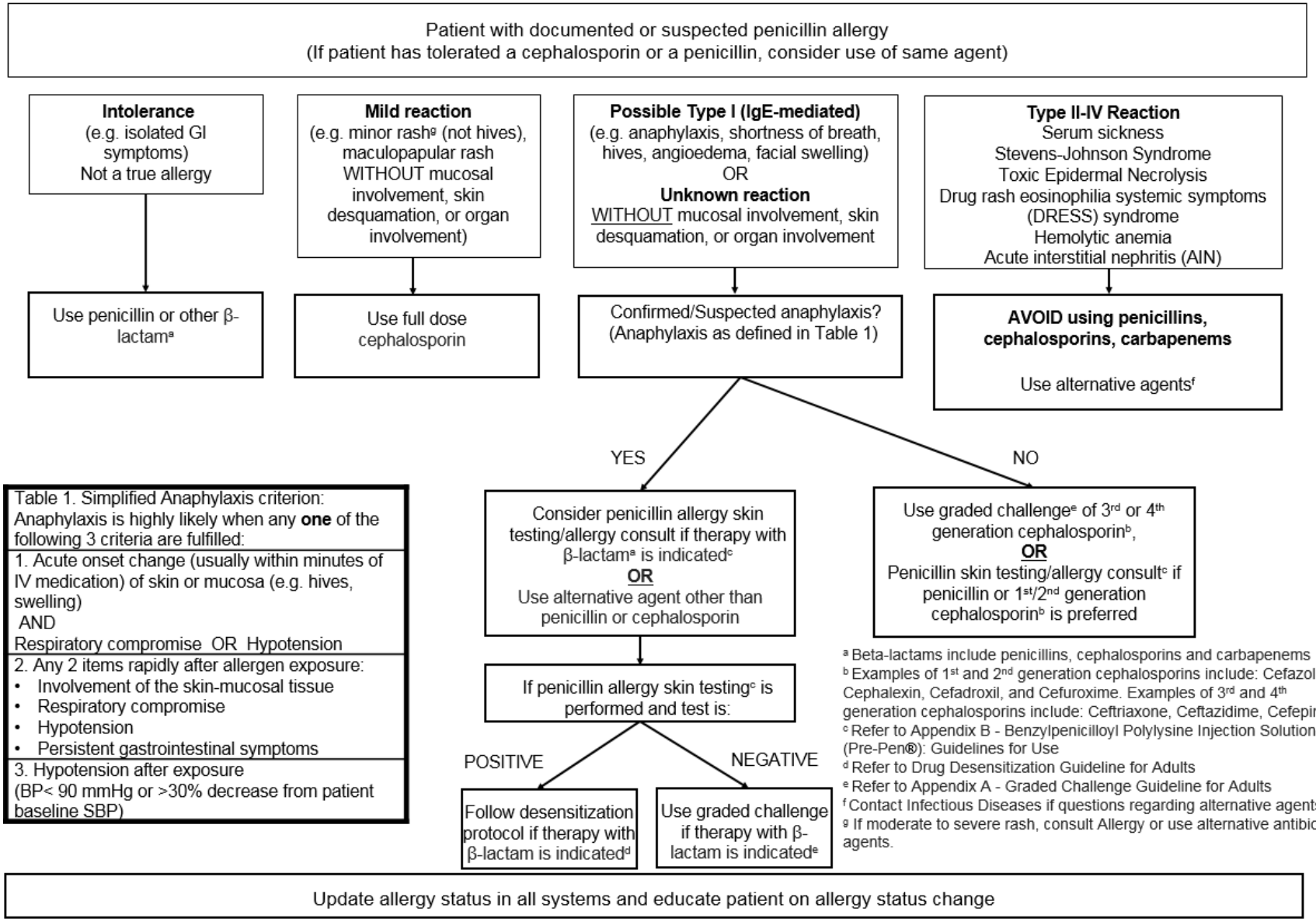
a. Taking a History of Drug Allergy

i. Detailed assessment of a reported beta-lactam allergy is key to appropriate antimicrobial management of patients, and should be evaluated using the questions listed below

ii. Definitions:
1. Allergy: An abnormal reaction to an ordinarily harmless substance (allergen), which is usually immune-mediated
2. Intolerance: An undesirable pharmacologic effect, not immune-mediated, resulting in an exaggerated sensitivity
3. Idiosyncratic reactions: Adverse reactions which are unpredictable and cannot be explained on the basis of the pharmacology

iii. Questions to consider:
1. What was the patient's age at the time of the reaction?
2. Does the patient recall the reaction? If not, who informed them of it?
3. How long after beginning the medication did the reaction occur?
4. What happened when the patient received the medication, e.g. did the patient experience rash, hives, throat swelling, difficulty breathing?
5. Was there organ involvement (e.g. liver enzyme elevation or acute kidney injury)?
6. What happened when the medication was discontinued?
7. Has the patient taken similar medications before or after the reaction (e.g. cephalosporins in a patient with suspected penicillin allergy)? If yes, what was the result?

II. ALLERGY ALGORITHMS:



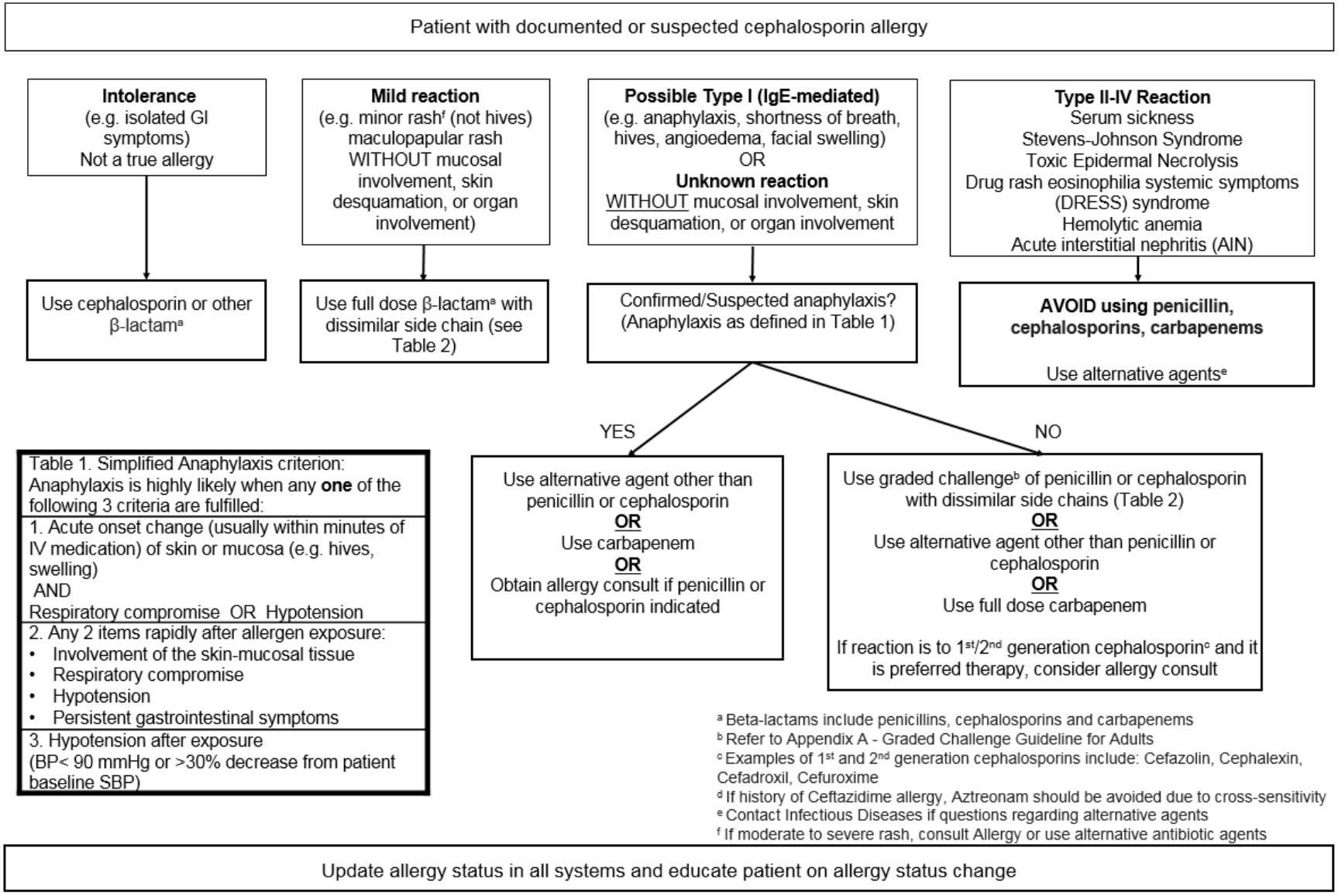

Patient with documented or suspected cephalosporin allergy
Intolerance
(e.g. isolated GI symptoms)
Not a true allergy
Use cephalosporin or other β-lactam[a]
Mild reaction
(e.g. minor rash[f] (not hives) maculopapular rash WITHOUT mucosal involvement, skin desquamation, or organ involvement)
Use full dose β-lactam[a] with dissimilar side chain (see Table 2)
Possible Type I (IgE-mediated)
(e.g. anaphylaxis, shortness of breath, hives, angioedema, facial swelling)
OR
Unknown reaction
WITHOUT mucosal involvement, skin desquamation, or organ involvement
Confirmed/Suspected anaphylaxis? (Anaphylaxis as defined in Table 1)
YES
Use alternative agent other than penicillin or cephalosporin
OR
Use carbapenem
OR
Obtain allergy consult if penicillin or cephalosporin indicated
NO
Use graded challenge[b] of penicillin or cephalosporin with dissimilar side chains (Table 2)
OR
Use alternative agent other than penicillin or cephalosporin
OR
Use full dose carbapenem
If reaction is to 1st/2nd generation cephalosporin[c] and it is preferred therapy, consider allergy consult
Type II-IV Reaction
Serum sickness
Stevens-Johnson Syndrome
Toxic Epidermal Necrolysis
Drug rash eosinophilia systemic symptoms (DRESS) syndrome
Hemolytic anemia
Acute interstitial nephritis (AIN)
AVOID using penicillin, cephalosporins, carbapenems
Use alternative agents[e]
Table 1. Simplified Anaphylaxis criterion:
Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:
1. Acute onset change (usually within minutes of IV medication) of skin or mucosa (e.g. hives, swelling)
AND
Respiratory compromise OR Hypotension
2. Any 2 items rapidly after allergen exposure:
• Involvement of the skin-mucosal tissue
• Respiratory compromise
• Hypotension
• Persistent gastrointestinal symptoms
3. Hypotension after exposure
(BP< 90 mmHg or >30% decrease from patient baseline SBP)
[a] Beta-lactams include penicillins, cephalosporins and carbapenems
[b] Refer to Appendix A - Graded Challenge Guideline for Adults
[c] Examples of 1st and 2nd generation cephalosporins include: Cefazolin, Cephalexin, Cefadroxil, Cefuroxime
[d] If history of Ceftazidime allergy, Aztreonam should be avoided due to cross-sensitivity
[e] Contact Infectious Diseases if questions regarding alternative agents
[f] If moderate to severe rash, consult Allergy or use alternative antibiotic agents
Update allergy status in all systems and educate patient on allergy status change

TABLE 2: BETA-LACTAM CROSS-REACTIVITY

- Cross reactivity between ß-lactams may occur due to the presence of the shared bicyclic ß-lactam ring structure or due to similar side chains (R groups). Literature suggests the R groups may play a larger role in cross reactivity.
- The following table describes risk of cross-reactivity between two drugs from the columns and rows. Boxes with an X indicate a similar side-chain, and therefore higher probability of cross-reactivity. Empty boxes indicate a lack of side chain similarity and lower probability of cross-reactivity.

	Penicillin G	Amoxicillin	Ampicillin	Cephalexin	Cefadroxil	Cefaclor	Cefazolin	Cefotetan	Cefoxitin	Cefprozil	Cefuroxime	Cefdinir	Cefixime	Cefotaxime	Cefpodoxime	Ceftazidime	Ceftriaxone	Cefepime	Ceftolozane	Aztreonam
Penicillin G									X											
Amoxicillin			X	X	X	X				X										
Ampicillin		X		X	X	X				X										
Cephalexin		X	X		X	X				X										
Cefadroxil		X	X	X		X				X										
Cefaclor		X	X	X	X					X										
Cefazolin																				
Cefotetan																				
Cefoxitin	X										X									
Cefprozil		X	X	X	X	X														
Cefuroxime									X					X			X	X		
Cefdinir													X							
Cefixime												X								
Cefotaxime											X				X		X	X		
Cefpodoxime														X			X	X		
Ceftazidime																			X	X
Ceftriaxone											X			X	X			X		
Cefepime											X			X	X		X			
Ceftolozane																X				X
Aztreonam																X			X	

X indicates a similar side chain and therefore greater potential for cross-reactivity

APPENDIX A: GRADED CHALLENGE

Patient-reported allergies limit the use of many preferred first-line therapies. A history of drug allergy should be carefully evaluated to classify the drug reaction, determine the likelihood of the drug in question to cause a reaction, and evaluate the risk of subsequent exposure. Based on their history and/or skin test results, patients who have a **low** likelihood of a true IgE-mediated drug allergy may undergo a graded challenge. A graded challenge is comprised of administration of two progressively increasing doses of the specific drug in question until a full dose is reached. The intention of a graded challenge is to introduce the drug in a controlled manner and to provide confirmation that administration of the drug will not result in an immediate reaction. Patients who complete a graded challenge without adverse events are considered to not have a true IgE-mediated drug allergy. While successful completion of a graded challenge does not rule out a delayed-type reaction to a drug, a graded challenge is considered safe in a patient with low-risk history.

Avoid a graded challenge in patients with a history of immediate hypersensitivity, unless penicillin skin testing has been performed and resulted negative for penicillin sensitization. Patients with a history of immediate hypersensitivity or with a higher likelihood of a true IgE-mediated drug allergy should undergo desensitization as per the "Drug Desensitization Guideline for Adults."

If any uncertainty exists, discussion with the Allergy/Immunology consult service is strongly recommended.

PROCEDURE:

1. Patient candidate criteria
   a. Drug reaction history deemed to be of low risk by negative penicillin skin testing or by use of an agent deemed to have lower probability of cross-reactivity (see allergy algorithms)
   b. Drug in question is medically necessary or preferred to treat the patient's condition
   c. Monitoring of the patient can be provided during the graded challenge as detailed below
   d. Medications to treat an allergic reaction are available during the graded challenge (e.g. epinephrine, albuterol, diphenhydramine, hydrocortisone). See below for medications and doses.
   e. For patients receiving beta-blockers, or anti-histamines such as diphenhydramine, these agents should be held. Anti-histamines should generally be held for 5-days prior (though diphenhydramine only requires 2-3 days); ACE-Inhibitors and beta-blockers should be held for at least 1-day; and H-2 antagonists such as famotidine and ranitidine should be held for 1-day prior to the challenge. Please contact Allergy/Immunology with specific questions regarding these agents.

2. Exclusion criteria
   a. Well documented history of immediate, severe reaction to the drug or drug class in question (e.g. anaphylaxis, angioedema, hives) without a negative penicillin skin test prior to graded challenge.
   b. History of a serious hypersensitivity reaction other than a type I, IgE-mediated reaction (e.g. hemolytic anemia, interstitial nephritis, Stevens-Johnson syndrome, blistering/peeling of skin, acute interstitial nephritis (AIN), or drug rash eosinophilia systemic symptoms (DRESS) syndrome)

3. Consider consulting the Allergy/Immunology consult service.
   a. Allergy/Immunology must be consulted if the patient has a history of a severe reaction and the identity of the allergen is unknown

4. Ordering
   a. Graded challenge must be ordered by the prescriber
   b. Challenge should be conducted between 9am and 5pm for maximal nursing staff availability
   c. The prescriber will enter the orders for the medication in the appropriate concentrations (10%, remaining 90% to complete dose)
   d. The prescriber must verify that the appropriate emergency medications are ordered for treatment of anaphylaxis:
      1. Epinephrine 1:1000 (1mg/mL) injection, 0.3 mL intramuscular (IM), may need to repeat dosing for anaphylaxis every 5 minutes for up to 3 doses (administer first, prior to diphenhydramine, in treatment of anaphylaxis)
      2. Diphenhydramine 50 mg intravenous push (IVP) over 5 minutes once as needed for anaphylaxis (administer after epinephrine)
      3. Hydrocortisone succinate 200 mg IVP over 2 minutes once as needed for anaphylaxis
      4. Famotidine 20 mg IVP over 3 minutes once as needed for anaphylaxis
      5. Sodium chloride 0.9% 500 mL bolus as needed for anaphylaxis

5. Pharmacist responsibilities
   a. The pharmacist will ensure that the graded challenge protocol is prepared and dispensed

Graded Challenge Protocol:

1. Pharmacy preparation instructions:
   a. Prepare one-tenth (10%) of full dose of drug in 50 mL diluent and label as bag #1
   b. Prepare remaining nine-tenths (90%) of full dose and label as bag #2
   c. Refer to ‘Reconstitution/Dilution/Filtration Data for Intravenous Medications’ for compatibility data
2. Administration

a. Beginning with bag #1, administer the full 50 mL. Observe for any immediate reaction following infusion and check for symptoms, vital signs within 10-15 minutes after the dose. If bag #1 is tolerated, administer of bag #2. If patient is tolerating bag #2 without symptoms of possible reaction for 1 hour, may place standing order.

3. Monitoring
    a. Obtain and document baseline blood pressure (BP), heart rate (HR), and oxygen saturation prior to first dose
    b. Obtain and document BP and HR 10-15 minutes after initiation of the first graded challenge dose
    c. Obtain and document BP and HR every 30 minutes until 1 hour after the graded challenge has been completed, then routine vital sign checks per Nursing Clinical Standard: CC 1825 Adult Patient Protocol
    d. At each vital sign check also check for signs of anaphylaxis: wheezing, stridor, tachycardia, hypotension, crampy abdominal pain/nausea/vomiting/diarrhea, angioedema/swelling of the lips, face or oropharynx, fever, rash/urticaria
        i. If any of these symptoms develop, stop infusion immediately, call Physician/Nurse Practitioner (NP)/Physician Assistant (PA) to bedside to evaluate for anaphylaxis, treat if necessary per the 'Adult and Pediatric Anaphylaxis Management Guidelines
        ii. Please refer to hospital anaphylaxis management guidelines for instructions on recognition and management of anaphylaxis: https://infonet.nyp.org/pharmacy/PharmacyM/AnaphylaxisManagementGuidelineAdult.pdf#search=anaphylaxis
4. Documentation
    a. Document in allergy section of the EMR with date of graded challenge
    b. If completed successfully without symptoms, the patient will not require future graded challenge for subsequent courses of challenged drug, and the allergy should be removed from the EMR *only if* the challenge was conducted with the same drug as the reported allergy.

APPENDIX B: INSTRUCTIONS FOR PENICILLIN SKIN TESTING IN ADULTS

Benzylpenicilloyl polylysine injection (Pre-Pen®) is a skin test reagent for the detection of benzylpenicilloyl IgE antibodies. It is indicated for the assessment of sensitization to penicillin (benzylpenicillin or penicillin G) in patients suspected to have a type I hypersensitivity to penicillin. A negative skin test under optimal conditions with both PrePen® and penicillin G is associated with an incidence of immediate allergic reactions of less than 5% after the administration of therapeutic penicillin.

PROCEDURE:

1. Penicillin skin tests are only to be administered via protocol (see Beta-Lactam Allergy Management Guideline) and by an allergist or other properly trained physician in a monitored setting.
2. Potential candidates for penicillin skin testing include:
    a. Patients with a distant history of penicillin allergy or
    b. Patients with a history of penicillin allergy in which the reaction is unknown or non-life-threatening, and
    c. Patients for whom penicillin is the drug of choice for a life-threatening infection and desensitization is being considered
3. Penicillin skin test supplies will be ordered through the Penicillin Skin Test Orderset
4. In addition to the results of the penicillin skin test, the decision to administer or not administer penicillin should account for individual patient factors.
5. Other considerations include the following:
    a. A negative skin test does not completely eliminate the risk of hypersensitivity reactions to penicillins.
    b. It is possible for a patient to have an anaphylactic reaction to therapeutic penicillin in the presence of a negative skin test and a negative history of penicillin hypersensitivity.
    c. If penicillin is the drug of choice for an infection, successful desensitization with therapeutic penicillin may be possible irrespective of a positive skin test and/or a positive history of penicillin hypersensitivity.
6. Skin testing responses can be attenuated by interfering drugs. For patients receiving beta-blockers, or anti-histamines such as diphenhydramine, these agents should be held. Anti-histamines should generally be held for 5-days prior (though diphenhydramine only requires 2-3 days); ACE-Inhibitors and beta-blockers should be held for at least 1-day; and H-2 antagonists such as famotidine and ranitidine should be held for 1-day prior to the challenge. Please contact Allergy/Immunology with specific questions regarding these agents.

7. Penicillin skin testing is useful only in assessing risk for IgE mediated drug reactions and cannot be used to assess risk for non-IgE mediated drug reactions
8. Obtain reagents for skin testing to include:
    a. Negative Control: Sodium chloride solution without preservative
    b. Penicillin G 10,000 U/ml (a minor determinant)
    c. PrePen(benzylpenicilloyl polylysine) full strength (major determinant)
    d. Ampicillin 20 mg/ml, to be considered for inclusion when:
        - Prior reaction was to amoxicillin/ampicillin or a semi-synthetic penicillin
        - Patient history is unclear regarding the beta-lactam drug associated with past reaction, and the patient requires treatment with amoxicillin/ ampicillin or a semisynthetic penicillin either immediately or predictably in the future
    e. Positive Control: Histamine
        - Percutaneous: histamine base 6 mg/ml (histamine dihydrochloride 10 mg/ml)
        - Intradermal: histamine base 0.1 mg/ml (histamine phosphate 0.275 mg/ml)
9. Start with percutaneous/prick testing, typically done on the volar aspect of the forearm
    a. Prepare surface of skin with alcohol swab
    b. Apply 1 drop of each reagent to skin
    c. Use Quintip or equivalent in each drop; apply pressure without breaking skin
    d. Read at 15 minutes. A positive test should have a wheal greater than 3 mm in diameter for either PrePen or Pen G, with appropriate negative and positive controls (saline with no wheal and histamine with wheal 3mm in diameter or greater)
10. If prick testing is negative to antibiotic reagents (with appropriate responses to saline and histamine), proceed with intradermal testing with each reagent, typically done on the lateral/dorsal aspect of upper arm.
    a. Prepare surface of skin with alcohol swab
    b. Using needles appropriate for intradermal skin testing with intradermal bevel (typically 26 to 28 gauge), inject 0.02-0.03 ml of each reagent intradermally to create bleb ~3 mm in diameter. Prepen intradermal test should be duplicated. Each injection should be 2 cm apart.
    c. Read testing at 20 minutes. Interpret results as follows:

- Negative response – no increase in the size of the original bleb for Prepen (both tests) and Pen G, or increase that is no greater than increase noted at the control site.
- Positive response – itching and significant increase in size of of either PrePen or Pen G's original bleb(s) 2-3 mm greater diameter than the saline control.

RESPONSIBILITY:

Enterprise Joint Subcommittee on Anti-Infective Use

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POLICY/GUIDELINE DATES:

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