UNC MEDICAL CENTER GUIDELINE

Inpatient Penicillin Allergy Assessment Guide

Being labeled with a penicillin (PCN) allergy can lead to several negative health outcomes for patients; however, improving documentation of PCN allergies in the electronic medical record can mitigate some of this risk. This guideline provides an overview of the mechanism of penicillin allergy and cross-reactivity between beta-lactams. It also provides guidance for inpatient pharmacists on how to assess, risk-stratify, document the past reaction, and provide recommendations for antibiotic use in the setting of a penicillin allergy.

Contents

PENCILLIN ALLERGY OVERVIEW

A. Approximately 10% of all U.S. patients report having an allergic reaction to a PCN class antibiotic; however when evaluated, less than 1% of the population are truly allergic to PCNs.
   - **a. Reasons for over-reporting of PCN allergy:**
     - i. Previous reaction was not a true IgE mediated allergy
       1. Example: rash to PCN as a child in the setting of a viral infection like Epstein-Barr Virus
     - ii. Waning of IgE antibodies over time
       1. Approximately 80% of patients with IgE-mediated PCN allergy lose their sensitivity after 10 years
     - iii. Inaccurate documentation
       1. Example: past reaction was nausea but was incorrectly labeled as hives/rash

Developed by: UNC Medical Center Carolina Antimicrobial Stewardship Program
Approved by: Anti-infective P&T Subcommitte, P&T Committee, and Acute Care Services Pharmacy Practice Council
Approved Date: December 2022
Last Revised Date: December 2022

B. All PCNs share the same core beta-lactam and thiazolidine ring structures but differ in their side chains.
    a. The ring structure is metabolized into major (penicilloyl) and minor (penicillin, penicilloate, and penilloate) antigenic determinates
    b. Immediate reactions are the result of IgE that cross-like on mast cells when exposed to the antigenic component
    c. The incidence of anaphylaxis to PCNs is rare (estimated 0.02 to 0.04%) and is mediated by IgE antibodies

C. Broad-spectrum antibiotics are often used as an alternative to PCNs and the use of broad-spectrum antibiotics in patients labeled "penicillin-allergic" is associated with higher healthcare costs, increased risk for antibiotic resistance, and suboptimal antibiotic therapy.

D. <u>Correctly identifying those who are not truly penicillin-allergic can decrease unnecessary use of broad-spectrum antibiotics and improve patient outcomes.</u>

CROSS REACTIVITY AMONG BETA-LACTAMS

A. Allergic reactions to cephalosporins are usually from the R-group side chains instead of the core beta-lactam structure. Therefore, cross-reactivity between PCNs and cephalosporins is usually caused by side chain recognition (FIGURE 1). Cross-reactivity between PCNs and cephalosporins varies by generation, but true cross-reactivity is estimated at 2-3 %.

    i. Example: Patients allergic to ampicillin should avoid cephalosporins with identical R-group side chains like cephalexin and cefaclor.
    ii. Cefazolin does not share the same side group chain with any PCN-class antibiotic (or cephalosporin) and could be considered in certain clinical scenarios.
    iii. **Recommendation:** In patients with a history of anaphylaxis to PCN, a structurally dissimilar cephalosporin can be administered without skin testing to additional precautions. **However, out of an abundance of caution, this guideline recommends administering a cephalosporin via graded challenge in the setting of prior anaphylaxis to a PCN class antibiotic.**

B. Cross-reactivity between PCNs and carbapenems is ~ 1% and risk of reaction is considered similar to the general population.
    i. **Recommendation**: Inn patients with a history of PCN or cephalosporin allergy (regardless of anaphylaxis or not), a carbapenem may be administered without testing or additional precautions a carbapenem can be administered via graded challenge based on provider preference or if patient has had multiple previous reactions to beta-lactams.

C. Cross-reactivity between PCNs and monobactams is < 1% and highly unlikely
    i. **Recommendation:** In patients with a history of PCN or cephalosporin allergy, aztreonam may be administered without prior testing unless there is a history of ceftazidime allergy given side chain similarity.

FIGURE 1: BETA-LACTAMS THAT SHARE IDENTICAL OR SIMILAR R1 AND IDENTICAL R2 SIDE CHAINS

	Penicillin G	Penicillin VK	Amoxicillin	Ampicillin	Nafcillin/Oxacillin	Piperacillin-Tazobactam	Cefazolin	Cephalexin	Cefadroxil	Cefuroxime	Cefoxitin	Cefdinir	Cefpodoxime	Ceftriaxone	Cefotaxime	Ceftazidime	Cefepime	Ceftaroline	Ceftolozane-Tazobactam	Aztreonam
Penicillin G		R1 *																		
Penicillin VK	R1 *																			
Amoxicillin				R1 *				R1 *	R1											
Ampicillin			R1 *					R1	R1 *											
Nafcillin/Oxacillin																				
Piperacillin-Tazobactam																				
Cefazolin																				
Cephalexin			R1 *	R1					R1 *											
Cefadroxil			R1	R1 *				R1 *												
Cefuroxime											R2									
Cefoxitin										R2										
Cefdinir																				
Cefpodoxime														R1						
Ceftriaxone													R1		R1		R1			
Cefotaxime														R1			R1			
Ceftazidime																				R1
Cefepime														R1	R1					
Ceftaroline																			R1	
Ceftolozane-Tazobactam																		R1		
Aztreonam																R1				

Key: R1 = Identical R1 side chain; R1* = similar side chain; R2 = Identical R2 side chain

PATIENT INCLUSION/EXCLUSION CRITERIA FOR ASSESSMENTS AND MEDICATION CHALLENGES

A. **Inclusion Criteria for Assessment**:
   i. Patient is ≥18 years old
   ii. Patient has a listed history of a reaction to any PCN class antibiotic including penicillin, amoxicillin, ampicillin, ampicillin-sulbactam, nafcillin, oxacillin, dicloxacillin, or piperacillin-tazobactam
   iii. Patient or family member able and willing to undergo assessment
      a. If patient is unable to undergo assessment (e.g. intubated, altered mental status, etc), a chart review could be conducted to determine if patient has received a PCN class antibiotic previously in the electronic medical record
      b. Patient's allergy history can only be updated if there is documentation that patient received and tolerated a PCN class antibiotic through an inpatient administration NOT an outpatient prescription

B. **Exclusion Criteria for oral amoxicillin challenge or graded challenge procedure:**
   i. If patient or patient's representative does not verbally consent to receiving or oral amoxicillin challenge or graded challenge. **Primary team will be responsible for obtaining and documenting consent prior to the procedure.**
      1. *For graded challenge:* if patient is altered or intubated, a risk vs. benefit discussion should be had with primary team and patient's representative prior to proceeding as patient will not be able to verbally state a response; however vital signs can be used as a surrogate marker for tolerance of graded challenge.
   ii. Pregnant
   iii. *For oral amoxicillin challenge:* Patient has taken a first generation H1 receptor antagonist (i.e. diphenhydramine) in the past 24 hours.
   iv. *For oral amoxicillin challenge and graded challenge:* Patient has taken a beta-blocker prior to challenge procedure as beta-blockers can blunt the effects of epinephrine.
      1. If patient is on a beta-blocker, next dose should be held and the challenge should be scheduled for the following morning prior to the first dose of the day.
   v. Nursing staff is unable to accommodate procedure based on current staffing.

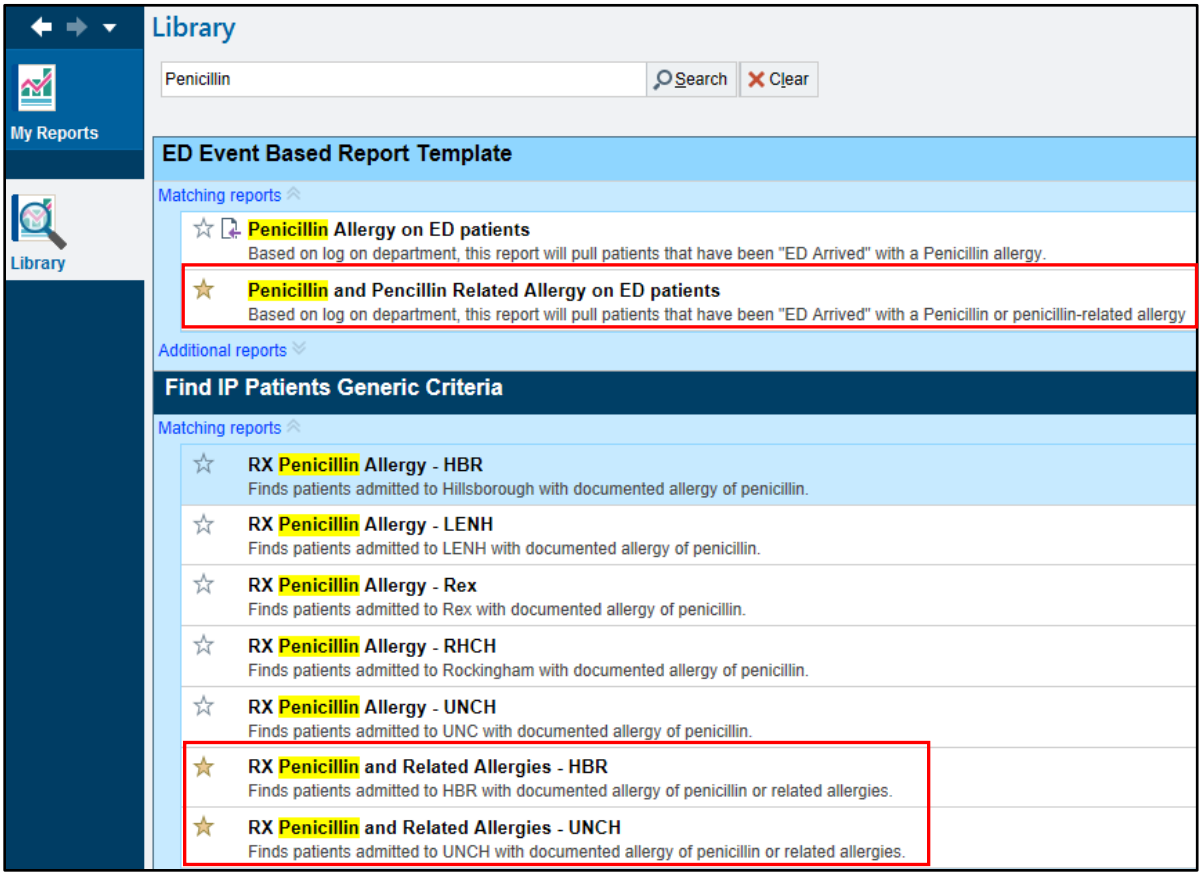
OVERVIEW OF PCN ALLERGY ASSESSMENTS

A. Penicillin allergy assessments can be conducted by a pharmacist, pharmacy resident, pharmacy student, mid-level practitioner, or any provider who is trained
   i. Assessments conducted by pharmacy resident or student must be reviewed by the primary preceptor prior to signing note

ii. In person training will be offered by a trained pharmacist or through a recorded PowerPoint presentation

B. Patients will be identified for allergy assessments by service pharmacist through either an EPIC report or addition of "RX PCN Allergy" as a column in patient list.
   i. **For Patient column:** Select Properties → Search RX PCN → Add RX PCN Allergy to patient list
   ii. **For EPIC Report:** Click Epic drop down menu and go to Reports → My Reports → Library → Search for report based on hospital location (FIGURE 2)

FIGURE 2: PENICILLIN ALLERGY REPORT

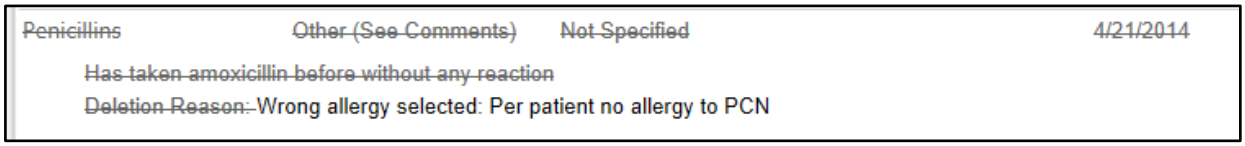


iii. Report can be starred and can be added to favorite reports
   1. **UNC MC**: Rx Penicillin and Related Allergies – UNCH
   2. **UNC ED**: Penicillin and Penicillin Related Allergy on ED patients
   3. **Hillsborough:** RX Penicillin Allergy and Related Allergies – HBR

iv. After report has run, Select "Filters" in top left corner to narrow patient list by service.
   1. Click "Service" → Select appropriate medicine/surgery service

v. Report includes patient's name, MRN, room/hospital location, service, allergies, and active orders for antimicrobials
    1. Report does identify patients who have been previously de-labeled (FIGURE 3) as penicillin is still listed in allergy section. **These patients do not need to undergo an assessment.**

FIGURE 3: DELETED PENICILLIN ALLERGY



C. Service pharmacist should prioritize assessments for patients on concomitant antibiotic therapy and an assessment could have an impact on current antimicrobial plan of care.

D. Pharmacist allergy assessment will include the following:
    i. Patient interview
    ii. Review EMR for prior antibiotic administration
    iii. Update of the allergy record with pertinent findings

E. If indicated, pharmacist will provide recommendation to the primary team regarding changes in antibiotic therapy.

F. If a patient undergoes an oral amoxicillin or graded challenge procedure, the pharmacist will document the results of the allergy assessment EPIC and update the patient's allergy information.

DOCUMENTATION OF ALLERGY ASSESSMENT

A. Allergy Assessment Note
    a. All activities related to the allergy assessment require documentation as a consult note in EPIC.
    b. Following dot phrase will be used for documentation: .PENICILLINALLERGYINPT (Appendix: FIGURE 2)
    c. After history is obtained, patient's allergy should be stratified into the following categories: intolerance, not allergic (de-label), low-risk, moderate-high risk, or severe non-IgE risk.
    d. Inpatient Risk Stratification Chart (Appendix: FIGURE 1) should be used as a reference for risk stratification

ORAL AMOXICILLIN CHALLENGE OVERVIEW AND PROCEDURE

A. An oral amoxicillin challenge can be considered to evaluate true PCN allergy when risk of allergic reaction is considered low risk based on history (Appendix: FIGURE 1)

B. An oral amoxicillin challenge can be administered on all inpatient units, step-down units, and/or intensive care units

C. Providers must obtain consent prior to proceeding with challenge (.ATTESTCONSENT)

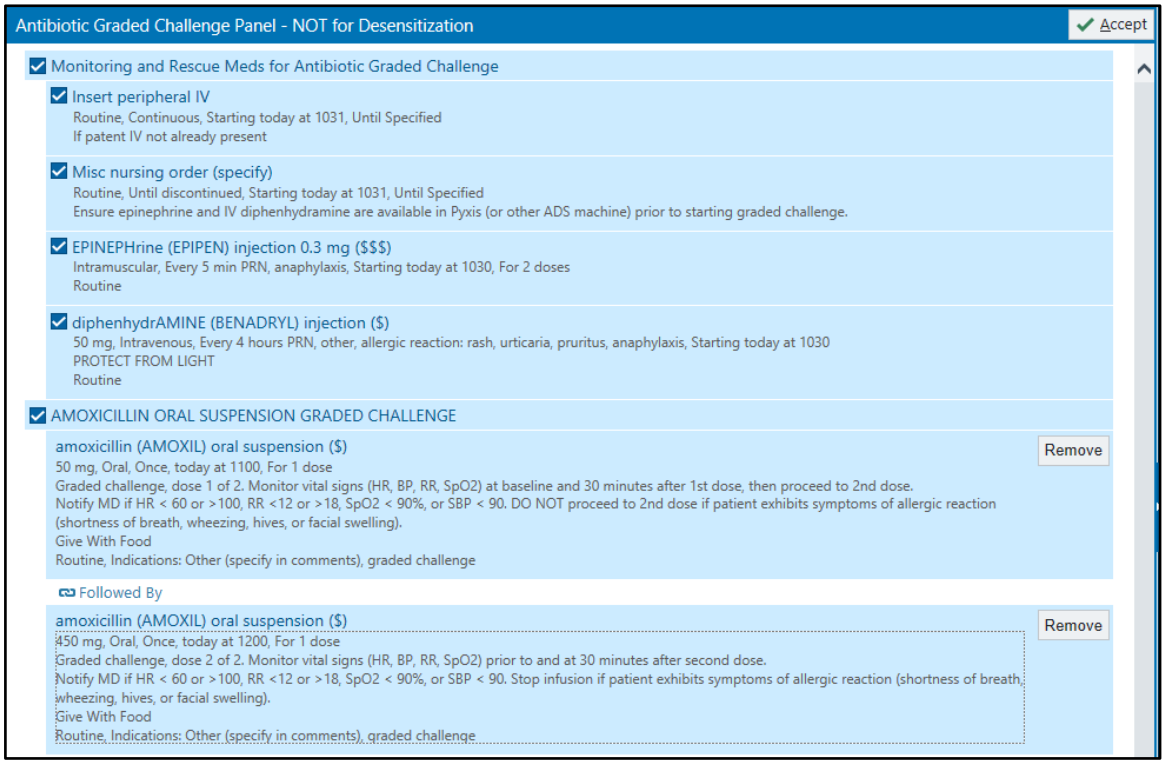
D. Oral amoxicillin challenge (FIGURE 4) can be ordered through the **ANTIBIOTIC GRADED CHALLENGE PANEL – NOT FOR DESENSITIZATION** order panel

E. Nurse will obtain vital signs (HR, BP, RR, SpO_2) at the beginning of procedure and 30 minutes after the dose has been ingested for one hour. The nurse should notify the primary team if there are vital sign abnormalities according the parameters in the Epic order panel.

F. A rapid response should be called if the patient experiences any signs of anaphylaxis (e.g., angioedema, SOB, wheezing, throat closing, faintness, etc.)

G. If a patient passes the oral amoxicillin challenge, the patient can receive other PCN class antibiotics as indicated at the normal dose and frequency

FIGURE 4: ANTIBIOTIC GRADED CHALLENGE PANEL – ORAL AMOXICILLIN CHALLENGE



INTRAVENOUS GRADED CHALLENGE OVERVIEW AND PROCEDURE

A. Graded challenges (also known as Test Dose Procedure) are a method of cautiously administering a medication when the risk of allergic reaction is low

B. Graded challenges can be administered on all inpatient units, step-down units, and/or intensive care units

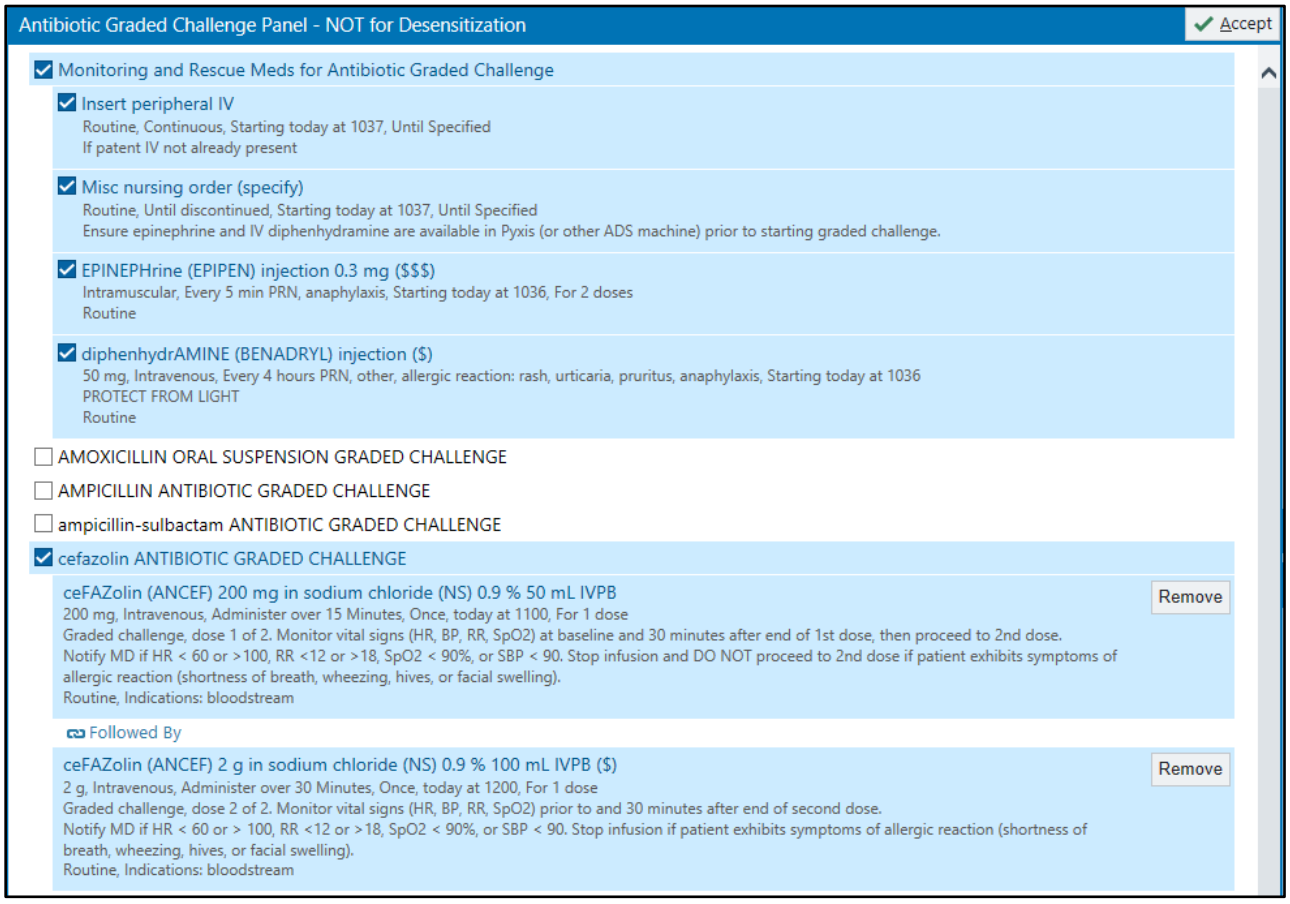
C. Providers must obtain consent prior to proceeding with challenge (.ATTESTCONSENT)

D. Graded challenges are not desensitization and should be used as directed (Appendix: FIGURE 1)
   a. Provider will order antibiotic from the **ANTIBIOTIC GRADED CHALLENGE PANEL – NOT FOR DESENSITIZATION** (FIGURE 5) order panel
   b. Nursing orders are included in medication administration comments. The nurse should notify the primary team if there are vital sign abnormalities according the parameters in the Epic order panel.

      i. Dose 1 of 2: Administer 1/10th therapeutic dose over 15 minutes
         a. Dose will be compounded in the central inpatient pharmacy.
         b. Nursing instructions: Monitor vital signs (HR, BP, RR, SpO2) at baseline and 30 minutes after end of 1st dose, then proceed to 2nd dose. Notify MD if HR < 60 or > 100, RR <12 or >18, SpO2 < 90%, or SBP < 90. Stop infusion and DO NOT proceed to 2nd dose if patient exhibits symptoms of allergic reaction (shortness of breath, wheezing, hives, or facial swelling).

      ii. Dose 2 of 2: Administer full dose over either 30 minutes to an hour
         a. Dose will be provided by the central inpatient pharmacy or could be available on the floor depending on location.
         b. Nursing instructions: Monitor vital signs (HR, BP, RR, SpO2) prior to and 30 minutes after end of second dose. Notify MD if HR < 60 or > 100, RR <12 or >18, SpO2 < 90%, or SBP < 90. Stop infusion if patient exhibits symptoms of allergic reaction (shortness of breath, wheezing, hives, or facial swelling).

FIGURE 5: ANTIBIOTIC GRADED CHALLENGE PANEL – CEFAZOLIN GRADED CHALLENGE EXAMPLE



E. A rapid response should be called if the patient experiences any signs of anaphylaxis (e.g., angioedema, SOB, wheezing, throat closing, faintness, etc.)

F. When a patient passes a graded challenge, this proves they do not have an IgE-mediated allergy to the medication. The medication can be administered at the usual dose and frequency for subsequent doses as long as no new reaction has developed.

G. If the challenge is passed to the same medication listed as an allergy (e.g. penicillin allergy listed and patient tolerates nafcillin graded challenge), this allergy should be deleted from the patient's medical record.

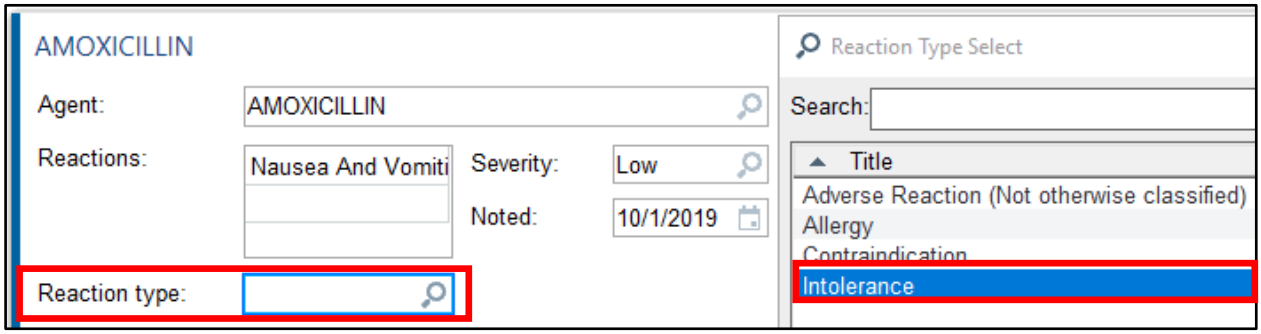
   i. If the challenge medication is in a related medication class (e.g. penicillin allergy listed and patient passes graded challenge to ceftriaxone), allergy history should be updated to include that patient has tolerated that medication but the allergy to the original medication should not be removed (FIGURE 8).

UPDATING THE ALLERGY HISTORY

A. Allergy information should be updated in the EMR to reflect the findings of the allergy history and/or oral amoxicillin challenge/graded challenge in addition to writing the consult note.

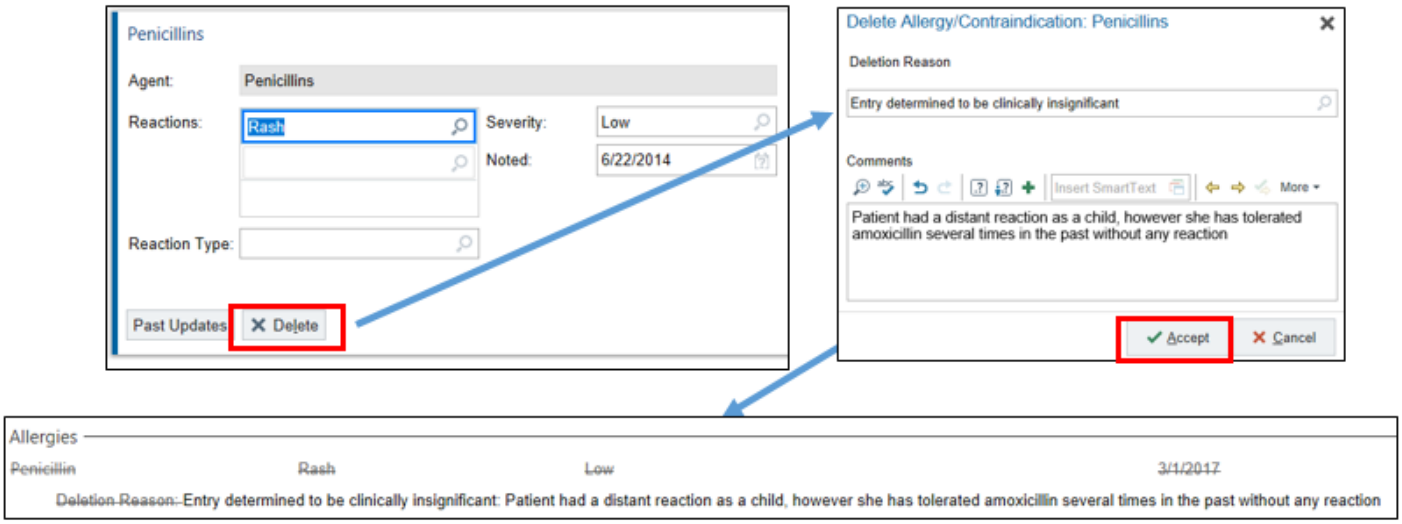
B. Updating Allergy to Intolerance (FIGURE 6)
   i. If symptoms are listed as an allergy but are actually more indicative of an intolerance, allergy section should be updated
   ii. Click into allergy and choose "Intolerance" for reaction type
   iii. This will update allergy to appropriately display in the intolerance section

FIGURE 6: UPDATING ALLERGY TO INTOLERANCE



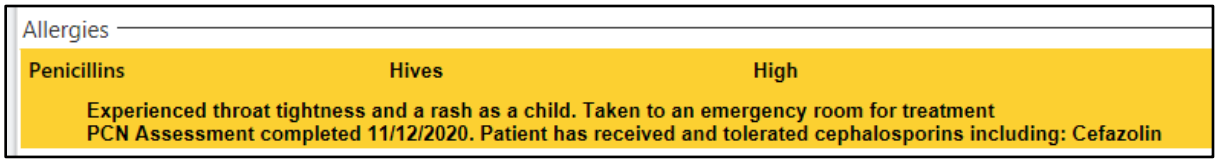
C. Deleting the PCN Allergy (FIGURE 7)
   i. If history demonstrates patient is not allergic to PCN (e.g. has taken and tolerated a PCN class antibiotic since initial reaction) OR if graded challenge to PCN class antibiotic or oral amoxicillin challenge is passed, allergy profile should be updated and listed allergy to PCN class antibiotic should be removed.
   ii. Click into allergy and select "Delete", choose the most applicable deletion reason, and enter into the comments reason for allergy deletion (e.g. "Patient has taken and tolerated amoxicillin since previous reaction").
   iii. Deletion reasons include:
      1. Entry determined to be clinically insignificant
      2. Entry miscategorized as an allergy
      3. Erroneous entry
      4. Wrong allergy selected
      5. Wrong patient selected

FIGURE 7: DELETING PCN ALLERGY



A. Updating Allergy Information after medication challenge/assessment (FIGURE 8)
   i. Updating allergy after allergy assessment
      1. Regardless of if patient undergoes a challenge, allergy history should be updated to include what other beta-lactams the patient has received and tolerated
      2. If patient tolerates a cephalosporin graded challenge, this information could be added to patient's allergy history to include what beta-lactams the patient has received/tolerated; however the allergy to the PCN class antibiotic will not be removed.
         a. This information can be can be free-texted in or by using .PENICILLINALLERGYUPDATE dotphrase (FIGURE 8):
         b. Assessment completed **/**/**. Patient {Blank single:19197:: "has received and tolerated cephalosporins including ***", "has not received any documented cephalosporins"}. Patient {Blank single:19197:: "has received and tolerated carbapenems

FIGURE 8: UPDATED ALLERGY AFTER ASSESSMENT

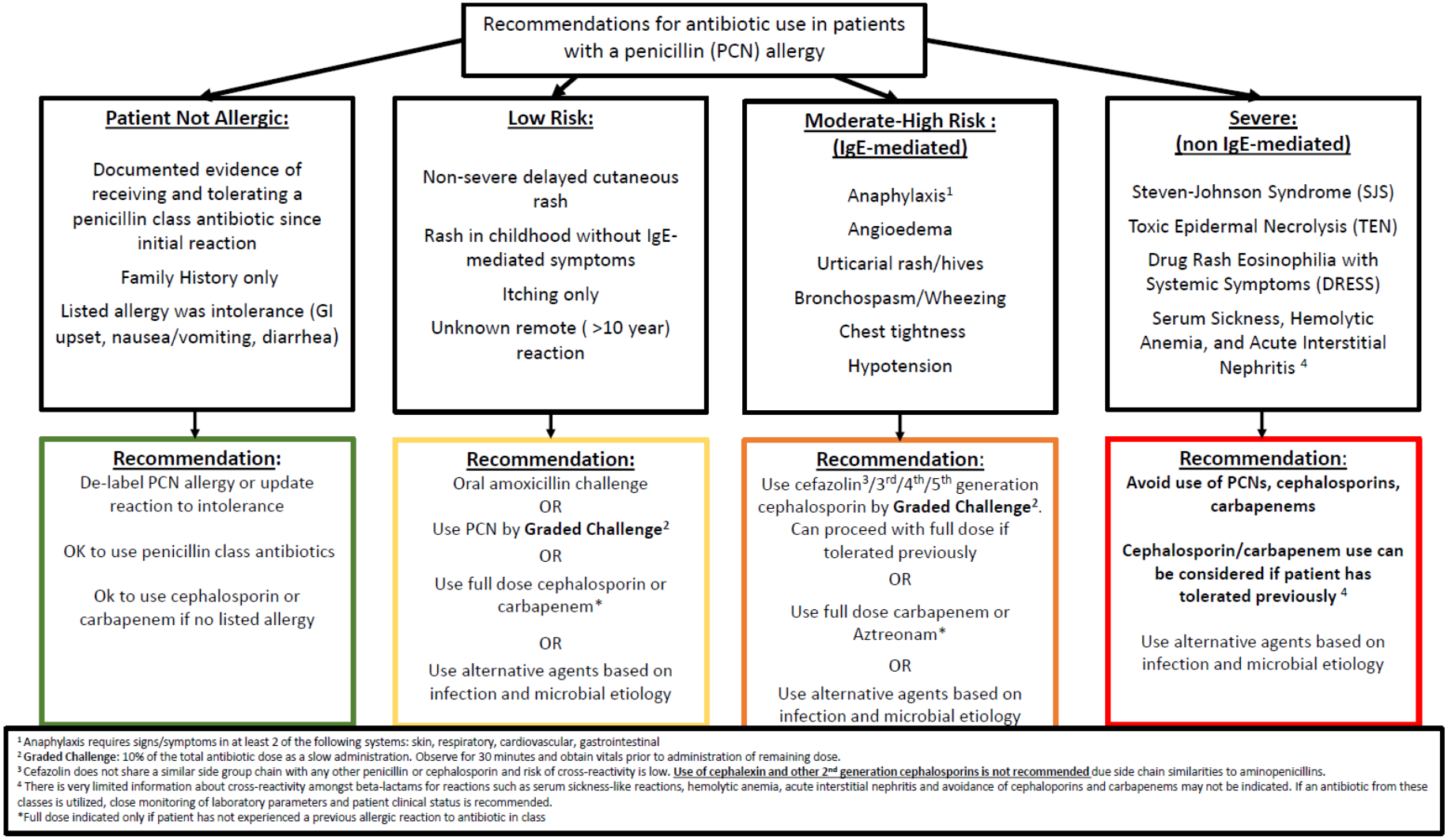


PATIENT EDUCATION

A. To prevent relabeling, patients who are delabeled through pharmacy assessment, oral amoxicillin challenge, or IV PCN class graded challenge should receive counseling to no longer consider themselves allergic to penicillin or penicillin class antibiotics.
    a. Delabeled patients should also be instructed to update their allergy history by requesting removal of the listed PCN allergy at their pharmacy and outside provider offices.

APPENDIX:

FIGURE 1: RISK STRATIFICATION CHART AND ANTIBIOTIC USE IN PATENTS WITH A PCN ALLERGY



[1] Anaphylaxis requires signs/symptoms in at least 2 of the following systems: skin, respiratory, cardiovascular, gastrointestinal
[2] **Graded Challenge**: 10% of the total antibiotic dose as a slow administration. Observe for 30 minutes and obtain vitals prior to administration of remaining dose.
[3] Cefazolin does not share a similar side group chain with any other penicillin or cephalosporin and risk of cross-reactivity is low. **Use of cephalexin and other 2nd generation cephalosporins is not recommended** due side chain similarities to aminopenicillins.
[4] There is very limited information about cross-reactivity amongst beta-lactams for reactions such as serum sickness-like reactions, hemolytic anemia, acute interstitial nephritis and avoidance of cephaloporins and carbapenems may not be indicated. If an antibiotic from these classes is utilized, close monitoring of laboratory parameters and patient clinical status is recommended.
*Full dose indicated only if patient has not experienced a previous allergic reaction to antibiotic in class

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FIGURE 2: ASSESSMENT DOT PHRASE (.PENICILLINALLERGYINPT)

Penicillin Allergy Assessment

Pt is a @AGE@ YO @SEX@ with undergoing assessment of listed penicillin allergy.

PATIENT REPORTED ALLERGY HISTORY:
Medication associated with reaction: {Penicillins:71596}
Route of administration: {Blank single:19197:: "oral", "intravenous", "intramuscular", "unknown"}
Indication for antibiotic: ***
Description of Reaction:

- How long ago was the reaction? {Blank single:19197:: "< 6 months", "6 months - 5 yrs", "6-10 yrs", "> 10 yrs", "unknown"}
- What symptoms occurred?
  - Intolerances: {Intolerances:61557}
  - Low-risk: {Low Risk Inpatient :79325}
  - Moderate-high risk: {Moderate-high risk allergy histories:61560}
  - Severe non IgE-mediated: {Severe Non IgE-Mediated Reactions:79647}
  - Other: {Blank single:19197:: "family history only", "***", "N/A"}
- Timing/onset till symptoms: {Blank single:19197:: "Immediate (< 4 hrs)", "Intermediate (4 - 24 hrs) ", "Delayed (> 24 hr)", "Unknown"}
- Treatment: {Treatment Allergy:71597}

Have you taken and tolerated any penicillin-class antibiotics since this reaction? {Blank single:19197:: "Yes, patient has taken ***", "No", "Unsure"}

Documentation of patient receiving penicillin-class antibiotic in the medical record: {PCN ALLERGY CHART REVIEW:71602}

Documentation of patient receiving a cephalosporin in the medical record: {PCN ALLERGY CHART REVIEW:71602}

Documentation of patient receiving a carbapenem in the medical record: {PCN ALLERGY CHART REVIEW:71602}

ASSESSMENT/PLAN:

- Based on allergy and medication history, would classify patient's penicillin allergy as {Blank single:19197:: "an intolerance and allergy updated to reflect intolerance.", "inaccurately labeled as patient has received and tolerated a penicillin class antibiotic after initial reaction.", "low-risk.", "moderate-high risk IgE-mediated allergy.", "a severe non IgE-mediated allergy."}
- {Inpatient PCN Plan:79327}

Time Spent: {Time Spent:79561}

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