CLINICAL DECISION SUPPORT TOOL FOR ANTIBIOTIC ALLERGIES

This document accompanies and explains the basis of the Antibiotic Allergy Tool.

Background:

Antibiotic allergies are commonly reported by hospitalized patients and/or in their EMRs. Antibiotic allergy labels can complicate treatment of infections and are associated with many undesirable outcomes, including longer hospitalizations, less effective infection treatment, antibiotic resistance, and increased costs. Most antibiotic allergies can be safely revisited to either introduce a related antibiotic or to "delabel" the original antibiotic allergy. Beta lactams and vancomycin can often be safely reintroduced after appropriate evaluation ("risk stratification"), which may include skin testing and/or graded challenges ("test doses"). Over 80% of patients who report penicillin allergy can safely tolerate penicillins and other beta lactams. A significant portion of this evaluation could be accomplished by the inpatient primary team using a decision support tool, with Allergy consultation when appropriate. Partnership with Nursing and Pharmacy provides a coordinated system for cautious introduction of needed antibiotics. Evaluations of antibiotic allergies can improve use of first-line antibiotics and reduce use of costly, less effective, and/or unnecessarily broad antibiotics, which can improve treatment efficacy, reduce length of hospitalization, increase treatment options, and reduce costs.

A clinical decision tool to assist primary teams in doing an allergy evaluation has been developed by faculty from Allergy/Immunology and Infectious Diseases, based on the Drug Allergy Practice Parameters from the American Academy of Allergy, Asthma, and Immunology (2022), and on literature from Brigham and Women's Hospital and Massachusetts General Hospital (Blumenthal et al 2014, Blumenthal et al JACI IP 2017).

Purpose:

1. To guide clinicians in classifying and assessing risk in patients with known or suspected allergy to penicillins, cephalosporins, carbapenems, aztreonam, or vancomycin.
2. To guide clinicians in prescribing antibiotics in patients with history of beta-lactam or vancomycin allergy but thought to be at low risk for current allergy.

Procedure:

STEP 1: Assessing the Patient's Risk of Challenge

To be able to proceed with a hypersensitivity pathway, the patient should meet these criteria:

- Able to report symptoms, or to be closely monitored for symptoms
- Stable respiratory status (no acute wheezing or respiratory distress)
- No active angioedema or urticaria
- No unstable angina

- No contraindications to epinephrine
- No extensive skin disease that might obscure interpretation of a skin reaction
- If on a beta blocker (such as metoprolol, bisoprolol, atenolol, carvedilol, labetalol, propranolol, etc.), can tolerate holding the beta blocker starting 24 hours prior to challenge, until challenge is completed

Does the patient meet the above criteria?

- If yes, proceed with "Assessing and Classifying the Reaction."
- If no, but there is still interest in antibiotic challenge or desensitization, please call for an Allergy consult.

STEP 2: Assessing and Classifying the Reaction

Start with (A) and follow stepwise.

(A) Did the reaction include one or more of the following that was attributable to the antibiotic?

  - Severe cytopenias (including but not limited to hemolytic anemia)
  - Nephrotoxicity that was not dose-dependent, as in acute interstitial nephritis and DRESS (Drug Rash Eosinophilia Systemic Symptoms)/Drug-induced hypersensitivity syndrome (DIHS)
  - Transaminitis/hepatotoxicity that was not dose-dependent (includes standard transaminitis and DRESS/DIHS)
  - Other organ involvement (e.g., drug-induced pancreatitis, aseptic meningitis)
  - Joint pains (e.g., serum-sickness like reaction)
  - Fluid-filled blisters, ulcers, or significant peeling/sloughing of skin (skin and mucosa including eyes, mouth, perineum), as in Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN)
  - Extensive rash requiring hospitalization, with onset days or weeks after starting the culprit medication, +/- eosinophilia (possible DRESS/DIHS)
- If yes: classify as a "Type II-IV HSR" and go to **STEP 3**.
- If no: proceed to (B).

(B) Did the reaction involve one or more of the following that was attributable to the antibiotic, with onset within a few hours of administration?

  - Hives (i.e., welts / urticaria: large, raised, pruritic, red, migratory, changing over hours, each lesion lasting <24 hr)
  - Flushing
  - Angioedema (swelling of lips, eyes, tongue, or tongue)
  - Difficulty breathing, bronchospasm, wheezing, or dyspnea

- Throat constriction / laryngeal edema
- Hypotension
- Anaphylaxis
- Treated with epinephrine
- Resolved within hours to one day
- Unknown reaction without mucosal involvement, skin desquamation or organ involvement

- If yes: classify as “Type I HSR,” and go to **STEP 3**.
- If no: proceed to (C).

(C) Was the reaction limited to one of the following descriptions?

- Mild, red/pink, possibly itchy rash with small bumps (maculopapular), onset several days after starting the antibiotic, then subsiding over several days after stopping it, not requiring urgent evaluation
- Vague, nonspecific rash without concerning features, and subsiding within a few days without specific intervention
- Minor adverse effect, such as nausea, vomiting, diarrhea, or mild local injection reactions
- Medical record lists allergy, but patient reliably denies reaction

- If yes: then classify as "Mild Reaction", and go to **STEP 3**.
- If no: then proceed to (D).

(D) If the reaction does not fit in any of the above classifications, please call Allergy fellow to discuss. It may be helpful to also ask:

- How long ago was the reaction, and did it happen on other occasions?
- Has the patient tolerated related medications, particularly other antibiotics within the same class (penicillins, cephalosporins, carbapenems), and when were those exposures?

STEP 3: Picking a Pathway

Patient has history of reaction to:	**Desired antibiotic is:**	**Proceed with:**
Penicillin-class antibiotic	Penicillin Cephalosporin Carbapenem	Penicillin Hypersensitivity Pathway
Cephalosporin-class antibiotic	Penicillin Cephalosporin Carbapenem	Cephalosporin Hypersensitivity Pathway
Vancomycin	Vancomycin	Vancomycin Hypersensitivity Pathway

PENICILLIN HYPERSENSITIVITY REACTION (HSR) PATHWAY

(Adapted from Blumenthal et al JACI IP 2017)

TYPE II-IV HSR	**TYPE I HSR**	**MILD REACTION**
Serum sickness Stevens-Johnson Syndrome (SJS) Toxic Epidermal Necrolysis (TEN) Acute Interstitial Nephritis (AIN) Drug Rash Eosinophilia Systemic Symptoms (DRESS) Hemolytic anemia / cytopenias Drug Fever	Hives Anaphylaxis Angioedema Wheezing / bronchospasm Dyspnea Laryngeal edema Hypotension Urticaria OR Unknown reaction WITHOUT mucosal involvement, skin desquamation, or organ involvement	Minor rash (**not** urticaria/hives) Mild adverse reaction (nausea/vomiting, diarrhea) OR Allergy listed in medical record but patient reliably denies
↓	↓	↓
Avoid using beta-lactams (penicillins, cephalosporins, and carbapenems): Use alternative agent OR If clinical indication for beta-lactam present, please involve Infectious Diseases and Allergy services	If a cephalosporin or carbapenem desired, then check side chain chart. If there are shared side chains, consult Allergy. If there are no shared side chains, then give full dose. NB: can proceed with full dose of cefazolin. If penicillin is desired, then consult Allergy. OR Use alternative agent	If a cephalosporin or carbapenem desired, then give full dose If a penicillin is desired, then give by **Graded Challenge (Test Dose) Procedure**

CEPHALOSPORIN HYPERSENSITIVITY PATHWAY

TYPE II-IV HSR	**TYPE I HSR**	**MILD REACTION**
Serum sickness Stevens-Johnson Syndrome (SJS) Toxic Epidermal Necrolysis (TEN) Acute Interstitial Nephritis (AIN) Drug Rash Eosinophilia Systemic Symptoms (DRESS) Hemolytic anemia / cytopenias Drug Fever	Anaphylaxis Angioedema Wheezing / bronchospasm Dyspnea Laryngeal edema Hypotension Urticaria OR Unknown reaction WITHOUT mucosal involvement, skin desquamation, or organ involvement	Minor rash (not urticaria/hives) Mild adverse reaction (nausea/vomiting, diarrhea) OR Allergy listed in medical record but patient reliably denies
↓	↓	↓
Avoid using beta lactams (penicillins, cephalosporins, and carbapenems): Use alternative agent OR If clinical indication for beta-lactam, please involve Infectious Diseases and Allergy services	If penicillin or cephalosporin with similar side chains is needed, consult Allergy or use alternative agent. If carbapenem or penicillin/cephalosporin **without** similar side chains is needed, then give by **Test Dose Procedure**.	If penicillin or cephalosporin with similar side chains is needed, use **Test Dose Procedure**. If carbapenem or penicillin/cephalosporin **without** similar side chains desired, give full dose.

VANCOMYCIN HYPERSENSITIVITY PATHWAY

TYPE II-IV HSR	**TYPE I HSR OR "VANCOMYCIN INFUSION REACTION "**	**MILD REACTION**
Serum sickness Stevens-Johnson Syndrome (SJS) Toxic Epidermal Necrolysis (TEN) Acute Interstitial Nephritis (AIN) Drug Rash Eosinophilia Systemic Symptoms (DRESS) Hemolytic anemia / cytopenias Drug Fever Linear IgA bullous dermatosis	Anaphylaxis Angioedema Flushing Wheezing / bronchospasm Dyspnea Laryngeal edema Hypotension Urticaria OR Unknown reaction WITHOUT mucosal involvement, skin desquamation, or organ involvement	Minor rash (not urticaria/hives) Mild adverse reaction (nausea/vomiting, diarrhea) OR Allergy listed in medical record but patient reliably denies
↓	↓	↓
Avoid vancomycin: Use alternative agent OR If clinical indication for vancomycin, please involve Infectious Diseases and Allergy services	If reaction was severe and/or included angioedema, airway constriction, hypotension, or syncope, then **consult Allergy.** Otherwise, administer by **Vancomycin Modified Administration**	Administer by **Vancomycin Modified Administration**

Appendix A. Beta-lactam Side Chain and Cross-Reactivity Charts

I. Beta-Lactam Class (From Romano et al 2020)

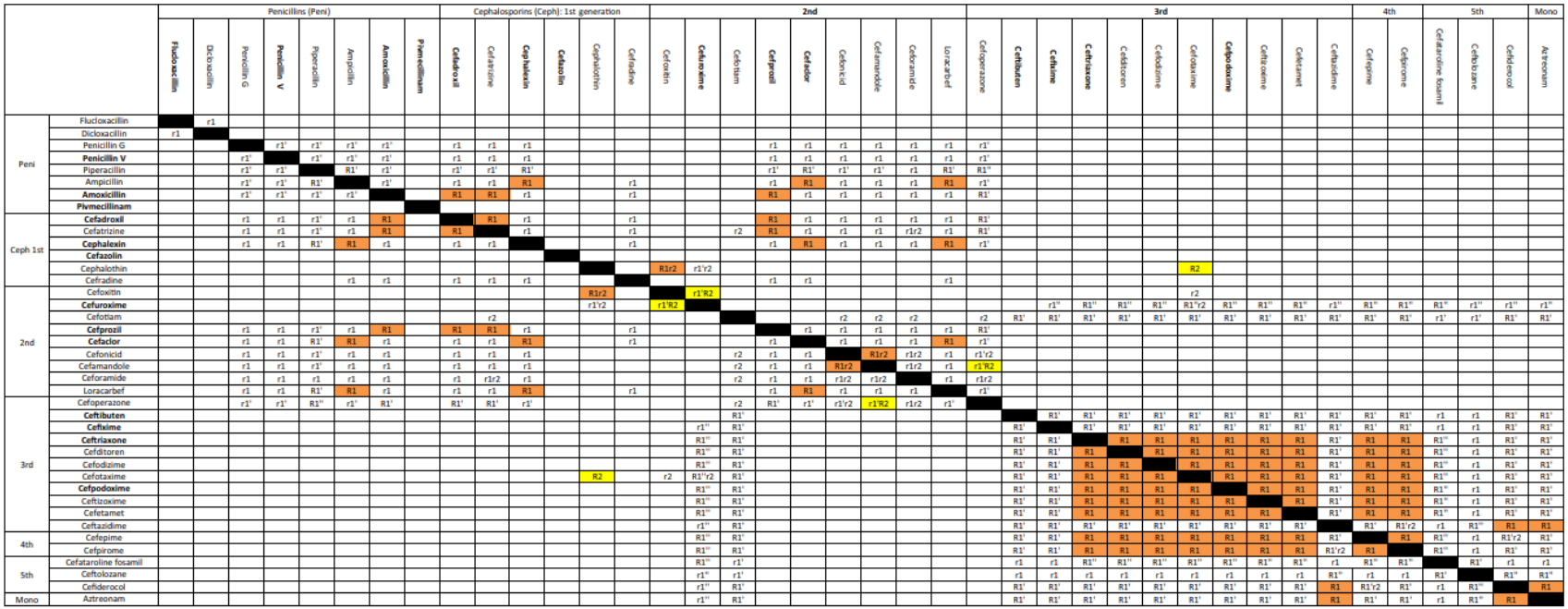
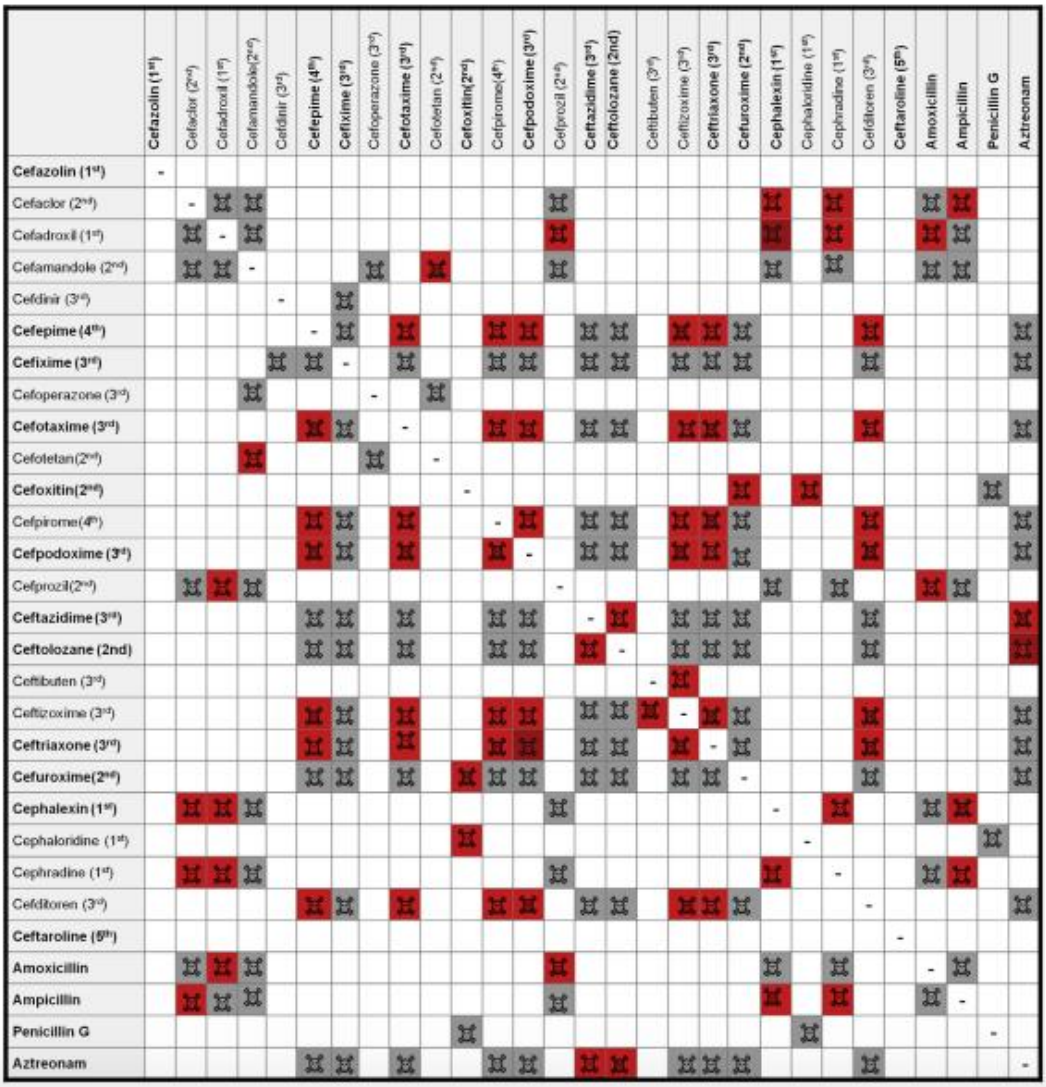


FIGURE 1 Comparison of R1 and R2 structural similarities between beta-lactams. Drugs that have identical R1 or R2 structures are listed as R1 (orange cell) or R2 (yellow cell). If only the ring or branch chain moiety of the R1 structure is identical, it is listed as R1′ or R1′′, respectively. Drugs that have similar R1 or R2 structures are listed as r1 or r2. If only the ring or branch chain moiety of the R1 structure is similar, it is listed as r1′ or r1′′, respectively. Blank cells imply no R1 or R2 structural similarities. Bold type for penicillins indicates that the related use represented more than 1% of total penicillin use in Europe in 2009. Bold type for cephalosporins indicates that the related use represented more than 1% of total outpatient cephalosporin use in Europe in 2009

II. Cephalosporin side chain chart (From Blumenthal et al 2017)



Appendix B. TEST DOSE (GRADED CHALLENGE) PROCEDURE (Adapted from Blumenthal et al 2014)

This is a procedure that can be performed by primary teams on a general hospital ward if recommended by the Antibiotic Allergy Tool in conjunction with allergist guidance. If the patient tolerates both the test dose and full dose, then this confirms that the patient does not have an immediate / Type I hypersensitivity reaction, including anaphylaxis. *This is not a desensitization.*

Use Epic orderset "Drug Graded Challenge [#1891]": As of January 2022, Allergy consultation is required to use the Graded Challenge orderset (except as part of Heme/Onc/BMT pilot, which requires phone review with Allergy fellow). For further guidance, please call unit pharmacist, or on-call Allergy fellow.

Graded Challenge procedure

1. Hold the following medications 24-hours prior to the day of the Test Dose Procedure:
    - Beta blockers (increase severity of allergic reaction and reduce response to treatment)
    - ACE inhibitors (may increase severity of allergic reaction)
2. PRN medications to be immediately available:
    - Epinephrine IM: 0.01 mg/kg IM PRN anaphylaxis (max 0.3 mg)
    - Diphenhydramine (Benadryl) IV: 1 mg/kg (max 50 mg/dose) IV Q4h PRN cutaneous hypersensitivity reaction, flushing OR hives OR itching OR swelling of lips/tongue/uvula
    - Albuterol inhaled (NEB): 2.5 mg PRN respiratory hypersensitivity reaction, dyspnea OR wheeze OR stridor
    - Sodium chloride 0.9% IV bolus: 20 ml/kg IV PRN hypotensive hypersensitivity reaction, systolic blood pressure less than lower limit of normal for age listed in vital sign parameters
3. Antibiotic Order per allergist recommendation
4. Nursing procedure: RN to record vital signs (BP, HR, RR, O2 sat) prior to administering the drug (time 0) and every 30 minutes from the start of the procedure to the end of the procedure (time 120 min.).
5. If the patient remains asymptomatic and vital signs remain normal, then the patient will have successfully completed the test dose procedure without any reaction and can subsequently receive the medication as scheduled by the team.

Additional Instructions:

- If a reaction occurs during or as a result of the graded challenge procedure, please page the Allergy fellow (pager **2-ITCH**).
- Document any appropriate changes in "Allergies" in Epic once Test Dose Procedure is completed.

Appendix C. Vancomycin Modified Administration

Review medications for opioids, such as morphine, meperidine, codeine. Avoid giving vancomycin in close proximity to opioids, radiocontrast media, muscle relaxants.

Standard vancomycin administration by IV intermittent infusion is over 60 minutes at a concentration not to exceed 5 mg/mL. Higher doses may need infusion time longer than 60 minutes; infuse doses 1001-1500 mg over at least 90 minutes and doses 1501-2000 mg over 120 minutes (see the HSM for details).

If patient develops mild vancomycin flushing syndrome (a.k.a. vancomycin infusion reaction) pause, treat with diphenhydramine, then restart at 30-50% original rate. Higher doses may need infusion time of up to 120 minutes. For future doses of IV vancomycin, patient may be premedicated with diphenhydramine 1 mg/kg IV (max 50 mg). For PO dosing, refer to the LPCH diphenhydramine weight-banded dosing in the HSM.

If tolerated, then continue to administer future vancomycin doses at the tolerated rate with diphenhydramine premed or other antihistamines and update the patient's allergy in the EHR.