

Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment

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Applicability:

- Ambulatory Surgery Center Arrington
- Duke University Hospital (DUH) (both campuses)
- Davis Ambulatory Surgery Center (DASC)
- Durham Campus Only
- Duke Health Integrated Practice (DHIP)
- Duke Raleigh Campus Only
- Duke Health Lake Norman Hospital (DLNH)
- Patient Revenue Management Organization (PRMO)
- Duke Health Technology Services (DHTS)
- Population Health Management Office (PHMO)
- Duke HomeCare & Hospice (DHCH)
- Duke Primary Care (DPC)
- Duke Regional Hospital (DRH)

Duke Infectious Disease Clinic 1K Penicillin Allergy Assessment Protocol

Version 2.0

DUH P&T Approved: March 2025

Applicability: 1

Background 2

Scope: 3

Competencies/Skills: 3

Definitions/Acronyms: 3

Procedure: 4

Appendix A. Questionnaire for patients with reported penicillin allergy [approved by DUH P&T] 5

Appendix B. Penicillin allergy delabeling algorithm 8

Appendix C. PST procedure 9

Appendix D. Direct Oral Challenge Procedure..... 13

Appendix E. Chart documentation example 16

Appendix F. Patient education example..... 17

Appendix G. Medications to Avoid Prior to Penicillin Skin Testing..... 18

References:..... 19

Associated Regulatory Standards: N/A..... 20

Associated Policies: 20

Background

Up to 10% of the U.S. population reports a penicillin allergy. On formal testing, however, fewer than 5% of reported allergies are confirmed.¹ As a direct consequence, many reportedly allergic subjects receive alternative antibiotics that are unnecessarily broad spectrum, less effective, or more costly.²⁻⁵ Antibiotic allergy assessment tools are validated for risk-stratification to assist with prescribing and delabeling. Low risk direct oral penicillin challenge can be implemented in the outpatient or inpatient setting to aid delabeling with an ASP focus.

Penicillin skin testing is a simple, safe, and highly effective procedure for assessing penicillin allergy which allows around 95% of patients with a reported penicillin allergy to be cleared of their allergy history.⁶⁻⁸ As a result, treatment options are improved dramatically – especially with regard to penicillins, aminopenicillins, and cephalosporins which are a mainstay of treatment for a wide range of infections. Penicillin skin testing has also been widely employed across a range of outpatient settings.⁹⁻¹¹ In each instance, testing proved to be safe and effective.

A formal penicillin skin testing (PST) program was approved by the Duke University Hospital P&T Committee and successfully implemented for inpatients at Duke University Hospital in May 2016 and outpatients in the Duke Infectious Disease Clinic 1K in February 2022.

Since approval of the original policy, there has been a shift to the utilization of direct oral challenge programs without prior skin testing.¹² There are over 3000 published oral challenges reported from 21 studies, with a significant body of the literature performed by non-allergists (8/21 studies) and positive oral challenge rate ranging from 0-10% (average 3.17%), thus supporting the addition of direct oral challenge to this policy. Moreover, a simple clinical scoring tool can accurately identify subjects at very low risk of allergic response who are thus appropriate for direct oral challenge. The PEN-FAST score was developed to predict risk of allergic response on direct oral challenge, independently validated in a multicenter prospective cohort, and recently proved successful in a multinational randomized controlled trial (which included Duke as a site).^{13,14} Direct oral challenge and the PEN-FAST scoring tool have been safely incorporated into the inpatient allergy assessments at Duke University Hospital since August 2023.

Purpose:

Given the benefit of penicillin allergy assessment in patients seen by the Duke Infectious Diseases Clinic 1K, the following protocol was modified to add direct oral challenge as an option for allergy assessment in the Clinic 1K outpatient population. The specific intent is to create an efficient process for penicillin allergy assessment, without requiring external referrals, for outpatients under the care of the Duke Infectious Diseases Clinic.

As has been demonstrated in the inpatient setting, the penicillin allergy assessment program in our clinic will improve patient care, reduce medical complications, and improve care transitions through

Procedure Title: **DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment**

antimicrobial allergy screening, objective allergy assessment, and, as appropriate, penicillin skin testing (PST) and/or direct oral challenge.

Scope:

Duke Infectious Diseases Clinic 1K

Competencies/Skills:

Clinic 1K physicians & advanced practice providers (APP): identify patients suitable for formal allergy assessment

Clinic 1K pharmacists (AIM): perform formal allergy assessment screening prior to scheduled clinic visit

PST clinician (pharmacist, physician, APP, RN): perform penicillin skin testing procedure and evaluation

Nursing staff: room patient, monitor vitals every 15 minutes during oral challenge procedure

Definitions/Acronyms:

Drug Allergy- an immunologically mediated response to a pharmacological and/or formulation agent.

Anaphylaxis- immediate systemic reaction that occurs when a previously sensitized individual is re-exposed to an allergen. It is caused when mast cells rapidly release vasoactive mediators (IgE) from tissue mast cells and peripheral basophils.

Pseudoallergic (anaphylactoid) reactions- immediate systemic reactions that mimic anaphylaxis but are caused by non-IgE mediated release of mediators from mast cells and basophils.

Drug intolerance- undesirable pharmacologic effect that may occur at low or usual doses of the drug without underlying abnormalities of metabolism, excretion, or bioavailability of the drug.

Drug desensitization- one form of induction of immune drug tolerance by which effector cells are rendered less reactive or nonreactive to IgE-mediated immune responses by rapid sequential administration of incrementally-escalating doses of an allergenic substance.

Graded challenge- describes administration of progressively increasing doses of a medication until a full dose is reached. The intent is to verify that a patient will not experience an immediate reaction.

Oral drug challenge (i.e., provocation): Administration of a drug orally, as a 1-step or 2-step test, to determine tolerance. A direct oral challenge is the administration of drug to assess for allergic reaction without prior skin testing.

- **1-step:** a single full dose of drug is administered followed by monitoring for symptoms of allergic reaction. This 1-step strategy is recommended by the Drug allergy: A 2022 practice parameter update by both the American Academy of Allergy, Asthma, and Immunology and the

Procedure Title: **DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment**

American College of Allergy, Asthma, and Immunology¹⁵; however, a 2-step test may be required for reimbursement in some regions.

- **2-step:** a multi-step process in which 10-25% of the treatment dose is administered followed by observation and if no adverse reactions are observed, the remainder of the treatment dose is administered followed by observation.

Prick test- a procedure in which the skin surface is lightly pricked and exposed to a potential allergy-producing substance.

Delabeling: the act of removing a drug allergy through allergy history, drug challenge, and/or skin testing. Direct delabeling is the removal without testing via medical reconciliation alone.

Procedure:

The allergy assessment program in Clinic 1K will systematically address and improve antimicrobial therapy in patients with reported allergies to beta-lactam antimicrobials. This program includes:

- 1) **Formal History-Based Assessment of Reported Penicillin Allergies** ([Appendix A](#)) –outpatients with reported allergies to penicillin will be identified by their primary infectious disease provider or AIM pharmacists. These patients will undergo formal allergy review by the patient’s primary ID provider and/or the AIM pharmacist through direct interaction with the patient or patient’s family.
- 2) **Clinical Allergy Assessment** – Allergy history will be applied to the Penicillin Allergy Delabeling Algorithm (([Appendix B](#)) to determine recommendations for subsequent actions including:
 - a. *Delabel with history alone:* Patients that have confirmed tolerance of penicillin or amoxicillin after index allergic reaction can be directly delabeled. The primary ID provider or AIM should discuss the allergy removal with the patient at the time of removal.
 - b. *Oral challenge:* Patients with a PEN-FAST ([Appendix D](#)) score of zero or 1 have <5% risk of allergic reaction and can be considered for direct oral challenge following the procedure in Appendix D.
 - c. *Penicillin Skin Testing (PST):* Patients with a PEN-FAST score of 2 or more will be assessed for PST using inclusion and exclusion criteria in Penicillin Skin Testing Algorithm ([Appendix C](#)).
 - d. *No further action:* Patients meeting exclusion criteria for PST, clinically unstable, or not amenable to oral challenge/PST will have allergy history documented through a progress note with no further action performed.
- 3) **Performance of Interventions** – Assessment results and recommended interventions will be discussed with the primary ID provider prior to performing oral challenge or PST. AIM pharmacists and designated Infectious Diseases providers have been or will be trained to perform allergy assessment interventions for qualifying patients identified in Step #2. Training for PST administration and post-skin test observation is detailed in Appendix E of the DUH Pharmacy: Allergy Assessment, Oral Challenge, and Penicillin Skin Testing for Adult Inpatients policy. All individuals administering PST will have documented competency through this training. AIM pharmacists and select Infectious Diseases providers have been/will be trained to perform allergy assessment interventions for qualifying patients identified in Step #2, including pre-skin testing

**Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K
Penicillin Allergy Assessment**

assessment, PST administration, and post-skin test observation. These clinicians will have documented competency by DUH Allergy service Medical Director

Location: The interventions performed by the individuals noted above will be performed in a designated patient room in Duke Clinic 1K.

Procedure Codes and Billing: Recommended CPT codes for Duke’s PST procedure are 95018 (allergy testing via percutaneous/intradermal route) and 95076 (ingestion challenge portion).

Table 1. The immunologic mechanisms and clinical manifestations of commonly encountered beta-lactam immune-mediated allergies

Immunologically Mediated Mechanisms	
Type I, Immediate Hypersensitivity (IgE-mediated)	Urticaria, angioedema, bronchospasm, anaphylaxis, cardiovascular collapse
Type II, Cytotoxic Reaction	Hemolytic anemia, petechia, thrombocytopenia
Type III, Immune-complex Reaction	Small-vessel vasculitis, serum sickness, Arthus reaction
Type IV: Cellular mediated (Delayed)	Contact dermatitis, exanthems
T-Cell Mediated Mechanisms	
DRESS	Epidermal edema, lymphadenopathy, atypical lymphocytosis, fever, eosinophilia, and infiltration of skin and internal organs
SJS-TEN	Epidermal necrosis, subepidermal bullae, and involvement mucosal membranes
AGEP	Fever, neutrophilic leukocytosis, sterile pustules in stratum corneum and epidermis, dermal edema, and infiltration of immune cells

Appendix A. Questionnaire for patients with reported penicillin allergy [approved by DUH P&T]

Question	Patient or Family Member Response
What is the name of the medication that you reacted to? – Most common one is “penicillin”	
How long ago did the reaction occur? How long did it take for symptoms to resolve?	
Which symptoms were involved in the reaction and what were the characteristics? – Skin: rash, hives (Have patient describe. Was there blistering, skin sloughing, mucosal membrane involvement, etc.?) – Angioedema (swelling)	

**Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K
Penicillin Allergy Assessment**

<ul style="list-style-type: none"> - Breathing: shortness of breath, wheezing, feeling of “throat closing” - Anaphylaxis: rapid onset of itchy rash, throat or face swelling, low blood pressure - Gastrointestinal: nausea, vomiting, diarrhea 	
<p>When during the course did the reaction occur?</p> <ul style="list-style-type: none"> - Immediate (within 1-4 hours of taking medication) - Delayed (3 days or more after starting medication) 	
<p>Why was the medication prescribed? (ex: sinus infection, dental procedure, UTI)</p>	
<p>Were you taking any other medications at the same time (antibiotics or other meds)</p>	
<p>What happened as a result of the allergic reaction?</p> <ul style="list-style-type: none"> - Did patient self-discontinue medication? - Did patient have to take Benadryl® or use an EpiPen®? - Did patient need to go to urgent care or the hospital for treatment? 	
<p>Have you tolerated the same or similar medication after the reaction?</p> <p>For similar medications, ask about trade names like:</p> <ul style="list-style-type: none"> - “Augmentin” (sometimes used for sinus infections) - “Keflex” (sometimes used for dental procedures in penicillin-allergic patients) - “Ceftin” & “Omnicef” can be used for UTIs, community-acquired pneumonia, or cellulitis 	
<p>Have you had symptoms similar to the allergic reaction without taking any drug treatment?</p>	

PEN-FAST Flowsheet

PEN-FAST Flowsheet

	5/18/2023
PEN-FAST Tool	
Penicillin allergy reported by patient	Yes
Time - Five years or less since reaction	2
Phenotype - Anaphylaxis/angioedema OR severe cutaneous adverse reaction	2
Treatment required for penicillin allergy episode?	0
PEN-FAST Total Score	4

The **PEN-FAST** penicillin allergy clinical decision rule enables point-of-care risk assessment of patient-reported penicillin allergies. It requires three clinical criteria:

Time (five years or less) from penicillin allergy episode (2 points)

Phenotype (anaphylaxis/angioedema OR SCAR) (2 points)

Treatment required for penicillin allergy episode (1 point)

The likelihood of a positive penicillin allergy test can be predicted from these criteria:

0 points – Very low risk of positive penicillin allergy test <1%

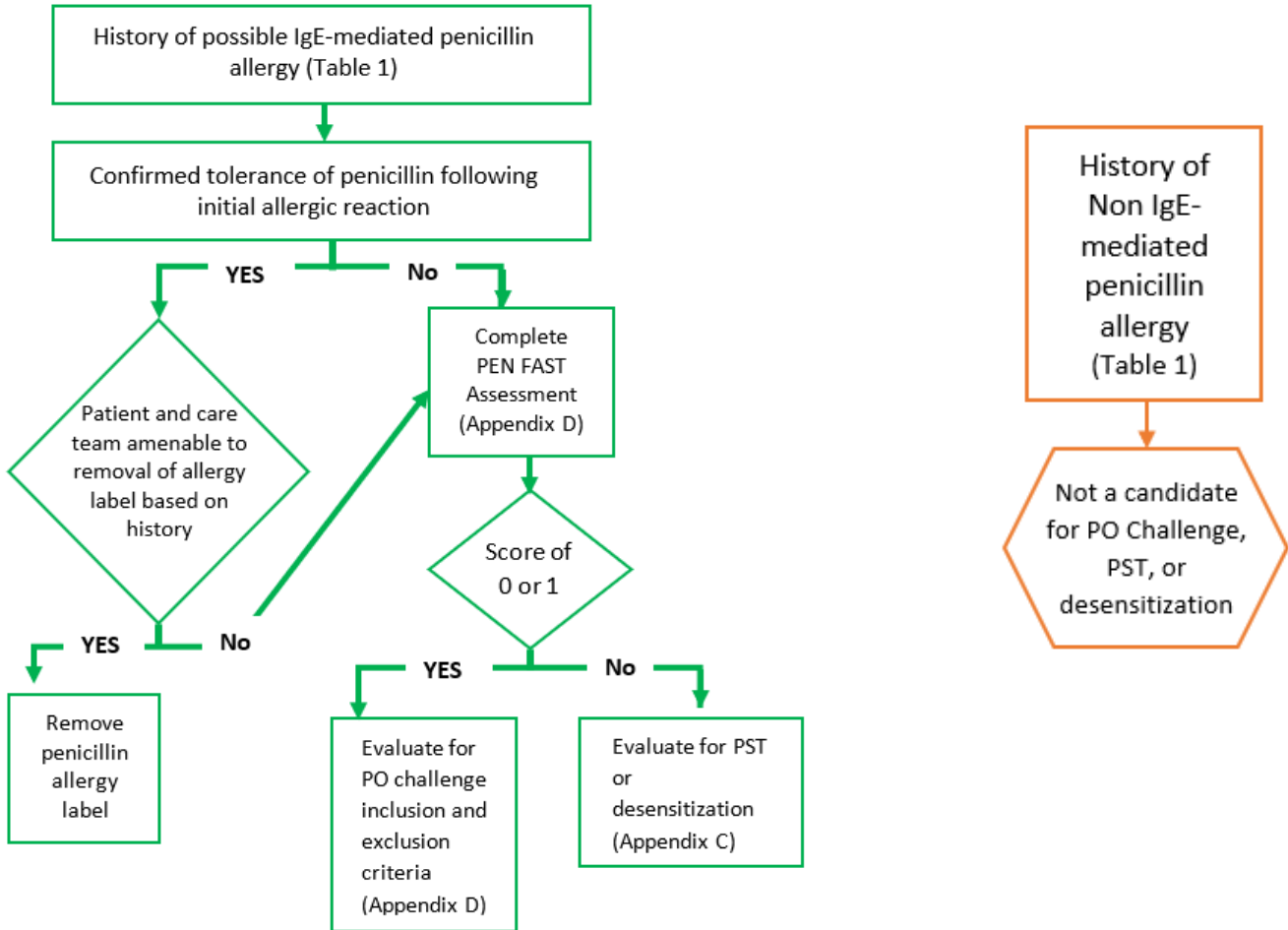
1-2 points – Low risk of positive penicillin allergy test 5%

3 points – Moderate risk of positive penicillin allergy test 20%

4-5 points – High risk of positive penicillin allergy test 50%

Reference: <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2762878>

Appendix B. Penicillin allergy delabeling algorithm



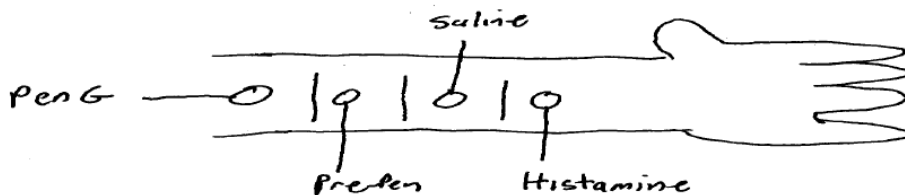
Procedure Title: **DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment**

Appendix C. PST procedure

1. PST clinicians can only administer PST after completing mandatory training by the Medical Director of the Allergy Consult service at DUH.
2. Prior to administration of the PST, patients must undergo a thorough allergy assessment to determine test eligibility. Assessment will be conducted in-person in clinic 1K or via telephone by a PST provider.
3. PST consult and order process:
 - a. The primary infectious disease provider will enter an inbox message to the 1K PST team for evaluation. The referral will prompt the PST clinician or designee to conduct an allergy assessment to determine eligibility for skin testing. Upon completion of the allergy assessment, the team member will inform the primary infectious disease provider whether or not the patient will benefit from a PST. Eligible patients will have an order processed for PST to be administered by the clinic 1K pharmacist or ID clinician. For patients not eligible for skin testing, alternative therapies will be discussed with the provider.
 - b. The clinic 1K pharmacist may identify a candidate for PST following thorough allergy assessment. They may enter a PST referral after a discussion with the primary infectious disease provider.
4. All PST components will be made available either by Clinic 1K supplies (items A-H) or Morris Pharmacy (items H-J). The supplies will be picked up by the clinic 1K pharmacist or PST team member.
 - a. Skin test syringes for intradermal testing (0.5mL)
 - b. Duotip-Test II skin test applicator for prick test
 - c. Alcohol swabs
 - d. 0.2 mL of 0.9% sodium chloride, preservative-free (negative control)
 - e. Ruler
 - f. Washable markers
 - g. Gloves
 - h. Histamine base 0.1 mg/mL (positive control)
 - i. 0.2 mL Pre-Pen®
 - j. 0.2 mL of penicillin G (diluted to a strength of 10,000 U/mL)
5. Inclusion Criteria
 - a. Patients \geq 18 years of age
 - b. Patient reports having Type 1 hypersensitivity reaction to penicillin > 5 years ago or unknown reaction > 5 years ago
6. Exclusion Criteria
 - a. Patient is pregnant
 - b. Patient has taken histamine antagonists, corticosteroids, or immunosuppressive medications in the past 72-96 hours (patient will need to have appropriate histamine response).
 - c. Patient reports a hypersensitivity reaction other than Type 1 (hemolytic anemia, Stevens-Johnson syndrome, acute interstitial nephritis, drug-induced hepatitis, etc)
 - d. Patient is severely immunocompromised (e.g. ANC <1000)
 - e. Notable anasarca and/or skin breakdown
7. Prick Test

Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment

- a. Sequential tests, spaced approximately 1 inch apart shall be made on either the volar surface of the forearm or the lateral aspect of the upper arm. Clean the designated area with an alcohol swab and let dry.
- b. Using an ink pen, draw 3 vertical lines approximately 1 inch apart on the designated testing area of the arm
- c. Draw up 0.25 mL of the 3 solutions (Pre-Pen®, diluted penicillin G, and saline negative control), and 0.1 mL of histamine positive control, in 4 separate syringes (0.5 mL)
- d. Apply a small drop of each solution to the separate pre-marked sites on the testing arm
- e. The histamine site should be the most distal site, followed up the arm by saline, Pre-Pen® and penicillin G
- f. Puncture the epidermis using a twisting motion at each drop site using the Duotip-Test II applicator. Do not draw blood.
- g. Read the test in 15-20 minutes. Interpretation is as follows:
 - The histamine positive control should produce a wheal of at least 3 mm in diameter. The saline control should be negative as the solution is inert. If the response for either control puncture is inappropriate, the PST is considered indeterminate and should be repeated.
 - Negative result: major determinant (Pre-Pen®) and minor determinant (penicillin G) produce no wheal, or a wheal < 3 mm larger than the saline negative control.
 - Positive result: major determinant (Pre-Pen®) and minor determinant (penicillin G) produce a wheal of >3 mm larger than the saline negative control
 - As soon as a positive response is clearly evident, the solution over the scratch should be wiped off immediately
 - If positive result obtained, do not proceed to intradermal testing
 - Document a positive penicillin allergy as appropriate

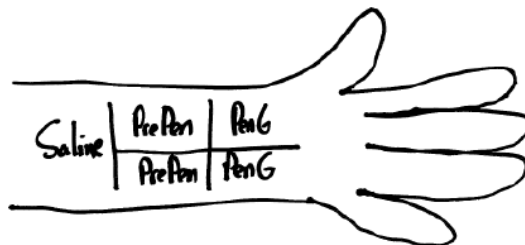


8. Intradermal Test

- a. Select 5 sites on either the volar surface of the forearm or the lateral aspect of the upper arm for intradermal testing. These sites should be on the opposite arm as the prick test, if possible.
- b. Using a 26-30 gauge, short bevel needle, intradermally inject 0.02 mL of Pre-Pen® solution twice (separate at least 2 cm apart). Mark the margins of the initial blebs with an ink pen
- c. Using separate needles and syringes, intradermally inject diluted penicillin G (0.02 mL = 200 units PCN) twice (separate at least 2 cm apart) and 0.02 mL of saline (separate at least 5 cm apart from other sites).
- d. Read in 15 minutes:
 - **Negative result:** major determinant (Pre-Pen®) and minor determinant (penicillin G) sites produce no wheal, or a wheal no greater than 3 mm larger than the saline negative control

Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment

- If negative result, document penicillin tolerance as appropriate in the EMR
- Proceed to amoxicillin oral challenge
- **Positive result:** both major determinant (Pre-Pen®) sites and minor determinant (penicillin G) sites produce a wheal of ≥ 3 mm larger than original injection site
 - Document positive penicillin allergy as appropriate in the record
- **Indeterminate skin test result:** both major determinant (Pre-pen®) sites or both minor determinant (penicillin G) sites do not produce the same result (e.g. one reads as positive and the other as negative)
 - If indeterminate result, the intradermal test will be repeated
- **Indeterminate control site reaction:** if wheal $>2-3$ mm from original control site bleb after 20 min, repeat skin test to look for dermatographic urticarial occurring in 4-5% of population



9. Oral Challenge: administer amoxicillin 250 mg PO x 1 dose and monitor patient for 30 minutes. If no signs/symptoms of a systemic reaction, the oral challenge is negative

10. Interpretation of Results

- a. Positive or indeterminate response to Pre-Pen® or penicillin G
 - Patient should not receive any penicillin antibiotics unless given via a desensitization protocol
- b. Indeterminate control response
 - Patient should not receive any penicillin antibiotics unless given via a desensitization protocol
- c. Negative response to Pre-Pen® or penicillin G (and amoxicillin oral challenge)
 - Proceed with treatment with a penicillin agent
 - The patients may also receive other cephalosporins and carbapenems as long as they do not have a pre-existing documented allergy to those medications

11. Reporting and Documentation

- a. The provider conducting the testing will chart administration of the PST on the MAR
- b. Completed documentation of the allergy assessment and PST will be placed in the progress notes by the PST clinician.
- c. The PST clinician will electronically update the patient's allergy information to reflect testing results and notify the primary infectious disease provider

**Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K
Penicillin Allergy Assessment**

12. Post PST Observation

- a. The primary clinic nurse designated to monitor the PST patient should monitor the patient's vital signs every 15 minutes for the first 30 minutes after the oral challenge dose of penicillin is given
- b. The primary nurse should also be informed to continue close monitoring of patient and any signs of an allergic reaction should be reported to PST provider
- c. The PST provider shall remain in Clinic 1K until patient checks out from visit

13. Anaphylaxis Procedures

- a. Anaphylaxis kit to be kept in clinic Omnicell in preparation for any testing and will consist of the following:
 1. Epinephrine 1 mg/mL (1:1000), 1 mL vial
 2. 1 mL syringe (x2)
 3. 1.5 inch 25 g needle (x2)
 4. Diphenhydramine 25 mg tablets
- b. At least 1 provider present during testing must have active ACLS certification
- c. In the event of any suspected anaphylactic reaction, provider and clinic physician should be notified immediately. The anaphylaxis reaction protocol can be initiated by an RN while awaiting physician contact
- d. Anaphylaxis treatment:
 1. Anaphylaxis is suspected with the combination of any of the following signs/symptoms: bronchospasm, stridor, wheezing, respiratory depression, generalized urticaria, hypotension (SBP <90 mm Hg), tachycardia, angioedema, shock, or loss of consciousness
 2. Treatment protocol:
 - a. 0.3 mg IM epinephrine (repeat q5 minutes if necessary)
 - b. Diphenhydramine 25-50 mg PO/IV
 - c. If symptoms do not respond to above, active code team
 - d. If epinephrine is given, recommend referral to ER for monitoring afterwards in case of delayed recurrent reaction

Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment

Appendix D. Direct Oral Challenge Procedure

PEN-FAST is a simple prospectively derived clinical decision rule developed from a published cohort study in Melbourne (Australia), externally validated in a multi-center prospective cohort, and recently supported by a multinational randomized controlled clinical trial.¹⁴

Figure. PEN-FAST Penicillin Allergy Clinical Decision Rule

PEN	Penicillin allergy reported by patient	<input type="checkbox"/> <i>If yes, proceed with assessment</i>
F	Five years or less since reaction ^a	<input type="checkbox"/> 2 points
A	Anaphylaxis or angioedema	<input type="checkbox"/> 2 points
S	OR Severe cutaneous adverse reaction ^b	
T	Treatment required for reaction ^a	<input type="checkbox"/> 1 point
		<hr style="width: 50%; margin: 0 auto;"/> <input type="checkbox"/> Total points
Interpretation		
Points		
0	Very low risk of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy)	
1-2	Low risk of positive penicillin allergy test 5% (1 in 20 patients)	
3	Moderate risk of positive penicillin allergy test 20% (1 in 5 patients)	
4-5	High risk of positive penicillin allergy test 50% (1 in 2 patients)	

The PEN-FAST clinical decision rule for patients reporting a penicillin allergy uses 3 clinical criteria of time from penicillin allergy episode, phenotype, and treatment required. A total score is calculated using PEN-FAST score in the upper panel, and interpretation for risk strategy is provided in the lower panel.

^a Includes unknown.

^b Forms of severe delayed reactions include potential Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Patients with a severe delayed rash with mucosal involvement should be considered to have a severe cutaneous adverse reaction. Acute interstitial nephritis, drug induced liver injury, serum sickness and isolated drug fever were excluded phenotypes from the derivation and validation cohorts.

Specific considerations for oral challenge eligibility are delineated below with specific inclusion/exclusion criteria. Notably, PEN-FAST was not effective in a pediatric cohort and thus should not be applied outside of this adult policy.¹²

H2 antagonists (e.g., ranitidine) do not appear to impact testing, whilst H1 antagonists (e.g. cetirizine, loratadine, fexofenadine) may impact, and should be avoided in patients with high-pretest probability of true allergy.¹² Beta-blockers remain a relative contraindication in drug allergy testing; however, in low-risk cohort studies these have not been excluded.¹²

Although there are no studies directly comparing safety and efficacy between single and multi-step oral challenges, test performance is very similar across published cohorts using each strategy. Additionally, PALACE – the recently completed randomized controlled trial assessing the PEN-FAST score – utilized single-step oral challenges with proven safety. Therefore, a single-step oral challenge is preferred when used in this low risk cohort (eg. PEN-FAST score 0-1).¹⁴

Procedure Title: **DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment**

Inclusion:

1. PEN-FAST score of 0 or 1
2. Clinically stable

Exclusion:

1. Age <18 years old
2. Pregnant
3. Concurrent Therapies: receipt of H1 antagonist without sufficient washout

Procedure:

1. Patients identified as meeting inclusion criteria and no exclusion criteria, after thorough allergy assessment, will be considered for direct oral challenge conducted in Clinic 1K
2. Orders shall be entered by the patient's primary ID provider team through the Adult Oral Amoxicillin Challenge Order Panel (screenshot below)
 - a. Patient shall receive a 250mg dose of amoxicillin.
 - b. Post Oral Challenge Observation
 - i. The patient's primary nurse should monitor the patient's vital signs every 15 minutes for the 30 minutes after the initial dose of amoxicillin is given.
 - ii. The primary nurse should report any signs of an allergic reaction to the primary ID provider
 - iii. The primary ID provider shall remain in Clinic 1K until the patient checks out from the visit
 - c. Anaphylaxis Procedures
 - i. The anaphylaxis reaction protocol can be initiated by an RN while awaiting physician contact.
 - ii. The primary ID provider should be notified ASAP
 - iii. Remaining anaphylaxis procedures remain identical to those listed in the PST procedures in Appendix C
 - d. Documentation
 - i. The primary ID provider or AIM pharmacist should remove the penicillin allergy from EPIC following successful oral challenge.

The primary ID provider should update the penicillin allergy comments if any reaction occurs during or after the oral challenge that is concerning for an allergic reaction.

Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment

ADULT Oral Amoxicillin Challenge Order Panel
✔ Accept

The PEN-FAST penicillin allergy clinical decision rule enables point-of-care risk assessment of patient-reported penicillin allergies in ADULTS (>=18). Patients with low PEN-FAST Scores (0-1) are appropriate for a direct oral challenge with amoxicillin due to the low risk of reaction (PALACE Study, JAMA Int Med 2023).

[Document PEN-FAST Score Here](#). Prior PEN-FAST Documentation (if any):

No data to display

Score	Risk of Positive PCN Allergy Test	Recommended Action
0-1	Very Low (< 1%)	Oral Challenge
2	Low (5%)	Ambulatory Referral for Penicillin Skin Testing OR If urgent inpatient assessment (DUH Only): Consult to ASET for PCN Skin Testing
3	Moderate (20%)	
4-5	High (50%)	

Patient should not be receiving histamine antagonists (eg. azelastine, cetirizine, clemastine, cyproheptadine, desloratadine, doxepin, fexofenadine, hydroxyzine, levocetirizine, olopatadine) without sufficient washout or stress dose steroids (i.e. > 50mg QID hydrocortisone [or steroid equivalent])
 - [CustomID Penicillin Allergy Guidance](#)

Oral Amoxicillin and Nursing Orders

- amoxicillin (AMOXIL) capsule 250 mg
250 mg, Oral, Once, today at 1400, For 1 dose
- Nursing: Document vitals for oral amoxicillin challenge, monitor for reaction
 Routine, Until discontinued, Starting today at 1354, Until Specified
 Instructions: Document vitals for oral amoxicillin challenge, monitor for reaction
 Document vitals and observe patient for rash or other signs of allergic reaction every 15 minutes for 1 hour after amoxicillin dose. === For MILD REACTION (mild urticaria): administer PRN benadryl and then notify first call. === For MODERATE REACTION (throat tightness, wheezing, significant urticaria): administer PRN IV benadryl and 0.3 mg IM epinephrine, then notify first call. === For SEVERE REACTION or ANAPHYLAXIS (hypotension, laryngeal edema): administer PRN IV benadryl and 0.3 mg IM epinephrine, call rapid response and notify first call.
- Nursing communication
 Routine, Until discontinued, Starting 1 hour after signing, Notify first call with results of oral amoxicillin challenge. If patient developed a reaction during the oral challenge, please update the allergy tab with details.
- diphenhydrAMINE (BENADRYL) injection 25-50mg (\$)
25-50 mg, Intravenous, Once PRN, Allergies, if no IV access or IV access lost, may give IM as appropriate, Starting 8/19/25, Dose = 25mg if patient < 50kg, Dose = 50mg if patient is >= 50kg, To be given if signs/symptoms of allergic reaction during oral amoxicillin challenge.
- EPINEPHrine (ADRENALIN) 1 mg/mL (1mL) injection
0.3 mg, Intramuscular, Once PRN, For MODERATE or SEVERE allergic reaction during oral amoxicillin challenge.
- amoxicillin (AMOXIL) 250 mg/5 mL suspension
250 mg, Oral, Once, Starting 8/19/25
- (DUH Only) Penicillin Skin Testing - Consult to ASET
Routine
- Ambulatory Referral to PCN Allergy Skin Testing Clinic
Internal Referral, Routine

🔔 Next Required
✔ Accept

Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment

Appendix E. Chart documentation example

Procedure: Patient Super Duper a 70 y.o. female who was evaluated for penicillin allergy on *** with the following reagents and results.

Product	Scratch Wheal/Flare (mm)	Intradermal #1 (mm)	Intradermal #2 (mm)	Results Pos/Neg/Equiv
Saline Control	***	***		Blank signal: equivocal
Histamine (1 mg/mL)	***			Blank signal: equivocal
PRE-PEN®	***	***	***	Blank signal: equivocal
Penicillin G (10,000 units/mL)	***	***	***	Blank signal: equivocal

Criteria for positive prick skin test: Induration ≥ 3 mm greater than saline control

Criteria for positive intradermal skin test: Significant increase in size of original bleb with wheal diameter 3 mm or more larger than saline control

Criteria for negative intradermal skin test: No increase in size of original bleb and no reaction greater than control site

Equivocal intradermal skin test: Wheal only slightly larger than initial injection bleb and control site, with or without erythematous flare OR duplicate are discordant - unable to rule out penicillin allergy.

Oral Challenge: Amoxicillin 250 mg po x 1 dose Blank signal: was not administered according to protocol. Reaction: Blank signal: yes

The patient was monitored in accordance with the Duke Stewardship Allergy and Assessment Protocol. Results were relayed to the primary care team.

Interpretation:

Based on the allergy assessment and skin testing results, **tested** Pre-PEN Skin Test **to penicillin allergy.**

The penicillin allergy was PCN Allergy the allergy tab in Epic for Gloria K Perry.

Thank you for allowing us to participate in the care of this patient. We will sign off. For questions please page 970-6666 (ASET Functional pager).

REBEKAH WRENN, PharmD
 Infectious Diseases/Antimicrobial Stewardship Pharmacist
 Pager: ***

[Duke Center for Antimicrobial Stewardship and Infection Prevention](#)



Duke Center for Antimicrobial Stewardship and Infection Prevention



Appendix F. Patient education example

Penicillin Allergy Facts

10% of all US patients report a penicillin allergy **BUT** many are not truly allergic. In fact, **Nine** out of ten patients reporting penicillin allergy are **NOT** allergic. ¹.

1 2 3 4 5 6 7 8 9 10



Image credit CDC²

Why are these numbers different?

1. It is possible to lose penicillin allergy with time
2. Patients can be mislabeled as allergic

Can I outgrow my allergy?

YES!

HOW DO I PREPARE FOR MY TESTING?

Certain medicines interfere with testing. You will receive a complete list of medications to stop before your visit. Contact our clinic if you have questions.

- References:**
1. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010 Oct; 105(4):259-273
 2. Image from the following CDC website: www.cdc.gov/getsmart/week/downloads/getsmart-penicillin-factsheet.pdf



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DUHS PPEGC Approved 10/2017
 Developed for Duke Health patients and their loved ones

Penicillin Allergy

Are you allergic to penicillin?

Information for Patients and Families



 **Duke Asthma, Allergy & Airway Center**
Duke University School of Medicine

Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K Penicillin Allergy Assessment

THIS INFORMATION IS IMPORTANT TO YOU IF:

1. You have a history of a penicillin allergy.
2. Your healthcare team has recommended a penicillin allergy evaluation as part of your treatment plan.

WHY IS PENICILLIN ALLERGY TESTING IMPORTANT?

Penicillin antibiotics are used to treat bacterial infections including pneumonia, sinus, throat, and skin infections.

Patients who are listed as having penicillin allergy often receive broad spectrum antibiotics (antibiotics that may be stronger than needed) which may be associated with:

- Longer hospital stays
- Ineffective treatment
- Some antibiotics can lead to new infections (for example severe diarrhea from Clostridium difficile)

TESTING

Penicillin skin testing can help if you have a history of an allergy to penicillin (rashes, hives, swelling, breathing difficulty are common symptoms of a drug allergy).

TESTING STEPS

Skin testing can tell if you are still allergic to penicillin. Step 1 is a skin prick test. If you are allergic (positive test), the area where penicillin was placed will become red and possibly itchy. If the skin prick test is negative, a small amount of penicillin will be injected into the skin of your arm.



1) Skin prick test



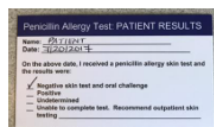
2) Intradermal test

If both skin tests are negative, this means that you are likely no longer allergic. You will receive a one-time dose of amoxicillin (type of penicillin) and will be monitored to make sure that you do not have a reaction.



TEST RESULTS

If the skin testing is negative and you have no reaction to the oral dose of amoxicillin, you are NO LONGER allergic to penicillin.



If your test is positive and you need penicillin, an allergist can help you choose other options (desensitization).

TESTING TIME

On average, the testing and visit will take from 1.5-2 hours.

Appendix G. Medications to

Avoid Prior to Penicillin Skin Testing

Recommendation for medications that patients should avoid prior to allergy testing. Upon initial contact, the PST provider will review if the patient is currently taking any of the following medications. If the patient is taking an interacting medication, the PST provider will instruct the patient to hold these medications for the stated period of time below (if clinically appropriate to hold the medication). During medication reconciliation at PST visit, the PST provider will review if patient is currently taking or recently received any of the following medications.

Preferred if the following medications (all histamine H1 antagonists) are not given **7 days** prior to testing:

azelastine
cetirizine
clemastine
cyproheptadine
desloratadine
doxepin
fexofenadine
hydroxyzine
levocetirizine
olopatadine

Preferred if the following medications are not given **3 days** prior to testing

brompheniramine
chlorpheniramine

**Procedure Title: DUH Durham Campus Only - Infectious Disease Clinic 1K
Penicillin Allergy Assessment**

cimetidine
diphenhydramine
famotidine
nizatidine
promethazine
prochlorperazine
ranitidine

Stop the following medications at **midnight the day prior** to testing

metoclopramide
montelukast
zafirlukast
zileuton

References:

1. Macy E. Penicillin and beta-lactam allergy: epidemiology and diagnosis. *Curr Allergy Asthma Rep.* Nov 2014;14(11):476. doi:10.1007/s11882-014-0476-y
2. Blumenthal KG, Ryan EE, Li Y, Lee H, Kuhlen JL, Shenoy ES. The Impact of a Reported Penicillin Allergy on Surgical Site Infection Risk. *Clin Infect Dis.* Jan 18 2018;66(3):329–336. doi:10.1093/cid/cix794
3. Phan A, Allen B, Epps K, Alikhil M, Kamataris K, Tucker C. Initiative to reduce aztreonam use in patients with self-reported penicillin allergy: Effects on clinical outcomes and antibiotic prescribing patterns. *Am J Health Syst Pharm.* Sep 1 2018;75(17 Supplement 3):S58–s62. doi:10.2146/ajhp170400
4. Turner NA, Moehring R, Sarubbi C, et al. Influence of Reported Penicillin Allergy on Mortality in MSSA Bacteremia. *Open Forum Infect Dis.* Mar 2018;5(3):ofy042. doi:10.1093/ofid/ofy042
5. Trubiano JA, Thursky KA, Stewardson AJ, et al. Impact of an Integrated Antibiotic Allergy Testing Program on Antimicrobial Stewardship: A Multicenter Evaluation. *Clin Infect Dis.* Jul 1 2017;65(1):166–174. doi:10.1093/cid/cix244
6. Park M, Markus P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol.* Nov 2006;97(5):681–7. doi:10.1016/s1081-1206(10)61100-3

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Penicillin Allergy Assessment**

7. Macy E, Ngor EW. Safely diagnosing clinically significant penicillin allergy using only penicilloyl-poly-lysine, penicillin, and oral amoxicillin. *J Allergy Clin Immunol Pract*. May–Jun 2013;1(3):258–63. doi:10.1016/j.jaip.2013.02.002
8. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. *Jama*. 2019;321(2):188–199. doi:10.1001/jama.2018.19283
9. Raja AS, Lindsell CJ, Bernstein JA, Codispoti CD, Moellman JJ. The use of penicillin skin testing to assess the prevalence of penicillin allergy in an emergency department setting. *Ann Emerg Med*. Jul 2009;54(1):72–7. doi:10.1016/j.annemergmed.2008.12.034
10. Gadde J, Spence M, Wheeler B, Adkinson NF, Jr. Clinical experience with penicillin skin testing in a large inner-city STD clinic. *Jama*. Nov 24 1993;270(20):2456–63.
11. Kufel WD, Justo JA, Bookstaver PB, Avery LM. Penicillin Allergy Assessment and Skin Testing in the Outpatient Setting. *Pharmacy (Basel)*. Sep 19 2019;7(3)doi:10.3390/pharmacy7030136
12. Chow TG, McDanel DL, Turner NA, Copaescu AM. Nonallergist Delabeling-Should Penicillin Allergy Delabeling Only Be Performed by Allergists? *J Allergy Clin Immunol Pract*. May 2025;13(5):1011–1017.e2. doi:10.1016/j.jaip.2024.11.028
13. Trubiano JA, Vogrin S, Chua KYL, et al. Development and Validation of a Penicillin Allergy Clinical Decision Rule. *JAMA Intern Med*. May 1 2020;180(5):745–752. doi:10.1001/jamainternmed.2020.0403
14. Copaescu AM, Vogrin S, James F, et al. Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy: The PALACE Randomized Clinical Trial. *JAMA Intern Med*. Sep 1 2023;183(9):944–952. doi:10.1001/jamainternmed.2023.2986
15. Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. *J Allergy Clin Immunol*. Dec 2022;150(6):1333–1393. doi:10.1016/j.jaci.2022.08.028

Associated Regulatory Standards: N/A

Associated Policies:

[DUH Pharmacy: Allergy Assessment, Oral Challenge and Penicillin Skin Testing for Adult Inpatients](#)