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Evaluation and management of antibiotic allergies

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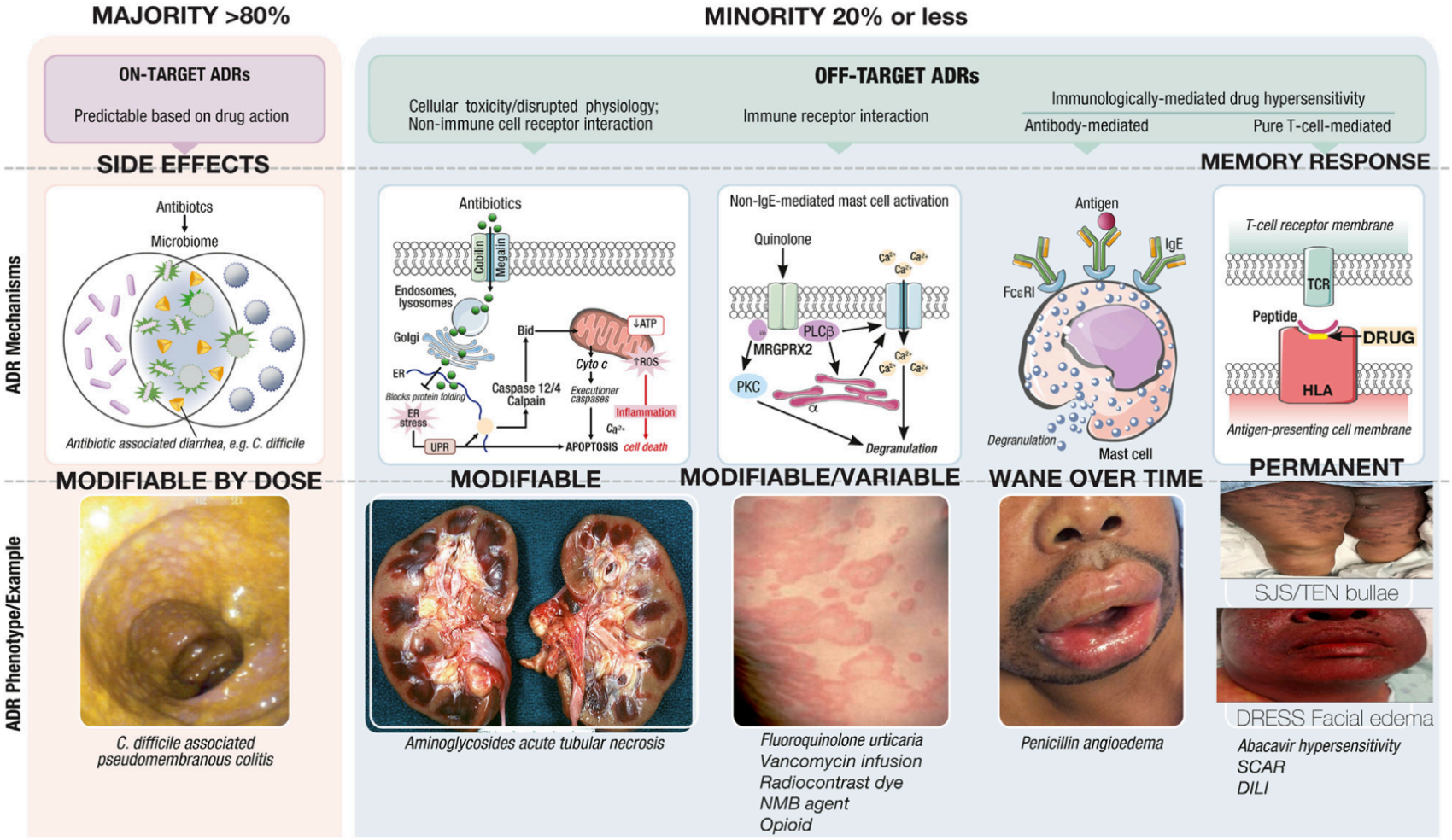
Objectives

- Describe the different types of hypersensitivity reactions based on clinical presentation and immunological mechanisms
- Recognize a patient history that will differentiate between immediate and delayed- type hypersensitivity reactions
- Describe the risk of cross-reactions between various beta-lactam antibiotics
- Describe the principles and contraindications for desensitization

On versus off-target adverse drug reactions (ADR)

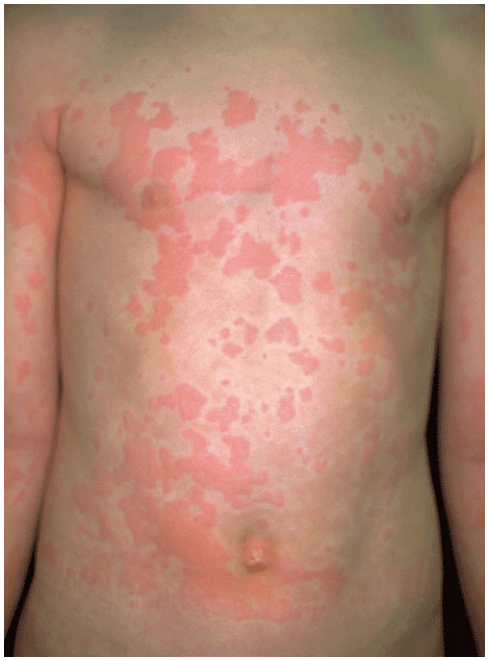


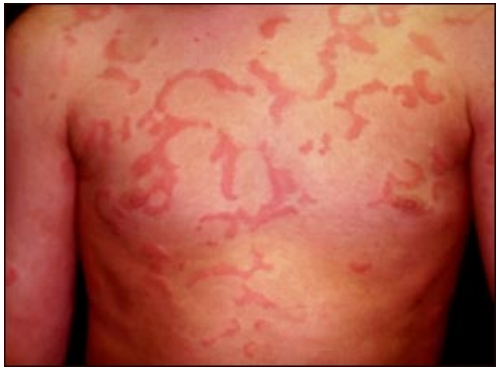
Macy E et al. J Allergy Clin Immunol Pract. 2023;11:80-91.

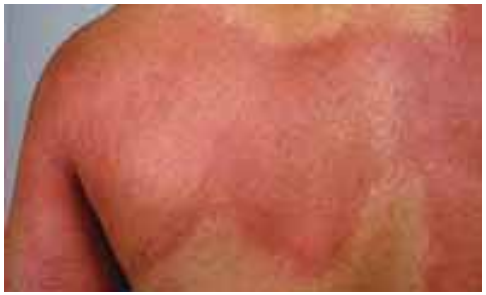
Classification of Drug-Induced Allergic Reactions

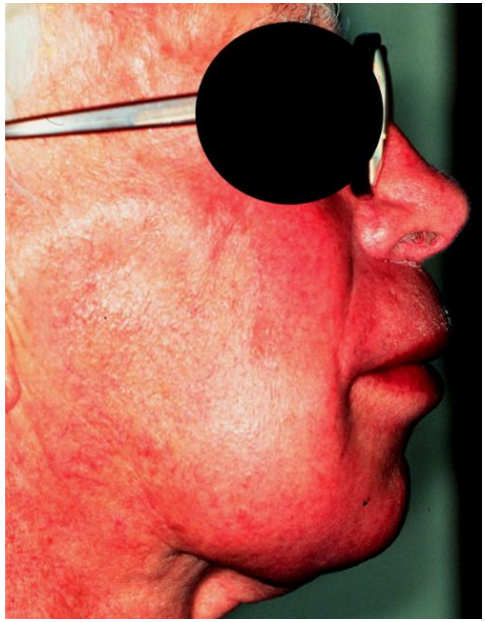
	Type I/Immediate	Type II	Type III	Type IV/Delayed
Immune mediator	**IgE**	**IgG**	**IgG**	**T lymphocytes**
Mechanism	Drug antigen binds and crosslinks IgE on allergic cells, which results in degranulation.	Drug antigen-specific IgG binds antigen on the cell surface or matrix and activated phagocytic cells.	Drug antigen-specific IgG binds to soluble antigen forming immune-complexes that activate complement and phagocytic cells.	Drug antigen-specific T lymphocyte receptors bind to drug antigens and activates T lymphocytes with effector cells including macrophages, eosinophils and/or cytotoxic T lymphocytes
Timing of onset	Minutes to hours	Days to weeks	Days to weeks	Days to weeks
HSRs	Anaphylaxis Angioedema Urticaria	Hemolytic anemia Thrombocytopenia	Serum sickness Drug fever	Maculopapular rash SJS/TEN
Testing/verification methods possible	Tryptase (acutely) Skin testing Drug challenge	Reaction-specific (e.g., Coombs testing for hemolytic anemia)	Complement levels	Prolonged drug challenges Patch testing Delayed intradermal testing
Abbreviations: Ig, Immunoglobulin; HSR, hypersensitivity reaction; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis				

Gell and Coombs system (c. 1975)

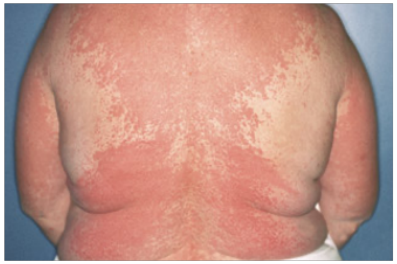


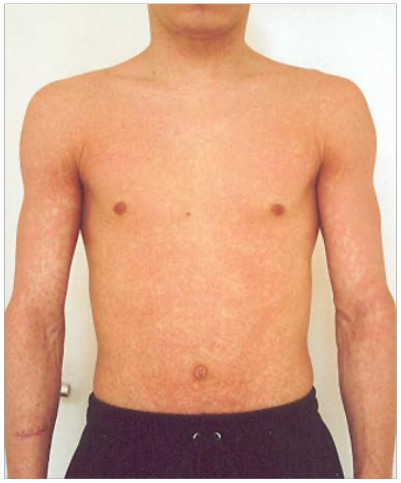


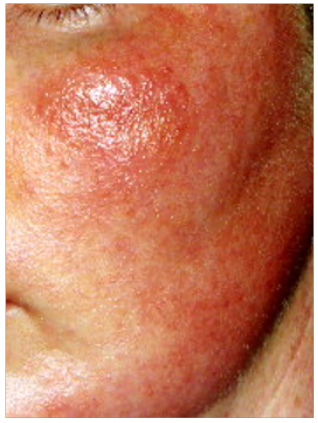


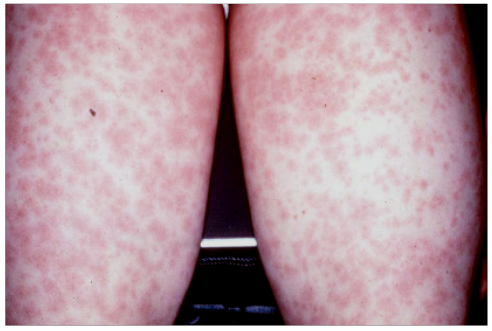


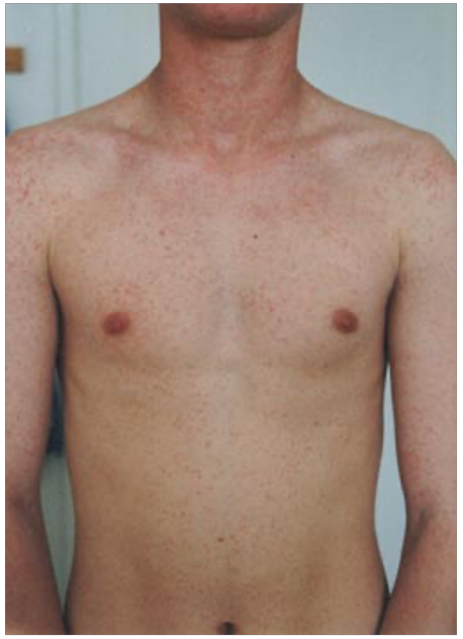
Urticaria (Hives)
and angioedema

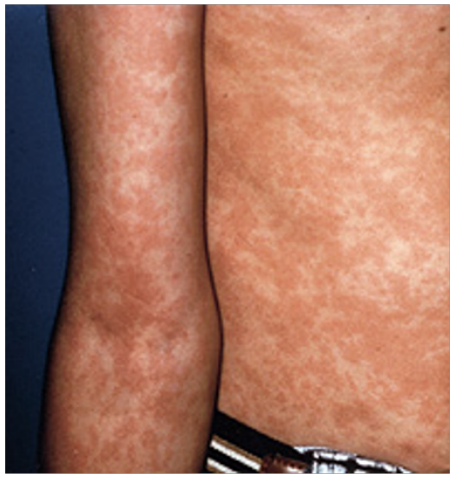






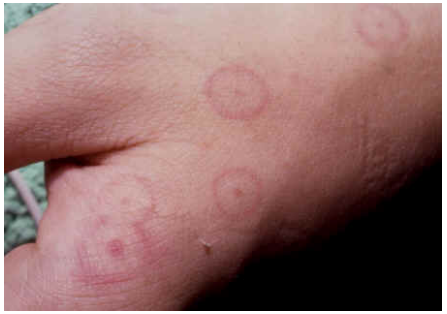


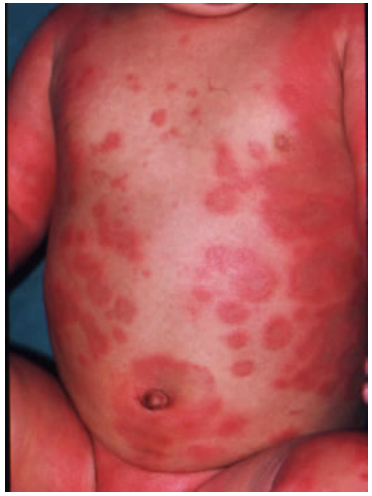


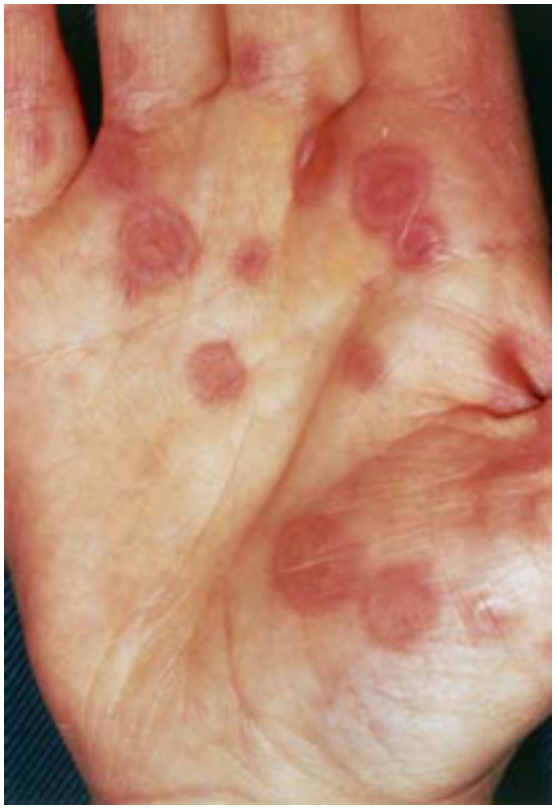


Delayed-type morbilloform reactions

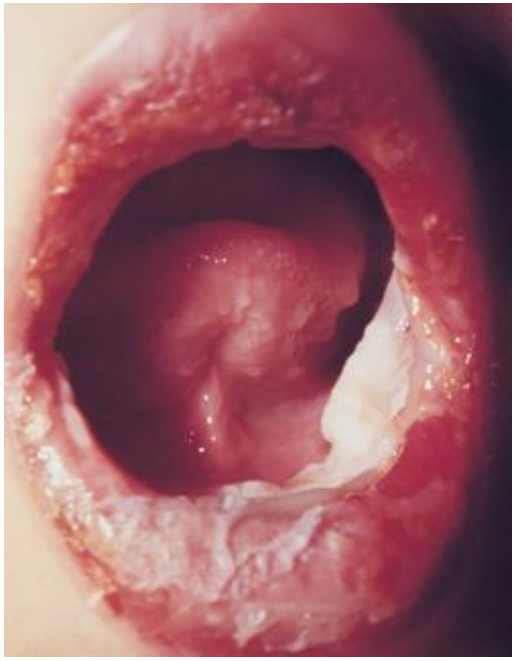
Erythema multifome

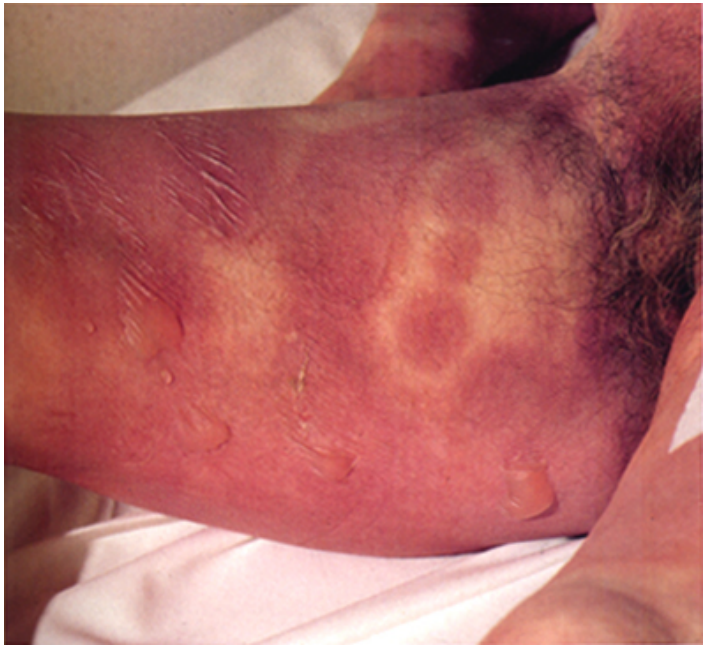






Stevens-Johnson Syndrome





Penicillin (PCN) allergy epidemiology

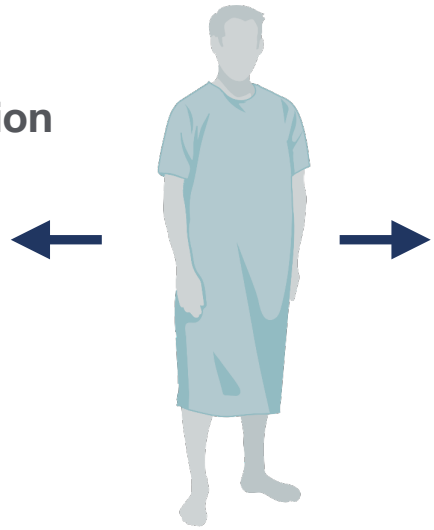
- 10-20% of patients have a reported PCN allergy
- Estimated 0.5%-2% of PCN administrations actually result in hypersensitivity reactions, most often rash
  - Of these 1% are IgE mediated
- The rate of **IgE PCN allergies** is **decreasing,** partially due to the reduced use of parenteral PCN, which degradation products in solution may be the primary culprit
- Statistics from the UK 1972-2007 oral amoxicillin course:
  - 1 death after anaphylaxis
- However, most reports of penicillin allergy describe unknown or cutaneous reaction

Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019;321:188-199.

Patient reports a (PCN) allergy…

5% need an allergy evaluation

- Blistering rash
- Hemolytic anemia
- Nephritis
- Hepatitis
- Fever and joint pain
- SCAR



95% can tolerate PCNs because…

- Delayed, benign rash (Type IV reaction) that often does not recur with rechallenge
- True IgE reaction wane over times, with 80% becoming tolerant after 10 years
- Many patients were *never* allergic, but had other symptoms they though represented a PCN allergy (concurrent viral infection, GI distress)

Unfortunately the majority of patients reporting beta-lactam allergies who are treated with alternative agents due to concerns for allergy are likely avoiding beta-lactam antibiotics unnecessarily.

Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019;321:188-199.

Impact of PCN allergy label on clinical outcomes Studies from Mass General Hospital (Harvard Univ.)

Study	Design	Outcomes assocaited with PCN allergy label	Reference
Blumenthal 2018	Population-based matched cohort study	Increased risk of *C. difficile* and MRSA	Blumenthal KG et al. BMJ. 2018;361:k2400.
Blumenthal 2018	Population-based matched cohort study in patients requiring antibiotic surgical prophylaxis	50% increased odds of surgical site infection	Blumenthal KG et al. Clin Infect Dis. 2018;66:329-336.
Blumenthal 2019		14% higher rate all-cause mortality	Blumenthal KG et al. J Gen Intern Med 2019;34(9):1685-1687.
Blumenthal 2020	2-year retrospective cohort study	A reported penicillin allergy conferred a 4-fold increased odds of beta-lactam alternative antibiotic use. Reporting penicillin allergy, with and without multiple drug intolerance syndrome, was associated with significantly more healthcare utilization	Blumenthal KG et al. Am J Manag Care. 2020;26:154-161.

Methods for clinical evaluation of a reported penicillin allergy

Clinical history

A
Page 1

Toolkit A

Penicillin Allergy History

Patient ID/ Sticker:

Date of reaction: _____

Route of last administration: ☐ Oral ☐ Intravenous

Reaction details (check all that apply):

Intolerance histories

- ☐ Isolated GI upset (diarrhea, nausea, vomiting, abdominal pain)
- ☐ Chills (rigors)
- ☐ Headache
- ☐ Fatigue

Low-risk allergy histories

- ☐ Family history
- ☐ Itching (pruritus)
- ☐ Unknown, remote (> 10 yr ago) reaction
- ☐ Patient denies allergy but is on record

Moderate-high risk allergy histories (potential IgE reactions)

- ☐ Anaphylaxis
- ☐ Angioedema/swelling
- ☐ Bronchospasm (chest tightness)
- ☐ Cough
- ☐ Nasal symptoms
- ☐ Arrhythmia
- ☐ Throat tightness
- ☐ Hypotension
- ☐ Flushing/redness
- ☐ Shortness of breath
- ☐ Rash
- ☐ Syncope/pass out
- ☐ Wheezing
- ☐ Dizzy/lightheadedness

Type of rash (if known):

HIGH RISK: Contraindicated penicillin skin testing/challenge (potential severe non-immediate reactions)

- ☐ Stevens-Johnson syndrome (rash with mucosal lesions)
- ☐ Serum sickness (rash with joint pain, fever, myalgia)
- ☐ Thrombocytopenia
- ☐ Fever
- ☐ Organ injury (liver, kidney)
- ☐ Erythema multiforme (rash with target lesions)
- ☐ Dystonia
- ☐ Anemia
- ☐ Acute generalized exanthematous (rash with pustules)
- ☐ Drug reaction eosinophilia and systemic symptoms (rash with eosinophilia and organ injury)

Other symptoms:

Continue to second page

A
Page 2

Toolkit A (continued)

Patient ID/ Sticker:

Timing/onset:

- ☐ Immediate (< 4 hrs)
- ☐ Intermediate (4-24 hrs)
- ☐ Delayed (> 24 hrs)
- ☐ Unknown

Treatment:

- ☐ None/penicillin continued
- ☐ Antihistamines
- ☐ Steroids (IV or PO)
- ☐ Epinephrine
- ☐ Penicillin discontinued
- ☐ IV Fluids
- ☐ Other:

How long ago was the reaction:

☐ < 6 mo ☐ 6 mo-1 yr ☐ 2-5 yrs ☐ 6-10 yrs ☐ > 10 yrs ☐ Unknown

Other beta-lactam use:

☐ Previous use of a penicillin or beta-lactam (prior to course that caused reaction)

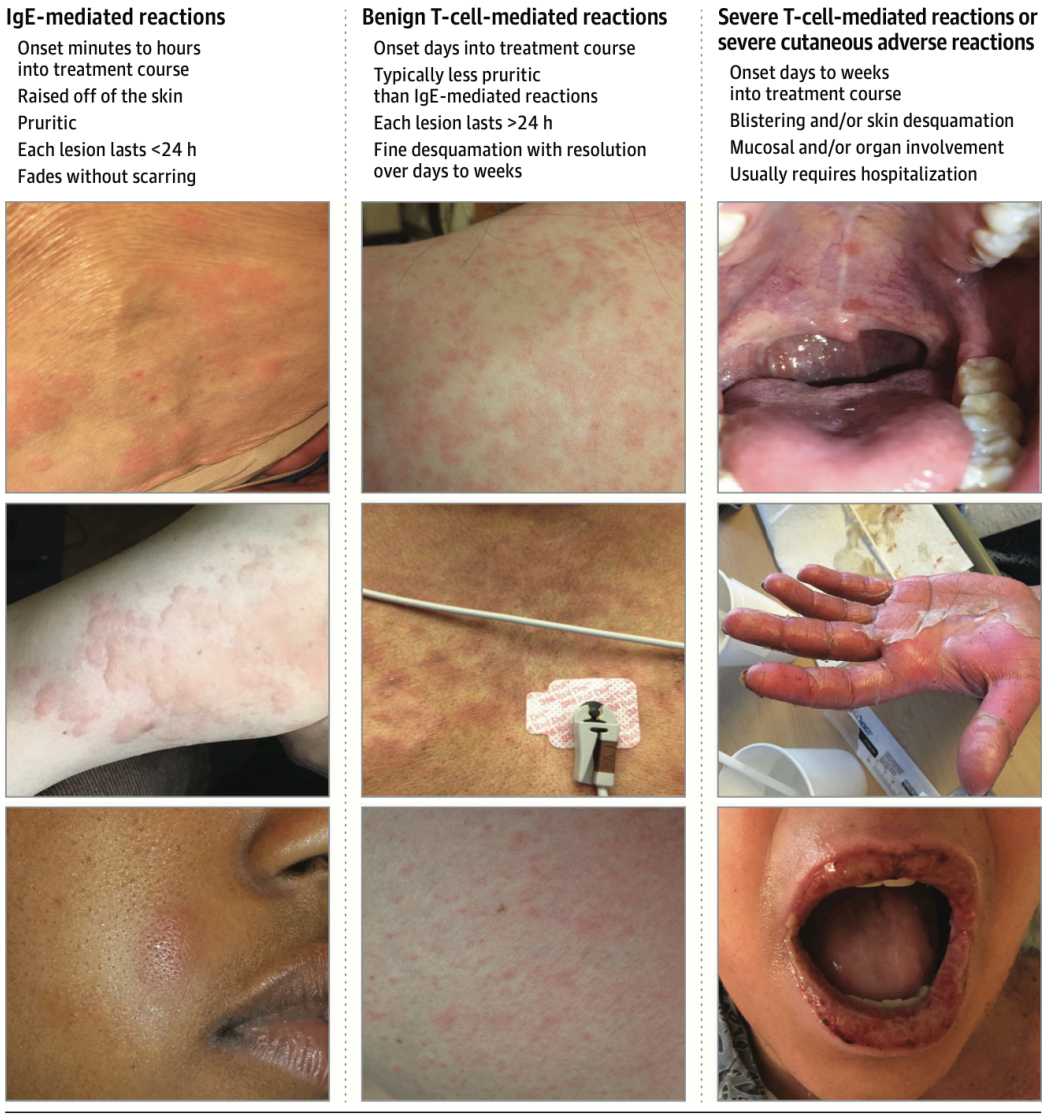
If yes, please list drugs:

☐ Subsequent use of a penicillin or beta-lactam (after the course that caused a reaction)

If yes, please list drugs:

History taken by

Print name: _____ Signature: _____ Date: _____



IgE-mediated reactions, benign T-lymphocyte-mediated reactions, and severe T-lymphocyte–mediated or severe cutaneous adverse reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms. Although benign T-cell–mediated eruptions are low-risk for rechallenge, it is often difficult to distinguish these from IgE-mediated reactions, and, therefore, considering all nonsevere cutaneous eruptions moderate risk is recommended.

Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019;321:188-199.

Risk stratification

Table 3. Risk Stratification for Penicillin Allergy Evaluation

	Low Risk	Medium Risk	High Risk
History[a]	Isolated reactions that are unlikely allergic (eg, gastrointestinal symptoms, headaches) Pruritus without rash Remote (>10 y) unknown reactions without features of IgE[b] Family history of penicillin allergy	Urticaria or other pruritic rashes Reactions with features of IgE but not anaphylaxis[b]	Anaphylactic symptoms[c] Positive skin testing Recurrent reactions Reactions to multiple β-lactam antibiotics
Action	Prescribe amoxicillin course or perform a direct amoxicillin challenge under observation.[d]	Skin test followed by amoxicillin challenge under observation if the skin test is negative.[e] Consider allergy/immunology referral.	Allergy/immunology referral or desensitization.

[a] No penicillin allergy testing should be performed on patients with possible penicillin-associated severe cutaneous adverse reaction, hemolytic anemia, organ-specific reaction, drug fever, or serum sickness. Patients with unstable or compromised hemodynamic or respiratory status and pregnant patients should never be considered low risk.

[b] IgE features classically include cutaneous symptoms, such as itching, flushing, urticaria, and angioedema, but also involve respiratory system (rhinitis, wheezing, shortness of breath, bronchospasm), cardiovascular system (arrhythmia, syncope, chest tightness), and gastrointestinal system (abdominal pain, nausea, vomiting, diarrhea) symptoms.

[c] The most severe IgE-mediated reaction is anaphylaxis (eFigure 1 in Supplement 1). Allergy/immunology consultation is advised.

[d] Considering patient comfort level with trying penicillin again and whether resources exist for observation.

[e] If skin testing is not possible, a graded amoxicillin challenge can be considered for medium-risk histories. A graded challenge often requires administration of a one-tenth to one-fourth full dose of the desired drug and a 30- to 60-minute period of monitoring followed by administration of a full dose of the desired drug and a final 30- to 60-minute period of monitoring (Toolkit C in Supplement 2).

Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019;321:188-199.

B
Page 1

Toolkit B

Direct Oral Amoxicillin Challenge for Low-Risk Patients

Patient ID/ Sticker:

Testing is not necessary if a penicillin class antibiotic has been tolerated since the index reaction

DO NOT perform any penicillin allergy testing if there is a history of penicillin-associated:

• Blistering rash • Hemolytic anemia • Nephritis • Hepatitis • Fever • Joint pains

Direct oral amoxicillin challenge can be performed in any patient with a history of the following symptoms associated with penicillin:

- Isolated reactions that are unlikely allergic (e.g., gastrointestinal symptoms, headaches)
- Pruritus without rash
- Remote (>10 years) unknown reactions without features of IgE/immediate hypersensitivity
- May also be used for patients with a family history of penicillin allergy or benign somatic symptoms

First penicillin skin test if:

- The reaction was cutaneous
- The reaction had features of IgE/immediate hypersensitivity
- The patient currently has unstable or compromised hemodynamic or respiratory status or is pregnant with low risk allergy history.

Proceed to amoxicillin challenge only if skin test is negative

Continue to second page

B
Page 2

Toolkit B (continued)

Patient ID/ Sticker:

Ordered by: _____ Performed by: _____ Date: ___/___/_____

Amoxicillin oral challenge given: ☐ 250 mg ☐ 500 mg

Time given: _____ Time observation end: _____

Observed challenge reaction:

☐ None ☐ Yes, please list signs and symptoms:

Time to onset:

Observed challenge reaction treatment given:

☐ None ☐ Yes, please list signs and symptoms:

Delayed challenge reaction reported:

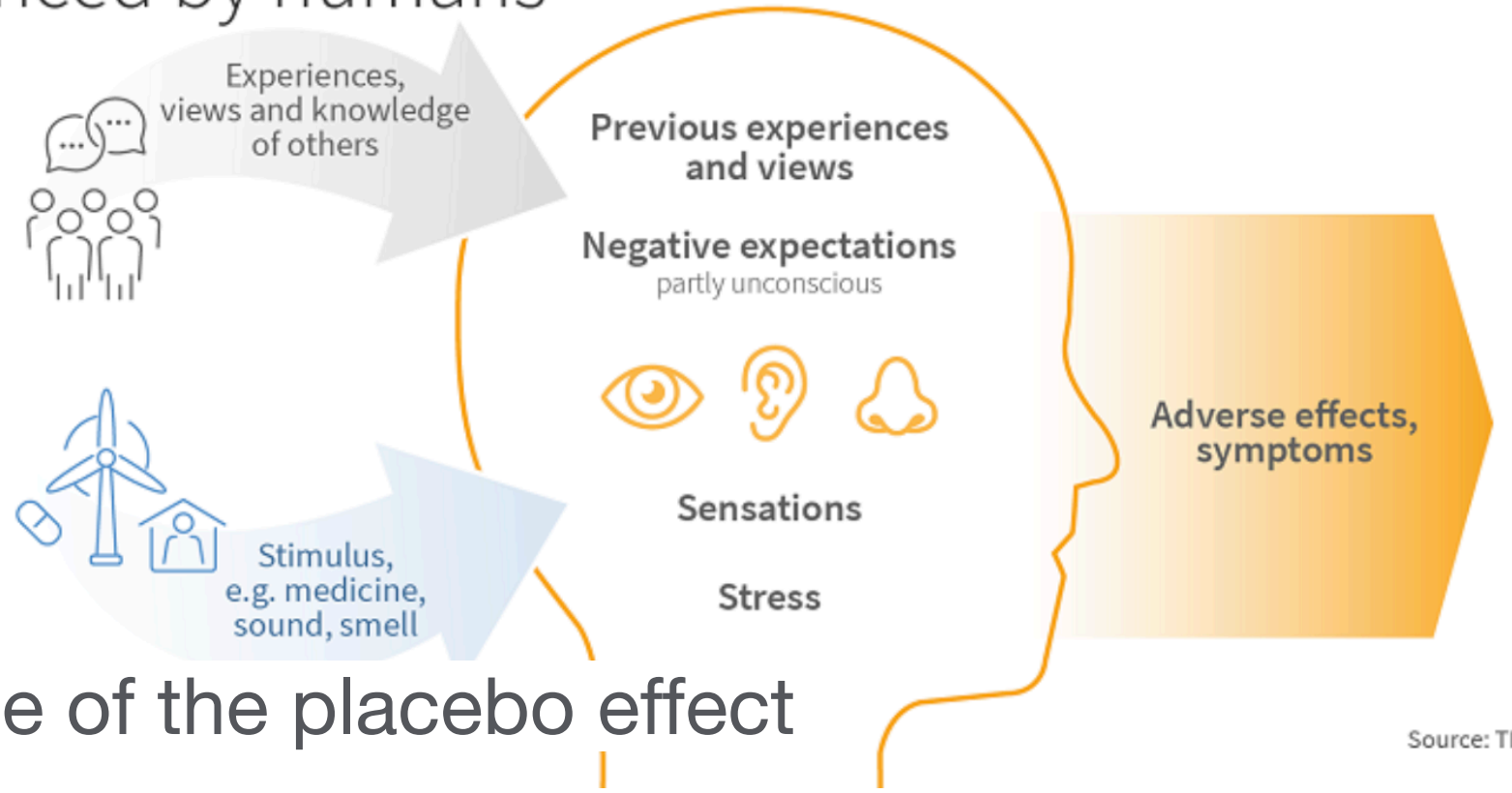
☐ None ☐ Yes, please list signs and symptoms:

Time to onset:

Delayed challenge reaction treatment given:

☐ None ☐ Yes, please list signs and symptoms:

Nocebo effect – negative preconceptions increase the number of adverse effects and symptoms experienced by humans



Opposite of the placebo effect

Source: THL 2020

Risk stratification

Table 3. Risk Stratification for Penicillin Allergy Evaluation

	Low Risk	Medium Risk	High Risk
History[a]	Isolated reactions that are unlikely allergic (eg, gastrointestinal symptoms, headaches) Pruritus without rash Remote (>10 y) unknown reactions without features of IgE[b] Family history of penicillin allergy	Urticaria or other pruritic rashes Reactions with features of IgE but not anaphylaxis[b]	Anaphylactic symptoms[c] Positive skin testing Recurrent reactions Reactions to multiple β-lactam antibiotics
Action	Prescribe amoxicillin course or perform a direct amoxicillin challenge under observation.[d]	Skin test followed by amoxicillin challenge under observation if the skin test is negative.[e] Consider allergy/immunology referral.	Allergy/immunology referral or desensitization.

[a] No penicillin allergy testing should be performed on patients with possible penicillin-associated severe cutaneous adverse reaction, hemolytic anemia, organ-specific reaction, drug fever, or serum sickness. Patients with unstable or compromised hemodynamic or respiratory status and pregnant patients should never be considered low risk.

[b] IgE features classically include cutaneous symptoms, such as itching, flushing, urticaria, and angioedema, but also involve respiratory system (rhinitis, wheezing, shortness of breath, bronchospasm), cardiovascular system (arrhythmia, syncope, chest tightness), and gastrointestinal system (abdominal pain, nausea, vomiting, diarrhea) symptoms.

[c] The most severe IgE-mediated reaction is anaphylaxis (eFigure 1 in Supplement 1). Allergy/immunology consultation is advised.

[d] Considering patient comfort level with trying penicillin again and whether resources exist for observation.

[e] If skin testing is not possible, a graded amoxicillin challenge can be considered for medium-risk histories. A graded challenge often requires administration of a one-tenth to one-fourth full dose of the desired drug and a 30- to 60-minute period of monitoring followed by administration of a full dose of the desired drug and a final 30- to 60-minute period of monitoring (Toolkit C in Supplement 2).

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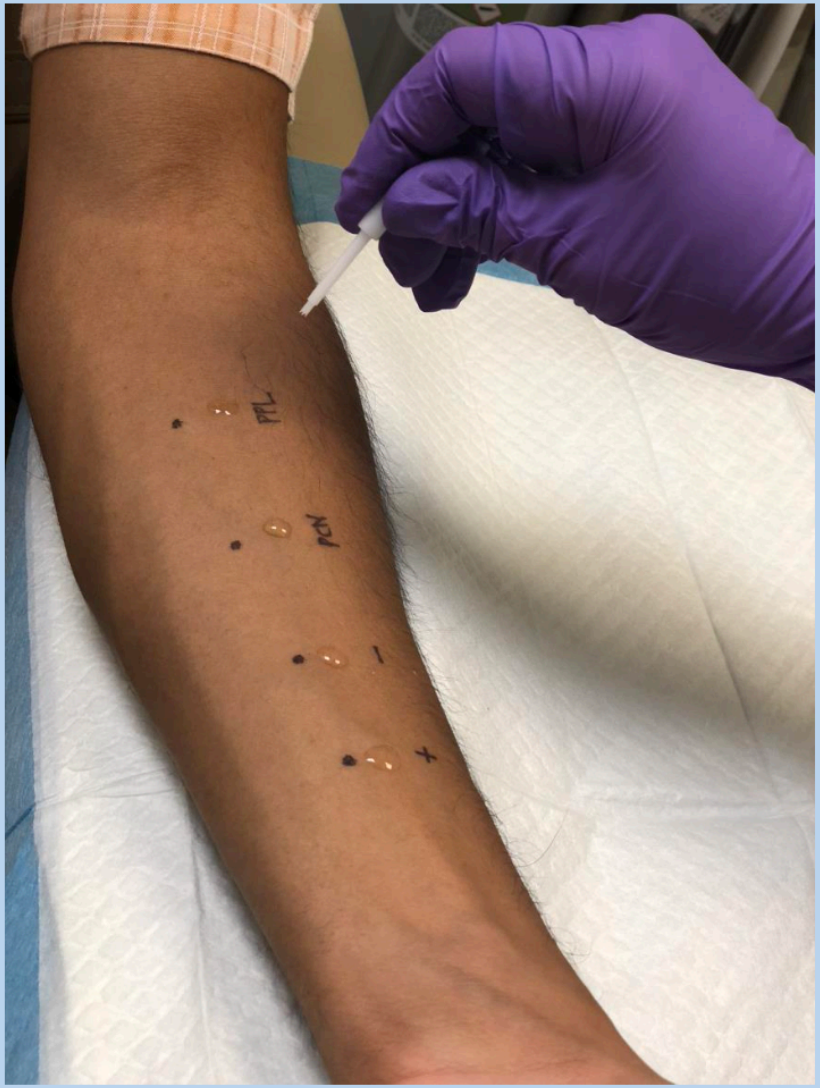
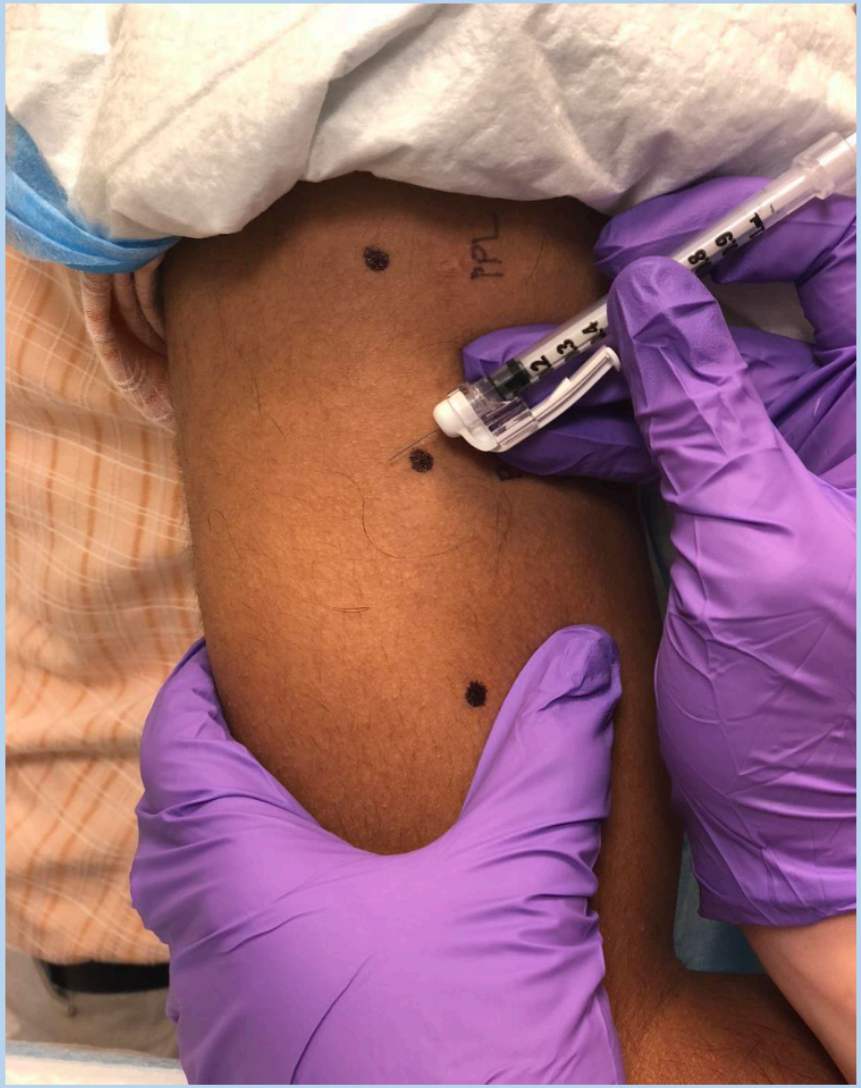
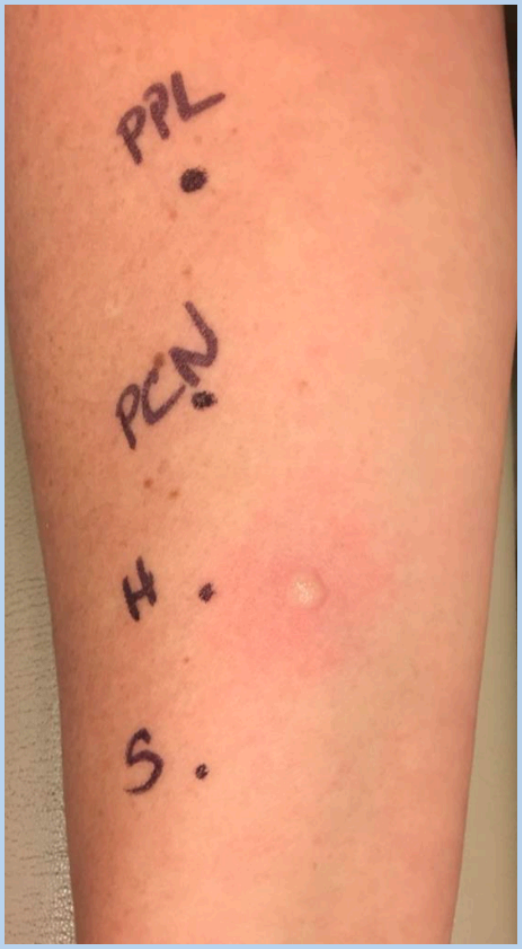
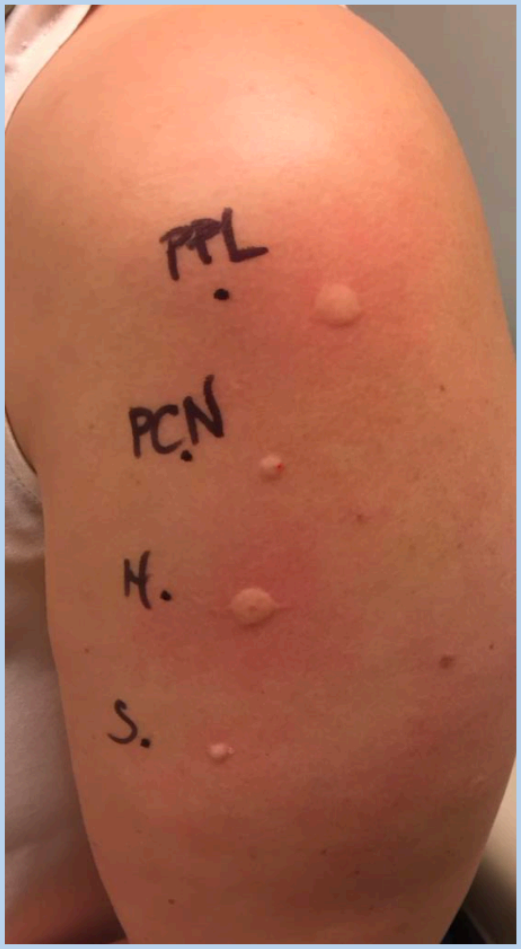
Percutaneous	Intradermal
	

Patient with a positive penicillin skin test

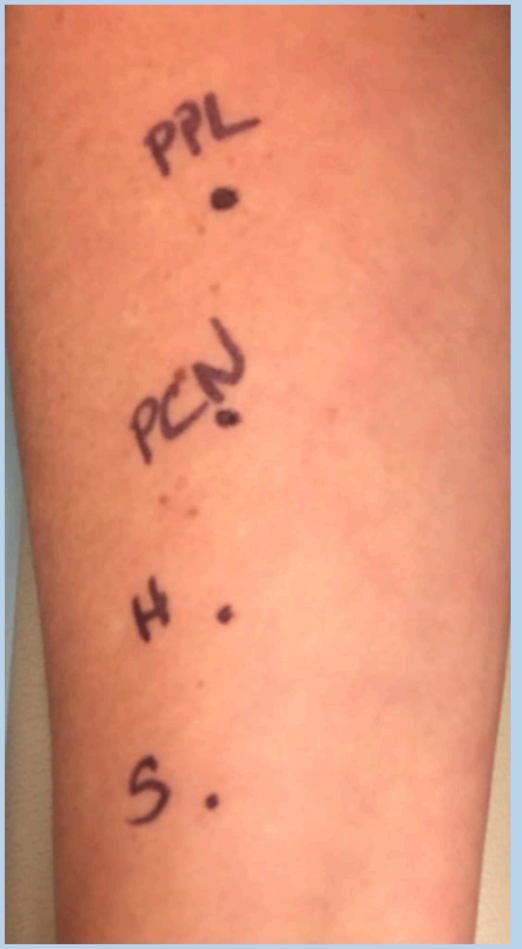


Negative Percutaneous Test

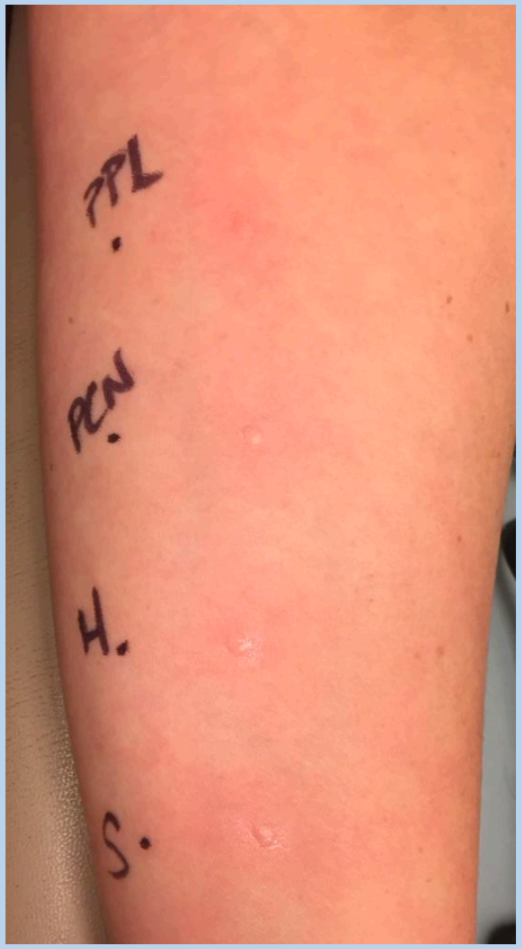


Positive Intradermal Test

Indeterminate skin test examples



Histamine Not Reactive



Saline Reactive

C
Page 1

Toolkit C

2-Step Amoxicillin Challenge for Moderate-Risk Patients (Skin Testing Not Available)

Patient ID/ Sticker:

Testing is not necessary if a penicillin class antibiotic has been tolerated since the index reaction

Note that this testing is recommended only in locations without access to skin testing materials. This procedure should be performed only after careful consideration of the potential benefit to the patient in question, weighed against the risk of potential harm from an allergic reaction.

DO NOT perform any penicillin allergy testing if there is a history of penicillin-associated:

• Blistering rash • Hemolytic anemia • Nephritis • Hepatitis • Fever • Joint pains

This testing is indicated if:

- The reaction was cutaneous
- The reaction had features of IgE/immediate hypersensitivity
- The patient currently has unstable or compromised hemodynamic or respiratory status or is pregnant with low risk allergy history.

This testing may also be used for low-risk reactions that include:

- Remote (>10 years) unknown reactions without features of IgE
- Pruritus without rash
- Isolated reactions that are unlikely allergic (e.g., gastrointestinal symptoms, headaches)

Continue to second page

C
Page 2

Toolkit C (continued)

Patient ID/ Sticker:

Ordered by: _____ Performed by: _____ Date: ___/___/_____

1 **Amoxicillin oral challenge given:** ☐ **25 mg** ☐ **50 mg**

Time given: **Time observed:** ☐ 30 min ☐ 60 min Time observation end:

Observed challenge reaction:

☐ None ☐ Yes, please list signs and symptoms:

Time to onset:

Observed challenge reaction treatment given:

☐ None ☐ Yes, please list signs and symptoms:

2 **Amoxicillin oral challenge given:** ☐ **250 mg** ☐ **500 mg**

Time given: **Time observed:** ☐ 30 min ☐ 60 min Time observation end:

Observed challenge reaction:

☐ None ☐ Yes, please list signs and symptoms:

Time to onset:

Observed challenge reaction treatment given:

☐ None ☐ Yes, please list signs and symptoms:

Delayed challenge reaction reported:

☐ None ☐ Yes, please list signs and symptoms:

Time to onset:

Delayed challenge reaction treatment given:

☐ None ☐ Yes, please list signs and symptoms:

D
Page 1

Toolkit D

Penicilloyl-Polylysine (PPL) Skin Testing Prior to Amoxicillin Challenge for Moderate Risk Patients

Patient ID/ Sticker:

DO NOT perform any penicillin allergy testing if there is a history of penicillin-associated:

• Blistering rash • Hemolytic anemia • Nephritis • Hepatitis • Fever • Joint pains

This testing is indicated if:

- The reaction was cutaneous
- The reaction had features of IgE/immediate hypersensitivity
- The patient currently has unstable or compromised hemodynamic or respiratory status or is pregnant with low risk allergy history.

Skin testing:

- Place test on arms.
- Place and read all puncture tests prior to placing any intradermal tests.
- Positive tests are defined as wheal ≥5mm with flare > wheal.
- **Do not record test if saline control is positive or histamine control is negative**

Ordered by: _____ Performed by: _____ Date: ___/___/_____

1 Prick/puncture

Time placed: Time read:

	wheal	flare
PPL		
Penicillin G		
Negative control		
Positive control (histamine)		

2 Intradermal

Time placed: Time read:

	wheal	flare
PPL		
Penicillin G		
Negative control		
Positive control (histamine)		

Continue to second page

D
Page 2

Toolkit D (continued)

Patient ID/ Sticker:

3 Amoxicillin challenge

Ordered by: _____ Performed by: _____ Date: ___/___/_____

Amoxicillin oral challenge given: ☐ 250 mg ☐ 500 mg

Time given: _____ Time observation end: _____

Observed challenge reaction:

☐ None ☐ Yes, please list signs and symptoms:

Time to onset:

Observed challenge reaction treatment given:

☐ None ☐ Yes, please list signs and symptoms:

Delayed challenge reaction reported:

☐ None ☐ Yes, please list signs and symptoms:

Time to onset:

Delayed challenge reaction treatment given:

☐ None ☐ Yes, please list signs and symptoms:

In medium-risk patients

- A negative skin test is assocaited with a 95% NPV for PCN allergy
- A negative skin test plus negative amoxicillin challenge approaches 100% NPV for PCN allergy
- If skin test is positive, amoxicillin challenge is not considered
- Patient should be feared to an allergy/immunologist or desensitisation considered

Risk stratification

Table 3. Risk Stratification for Penicillin Allergy Evaluation

	Low Risk	Medium Risk	High Risk
History[a]	Isolated reactions that are unlikely allergic (eg, gastrointestinal symptoms, headaches) Pruritus without rash Remote (>10 y) unknown reactions without features of IgE[b] Family history of penicillin allergy	Urticaria or other pruritic rashes Reactions with features of IgE but not anaphylaxis[b]	Anaphylactic symptoms[c] Positive skin testing Recurrent reactions Reactions to multiple β-lactam antibiotics
Action	Prescribe amoxicillin course or perform a direct amoxicillin challenge under observation.[d]	Skin test followed by amoxicillin challenge under observation if the skin test is negative.[e] Consider allergy/immunology referral.	Allergy/immunology referral or desensitization.

[a] No penicillin allergy testing should be performed on patients with possible penicillin-associated severe cutaneous adverse reaction, hemolytic anemia, organ-specific reaction, drug fever, or serum sickness. Patients with unstable or compromised hemodynamic or respiratory status and pregnant patients should never be considered low risk.

[b] IgE features classically include cutaneous symptoms, such as itching, flushing, urticaria, and angioedema, but also involve respiratory system (rhinitis, wheezing, shortness of breath, bronchospasm), cardiovascular system (arrhythmia, syncope, chest tightness), and gastrointestinal system (abdominal pain, nausea, vomiting, diarrhea) symptoms.

[c] The most severe IgE-mediated reaction is anaphylaxis (eFigure 1 in Supplement 1). Allergy/immunology consultation is advised.

[d] Considering patient comfort level with trying penicillin again and whether resources exist for observation.

[e] If skin testing is not possible, a graded amoxicillin challenge can be considered for medium-risk histories. A graded challenge often requires administration of a one-tenth to one-fourth full dose of the desired drug and a 30- to 60-minute period of monitoring followed by administration of a full dose of the desired drug and a final 30- to 60-minute period of monitoring (Toolkit C in Supplement 2).

Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019;321:188-199.

Example desensitization protocol

- Desensitization is absolutely contraindicated in patients with a history of a penicillin-induced exfoliative dermatitis, Stevens-Johnson syndrome, or toxic epidermal necrolysis
- Desensitization has no effect on the incidence of non-IgE mediated reactions such as serum sickness, hemolytic anemia, maculopapular rashes, drug fever, hepatitis, or interstitial nephritis
- If the patient does not receive a dose for a period of more than 24 hours, the risk for an immediate IgE-mediated reaction can be restored and repeat desensitization is required if the same drug is to be used again

* THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER **Inpatient**

Adult ICU Meropenem Intravenous Desensitization Pharmacy Guidelines

(For Use in Critical Care Unit Only)

Summary

- The patient will receive 13 consecutive meropenem doses of varied strengths intravenously.
- Upon successful completion of the protocol, the patient must begin regularly scheduled doses of intravenous meropenem at the ordered interval.
- Sensitization of the patient to meropenem will recur after 3 consecutively missed doses.

Precautions

- Desensitization is **contraindicated** in patients with a history of carbapenem induced-exfolative dermatitis.
- Desensitization has no effect on the incidence of non-IgE mediated reactions (ie. serum sickness, Stevens-Johnson syndrome, hemolytic anemia, maculopapular rash, drug fever, interstitial nephritis)
- Notify physician if patient has body weight less than 40 kg and/or is less than 18 years old.

Preparation Protocol

- The procedure is completed over 5 hours with 13 ascending doses of meropenem.
- If the final dose is less than 1 gm, stop protocol at the ordered dose. (ie. If the final ordered dose is 500 mg, stop desensitization protocol after Dose Number 12 and start scheduled doses as ordered.)

1. Doses 1-11 are infused over **20 minutes** and doses 12-13 are infused over **30 minutes**. The intravenous line should be completely flushed with 0.9% NaCl between doses.
2. 50 mL NaCl 0.9% minibags are used for each desensitization dose. Doses 11-13 will require the removal of additional milliliters of NaCl 0.9% from the minibags prior to the addition of meropenem.
4. Two stock solutions are required for compounding the meropenem desensitization doses.
   a. Solution A: 1gm vial of meropenem + 20 mL Sterile Water - Label Solution A meropenem 50 mg/mL
   b. Solution B: 1gm vial of meropenem + 20 mL Sterile Water - Label Solution B meropenem 50 mg/mL
5. Doses 7-12 are made using aliquots of Solution A. **Doses 7-13 should be made prior to doses 1-6.**
6. Dose 13 is made entirely from the stock Solution B.
7. Doses 1-6 are too small to measure accurately, so they are prepared from previously made doses (see table below).
8. Meropenem Intravenous Desensitization Schedule

Dose Number	Dose Strength (mg)	Preparation Instructions	Volume of dose (mL)
1	0.004 mg	Add 2 mL from **dose #3** to 50 ml 0.9% NaCl minibag	50 mL
2	0.02 mg	Add 1.5 mL from **dose #4** to 50 ml 0.9% NaCl minibag	50 mL
3	0.1 mg	Add 1.5 mL from **dose #6** to 50 ml 0.9% NaCl minibag	50 mL
4	0.6 mg	Add 1 mL from **dose #8** to 50 ml 0.9% NaCl minibag	50 mL
5	1.3 mg	Add 1 ml from **dose #9** to 50 ml 0.9% NaCl minibag	50 mL
6	4 mg	Add 0.2 mL from **dose #13** to 50 ml 0.9% NaCl minibag	50 mL
7	15 mg	Add 0.3 mL from **Solution A** to 50 ml 0.9% NaCl minibag	50 mL
8	30 mg	Add 0.6 mL from **Solution A** to 50 ml 0.9% NaCl minibag	50 mL
9	65 mg	Add 1.3 mL from **Solution A** to 50 ml 0.9% NaCl minibag	50 mL
10	125 mg	Add 2.5 mL from **Solution A** to 50 ml 0.9% NaCl minibag	50 mL
11	250 mg	Remove 5 mL from 50 ml 0.9% NaCl minibag **then** Add 5 mL from **Solution A**	50 mL
12	500 mg	Remove 10 mL from 50 ml 0.9% NaCl minibag **then** Add 10 mL from **Solution A**	50 mL
13	1000 mg	Remove 20 mL from 50 ml 0.9% NaCl minibag **then** Add 20 mL from **Solution B**	50 mL

Adapted from Wilson DL et al. Ann Pharmacother 2003;37:1424-1428.

ICU 00052 Sup V1 02/28/2007

NOT PART OF PATIENT'S MEDICAL RECORD

Common dogma-Cross reactivity with cephalosporins

- If a patient has a documented PCN allergy, the risk of cross reactions with cephalosporins is 10%
  - FALSE, the rate of cross reactivity is 2%
  - A subset of patients with history of anaphylaxis may have cross-reactivity. Cefazolin as a unique side chain and low cross-reactivity

Common amino R1 group	Common methoxyimino R1 group
Ampicillin Amoxicilin Cefaclor Cephalexin Cefadroxil	Ceftriaxone Cefotaxime Cefuroxime Cefepime Ceftazidime Cefpodoxime
*Beta-lactam antibiotics have shared beta-lactam rings and may have R1 (6/7 position) and/or R2 (3 position) side chains that can be structurally identical or similar. Cross reactivity appears highest for beta-lactams that share identical R1 side chains. More comprehensive cephalosporin cross-reactivity matrices[2] may be used if avoiding identical and similar structures at both side chain locations is desired.	

Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019;321:188-199.

What are the risks of cross-reactivity with carbapenems?

- Cross reactivity with penicillin allergy and carbapenems is less than 1%
- No cross reactivity between penicillins and monobactams (aztreonam)

- Skin testing with amoxicillin challenge is the simplest approach and makes determination of cross reactivity irrelevant

Special populations often not considered for skin testing

- Peri-procedure before elective surgery
  - Import of antibiotic timing/tissue levels at time of incision-less optimal with vancomycin that requires longer infusion
- Pregnant patients
  - PN allergy assocaited with increased risk of cesarian delivery, post-cesarian wound complications, and longer length of stay
  - Consider third trimester referral for testing in patients with planned cesarian delivery, group B streptococcus colonization
- Long term care facilities
  - Non-beta lactase have higher risk for drug interactions
  - High risk for adverse effects
- Oncology populations
  - Consider testing before chemotherapy or transplant (ones of immunosuppression
- STD clinics

Sulfonamide hypersensitivity

- **Incidence 8%**
  - cutaneous and GI tract
  - only 3% are considered true hypersensitivity reactions
  - however...sulfonamides are disproportionately associated with severe side effects (i.e. TEN, Stevens-Johnson Syndrome)
- **Mechanisms**
  - IgE-mediated are known to occur, but other poorly understood direct T-cell mediated mechanisms are more likely to be responsible

Slatore et al. Immunol Allergy Clin N Am 24 (2004) 477–490

arylamine

Sulfanilamide (basic sulfonamide structure)

hydroxylamine intermediate (CYPP450)

haptenate endogenous proteins

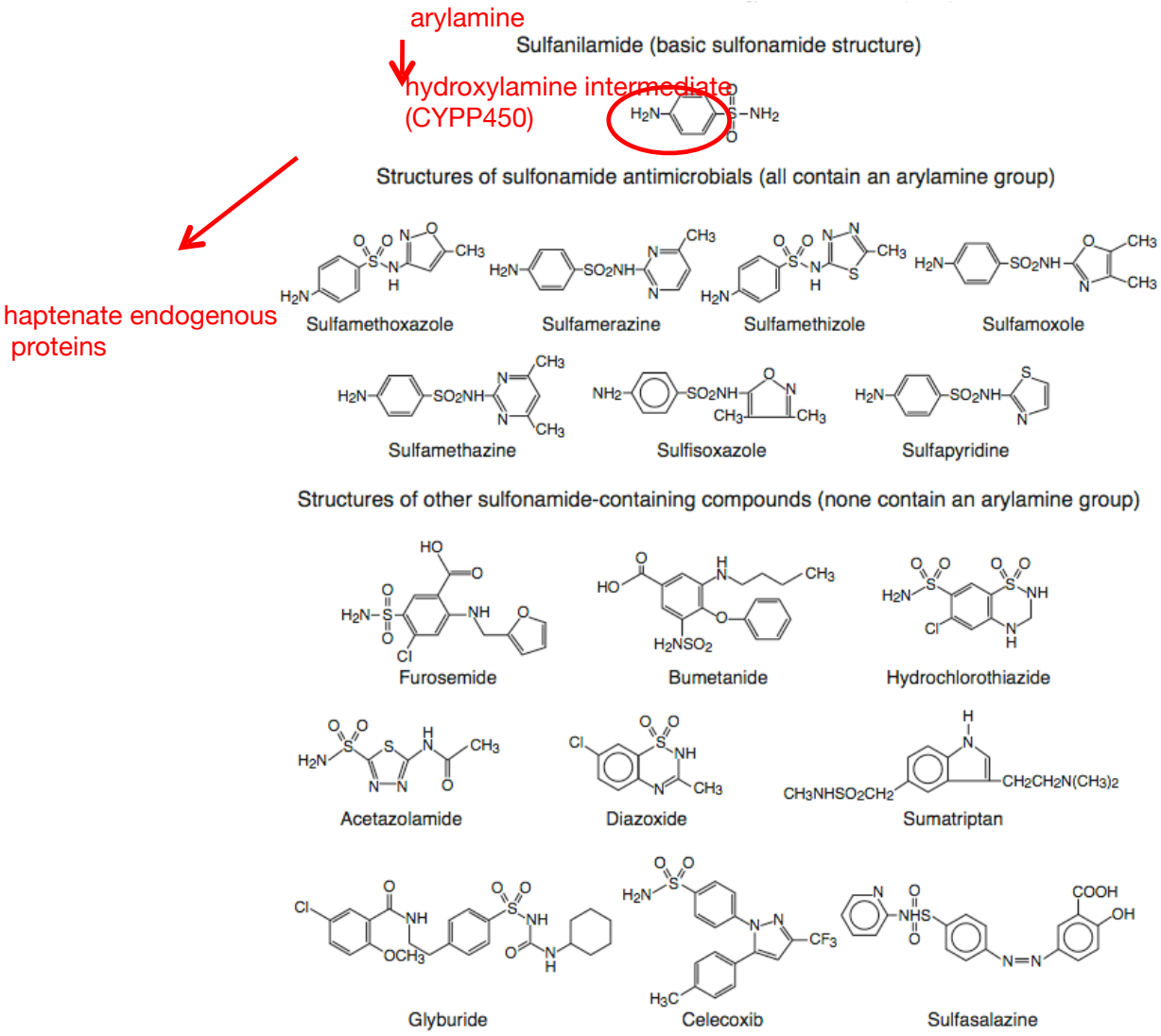
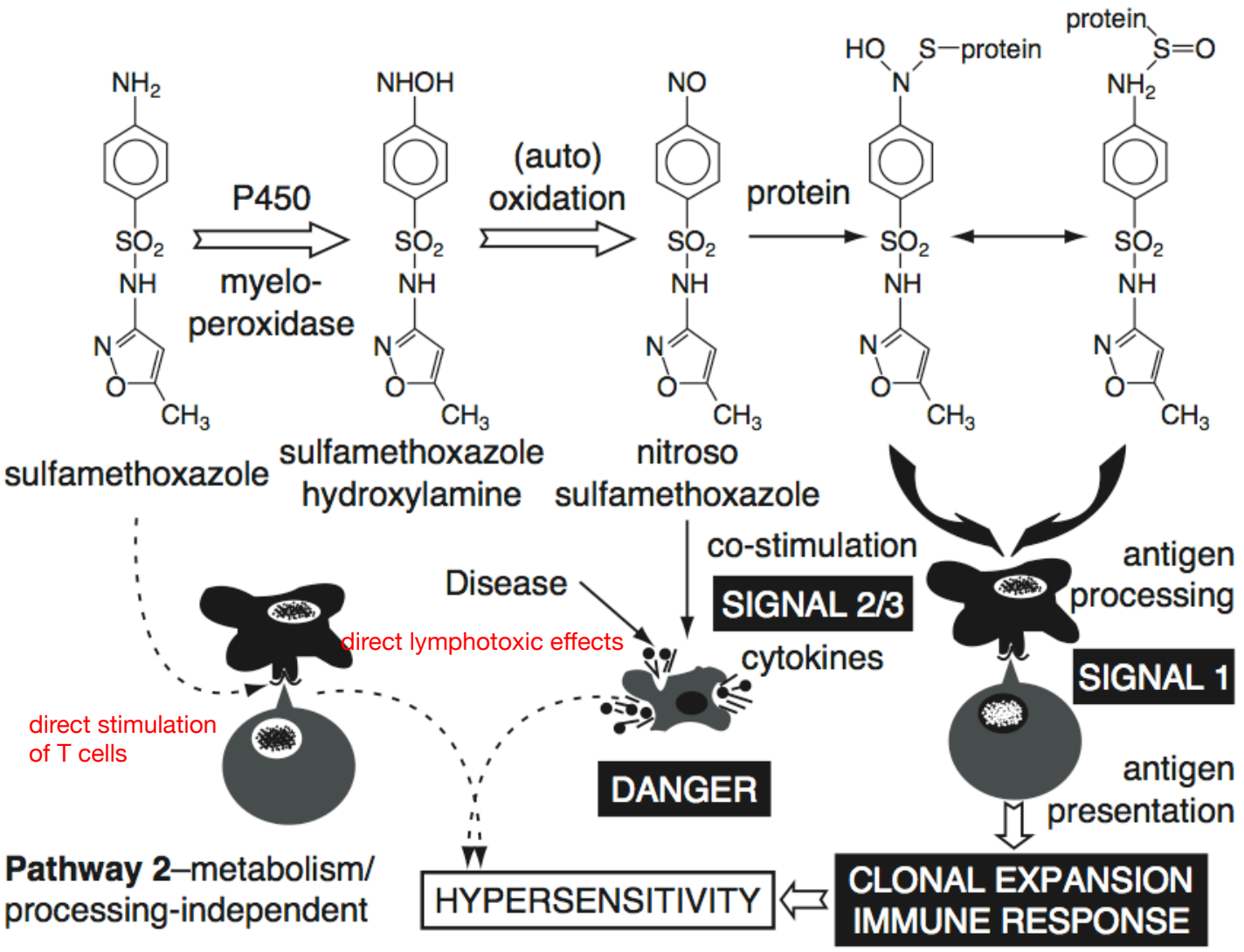


Fig. 3. Sulfanilamide and structurally related drugs. (*From* Tilles SA, Slatore CG. Hypersensitivity reactions to non–beta-lactam antibiotics. Clin Rev Allergy Immunol 2003;24:221–8; with permission.)



HIV infected patients- slow acetylation, altered levels of thiols, disulfides and plasma cysteine

Slatore et al. Immunol Allergy Clin N Am 24 (2004) 477–490