Penicillin and Antibiotic Allergies

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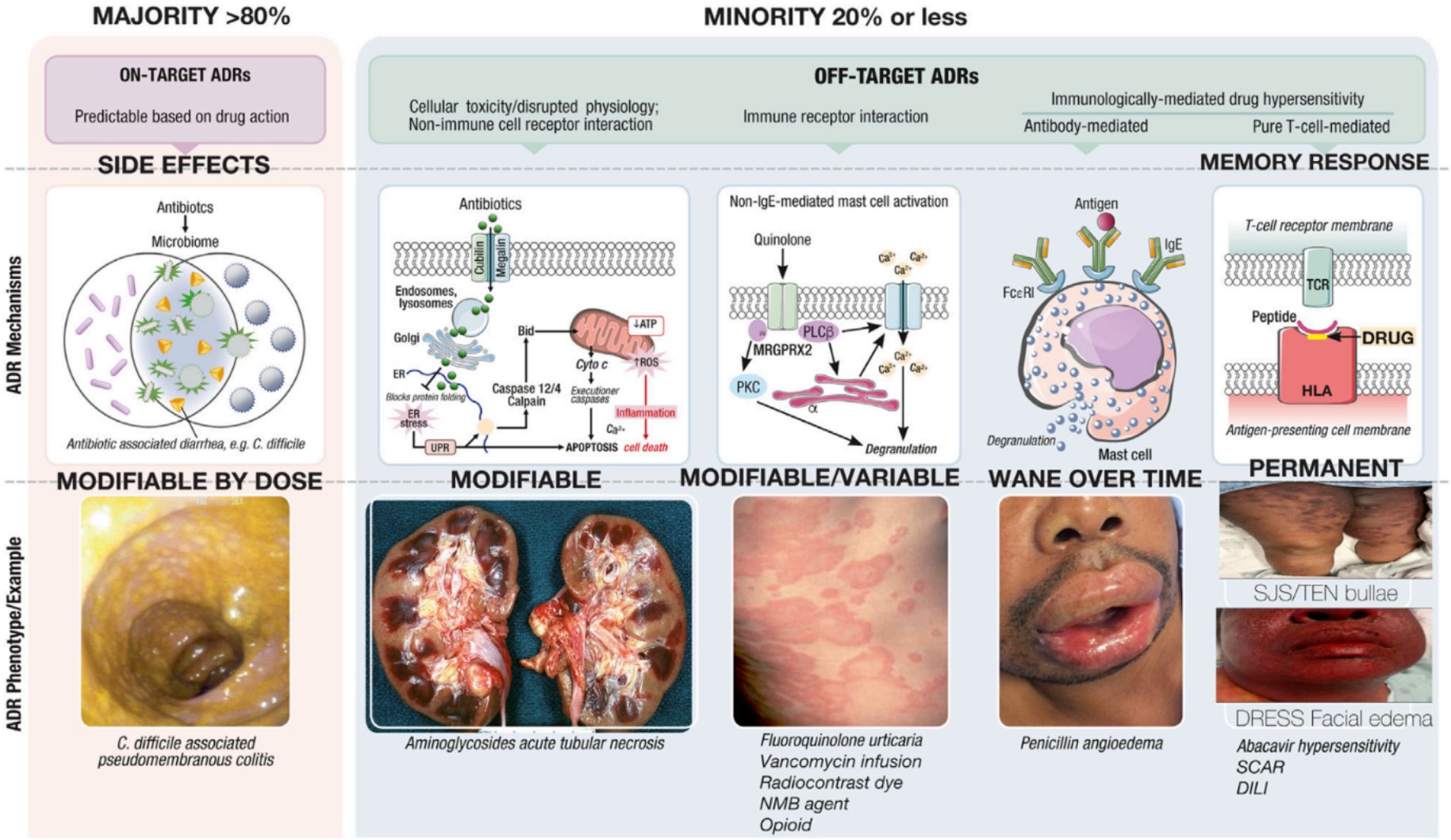
Slides and course materials: www.padovaid.com

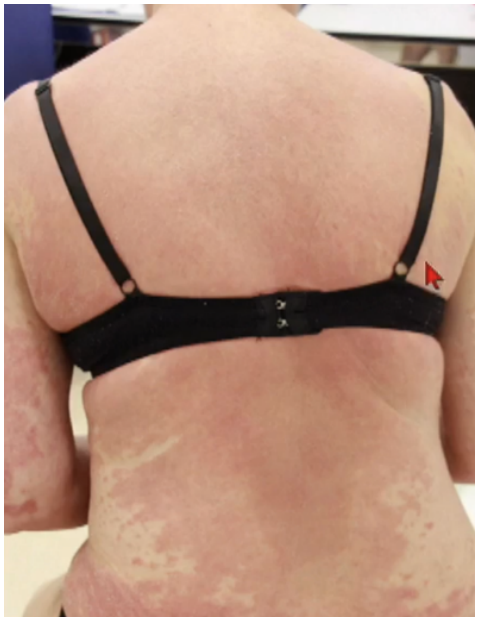
Objectives

- Describe the different types of hypersensitivity reactions based on clinical presentation and immunological mechanisms
- Recognise 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 desensitisation
- Describe the clinical manifestations, diagnosis and management of common non-beta-lactam antibiotic allergies

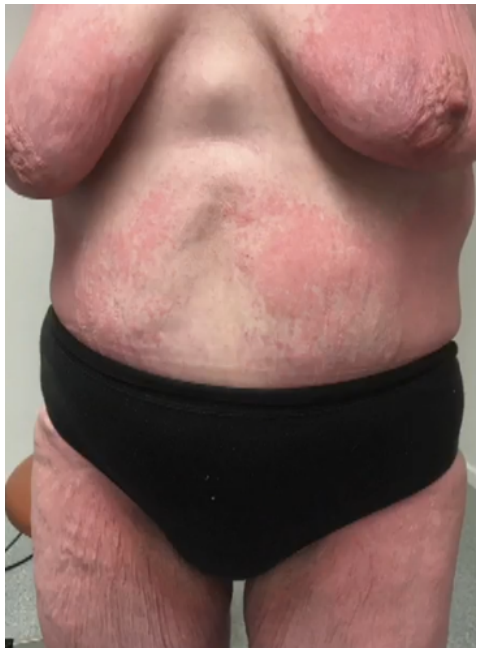
On target vs. off-target drug effects



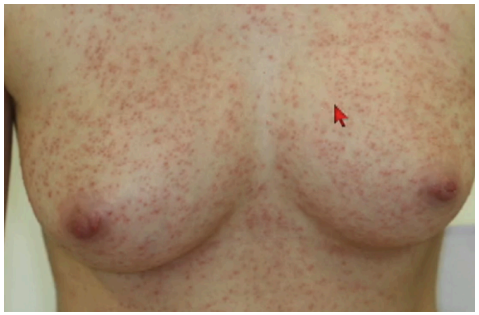
Variable cutaneous presentation of allergic drug reactions



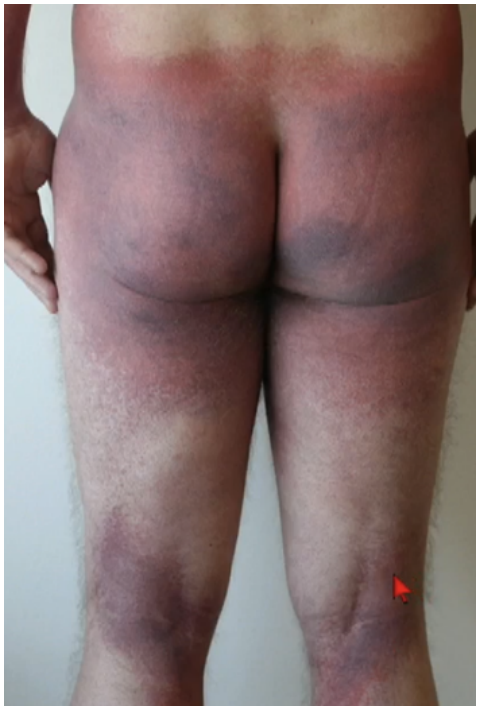
widespread macupapular



macupapular aspect

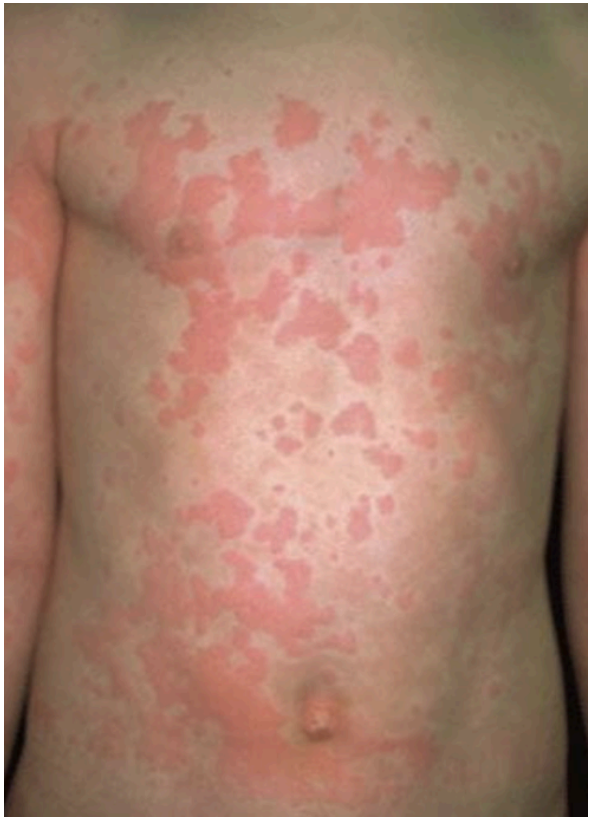


isolated follicular

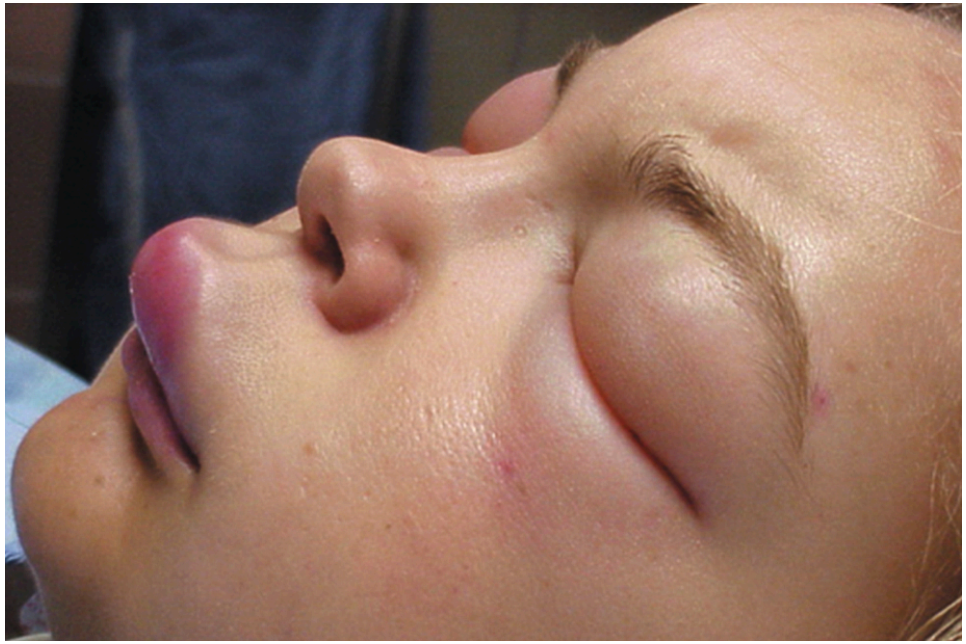


coalescing erythema

Urticaria and angioedema

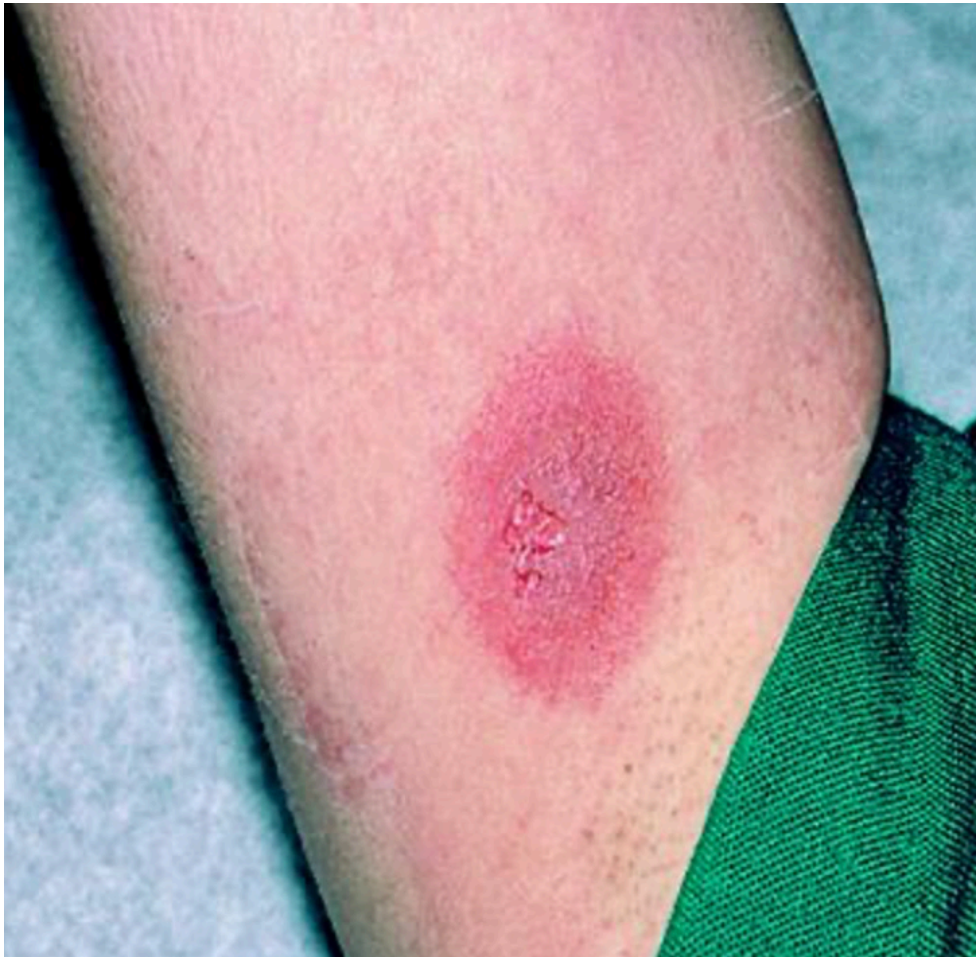


urticaria



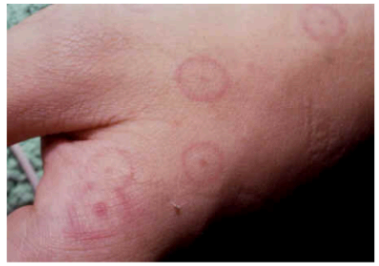
angioedema

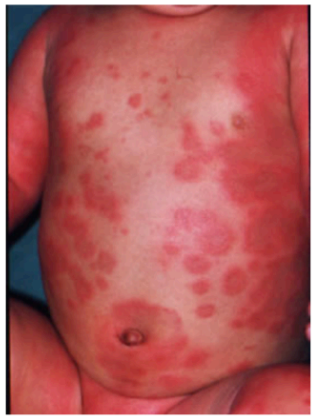
Fixed drug eruption

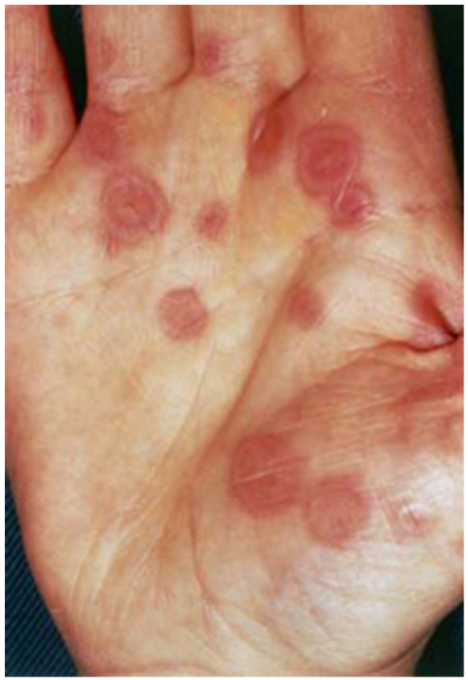


SCAR: Severe Cutaneous Adverse Reactions

Erythema multiforme,
Toxic epidermal necrolysis (TEN)



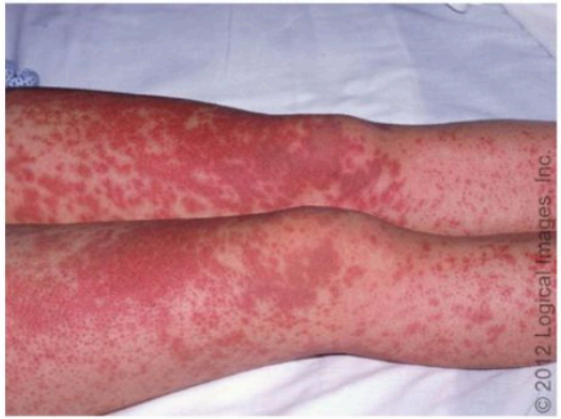




DRESS: Drug rash with eosinophilia and systemic symptoms

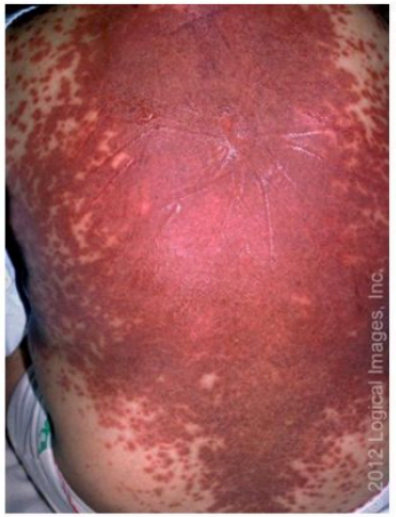
- **Latency:** 2-8 weeks
- **Non-specific symptoms:**
  - Fever (75%), lymphadenopathy (55-65%)
- **Hematological abnormalities:**
  - **Eosinophilia > 700 mcL (85-95%)**
  - **Leukocytosis (95%), neutrophilia (78%), monocytosis (69%)**
  - **Atypical lymphocytosis (35-67%)**
- **Visceral involvement:**
  - **Liver (53-90%)-cholestatic and/or hepatocellular**
  - **Pulmonary (30%)-shortness of breath, cough**
  - **Cardiac involvement (2-20%)-hypotension, tachycardia, dyspnea, LV dysfunction, myocarditis**

Drug reaction with eosinophilia and systemic symptoms (DRESS)



Confluent morbilliform skin eruption with follicular accentuation in a patient with drug reaction with eosinophilia and systemic symptoms (DRESS).

symptoms

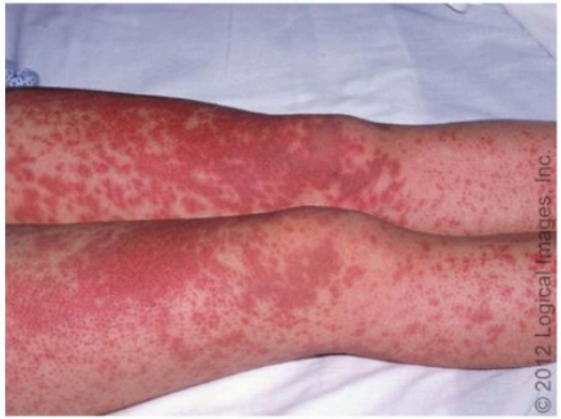


Diffuse and confluent skin eruption in a patient with DRESS.

DRESS: Pathophysiology and systemic symptoms

- **Pathophysiology:**
  - Type IV T-cell activation (CD4+/CD8+) producing TNF-α
  - Reactivation of viruses from the Herpesviridae family (eg, HHV-6, HHV-7, Epstein-Barr virus [EBV], cytomegalovirus [CMV]) occurs in up to 75 percent of patients-cause or consequence?
  - Some patient human leukocyte antigens are associated with higher risk
  - RegiSCAR scoring system is a commonly used tool for diagnosis
  - Symptoms may worsen or recur despite drug discontinuation or persisnt, requing immunosuppressive treatment

Drug reaction with eosinophilia and systemic symptoms (DRESS)



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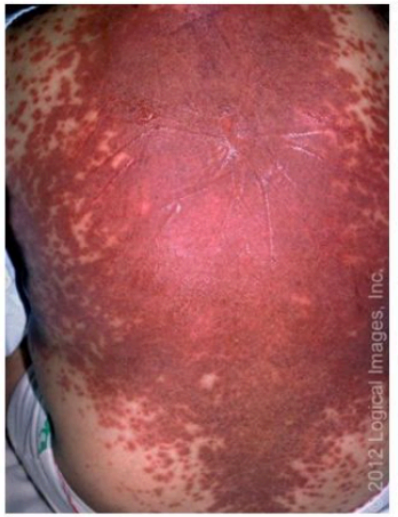


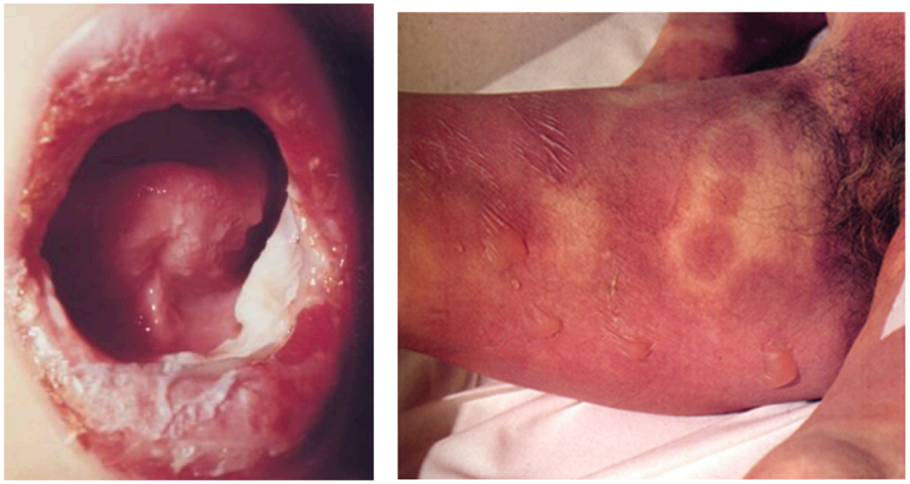
Diffuse and confluent skin eruption in a patient with DRESS.

Classic “high-risk” drugs for DRESS

- Allopurinol
- Aromatic antiepileptic agents (carbamazepine, phenytoin, lamotrigine, …)
- Sulphonamides
- Vancomycin
- Minocycline
- Nevirapine
- Anti-tuberculosis drugs
- Mexiletine

β-lactams are lower risk

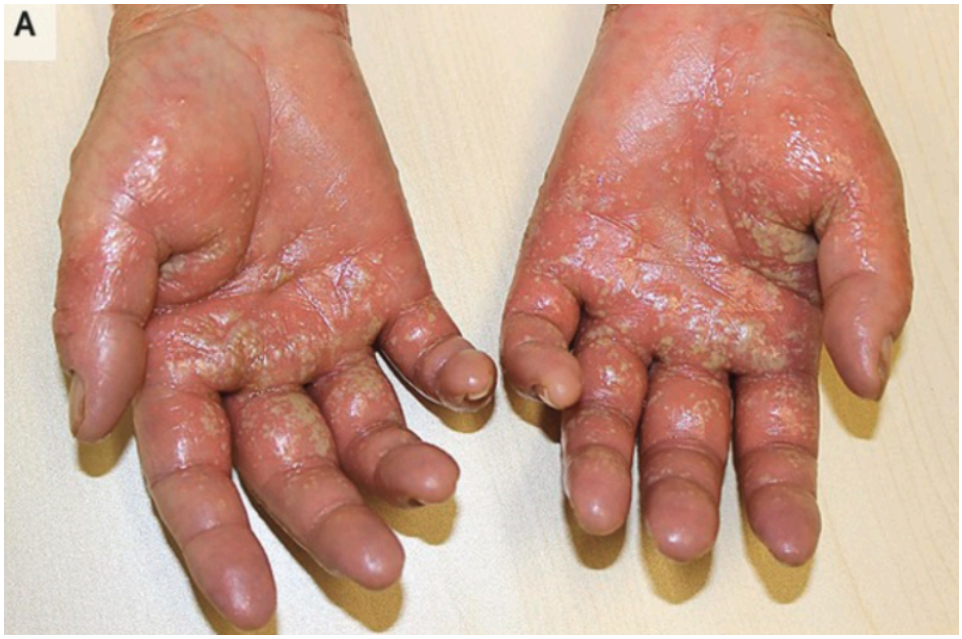
Stevens-Johnson Syndrome

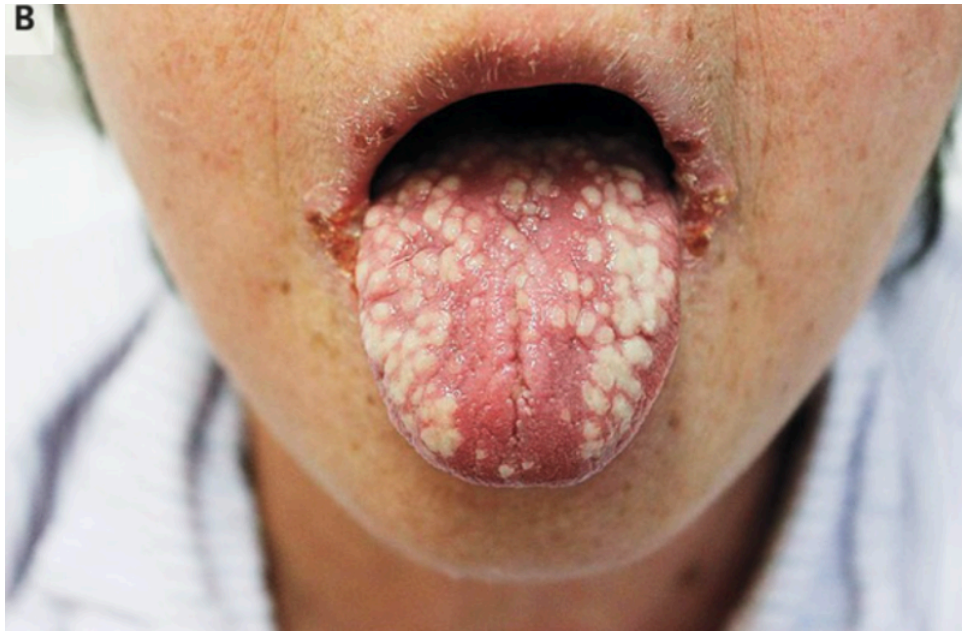


- Drug-sensitized cytotoxic CD8+ T cells mediate keratinocyte necrosis
- TEN has a mortality rate of approximately 30% that can exceed 50% in elderly or immunosuppressed patients
- The severity-of-illness score for TEN (SCORTEN) algorithm facilitates clinical diagnosis and prognostication
- SJS is associated with the maintenance of long-lasting tissue-resident memory T-cell responses in the skin that persist after SCAR, necessitating accurate identification and lifelong avoidance of the culprit antibiotic

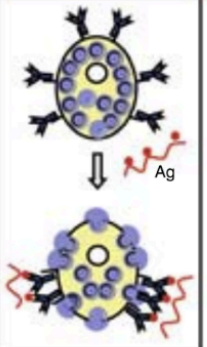
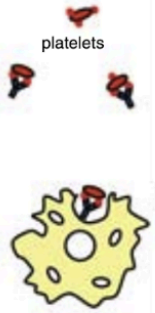
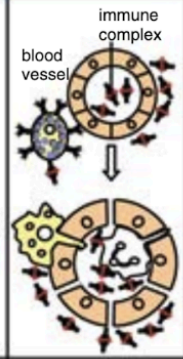
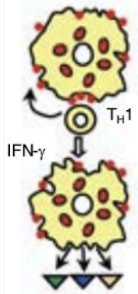
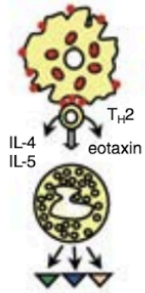
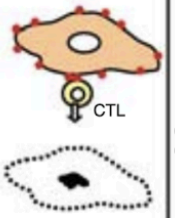
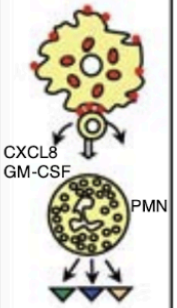
Acute generalized exanthematous pustulosis (AGEP)

- AGEP is a drug eruption characterized by an extensive sterile, nonfollicular pustular reaction superimposed on erythematous plaques, with a prominent leukocytosis and neutrophilic dominance
- Most cases of antimicrobial-induced AGEP, such as that caused by β-lactams and quinolones, typically cause symptoms within a day of exposure, whereas other drugs take 7 to 14 days of exposure before symptoms.

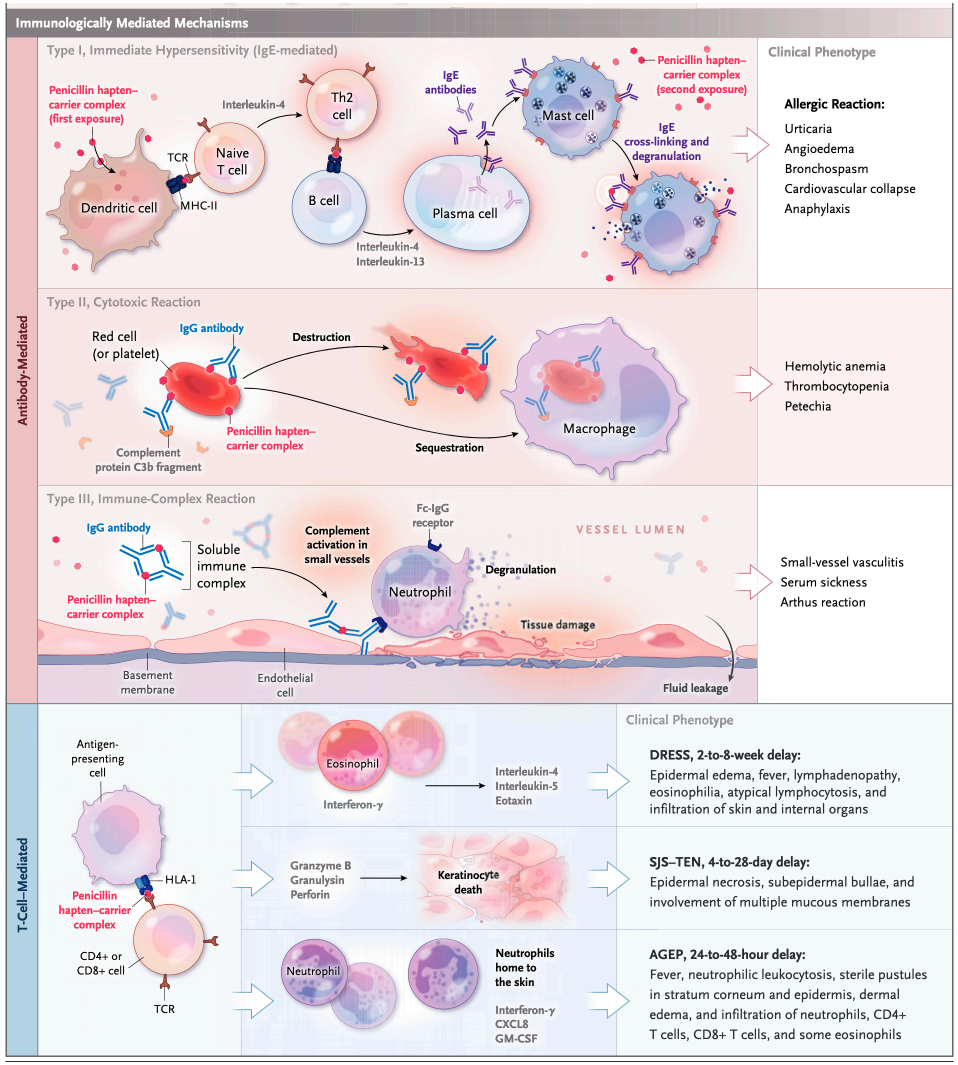




Modified Gell and Coombs Classification

	Type I	Type II	Type III	Type IV a	Type IV b	Type IV c	Type IV d
Immune reactant	IgE	IgG	IgG	IFNγ, TNFα (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ GranzymeB (CTL)	CXCL-8. GM-CSF (T-cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation	Cell-associated antigen or direct T cell stimulation	Soluble antigen presented by cells or direct T cell stimulation
Effector	Mast-cell activation	FcR⁺ cells (phagocytes, NK cells)	FcR⁺ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
				 chemokines, cytokines, cytotoxins	 cytokines, inflammatory mediators		 cytokines, inflammatory mediators
Examples	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g., penicillin)	Serum sickness, Arthus reaction	Tuberculin reaction , contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis Maculopapular exanthema with eosinophilia	Contact dermatitis, Maculopapular and bullous exanthema, hepatitis	AGEP Behçet disease

Immunological mechanisms



Penicillin allergy

Penicillin allergy epidemiology

- 10-20% of patients will report a history of an allergy to PCN therapy
- However, only 0.5%-2% of all PCN administrations actually result in hypersensitivity reactions, most often rash
  - Of these 1% are IgE mediated
- The incidence 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:
  - 1 death after anaphylaxis with oral amoxicillin (35 years and 100 million treatment courses)
- Most reports of penicillin allergy describe unknown or cutaneous reaction

Public health implications

A penicillin-allergy label is usually acquired in childhood

Personal Health Implications	Public Health Implications	Formal Allergy Assessment
Fewer efficacious antibiotic choices	Antibiotic resistance	<5% Labeled as allergic to penicillin are truly allergic
More toxic effects associated with alternative antibiotics	Higher rates of *C. difficile* infection	
Use of broad-spectrum antibiotics	Use of more costly antibiotics	
More postoperative surgical-site infections	Increased length of hospital stays	

So if a patient reports they have a penicillin allergy…

5% need allergy evaluation

- Recent history if true IgE type reaction
- Blistering rash
- Hemolytic anemia
- Nephritis
- Hepatitis
- Fever and joint pain
- Severe cutaneous adverse reaction (SCAR)

95% can tolerate penicillins

- Delayed, benign rash (Type IV reaction) that often does not recur with rechallenge
- True IgE reactions wane over time, 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)

Top 4 patient penicillin allergy myths

- **Once you have an penicillin allergy, you have it for life**
  - Allergy wanes over time, 80% of patients with type I (IgE-mediated reactions) will not have an allergy after a 10 year period
- **Viral rashes mistaken for antibiotic therapy**
  - E.g., child with a viral exanthematous rash treated with a course of penicillin
  - Pediatric studies have reported >90% of children who developed rashes on antibiotic therapy do not develop a rash when rechallenged with penicillin again
- **Adverse effects mistaken by the patient as drug allergy**
  - E.g. diarrhea, stomach cramps
- **“I have a family history of penicillin allergy”**
  - No genetic basis has been identified for penicillin allergies

Penicillin allergy history

A
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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:

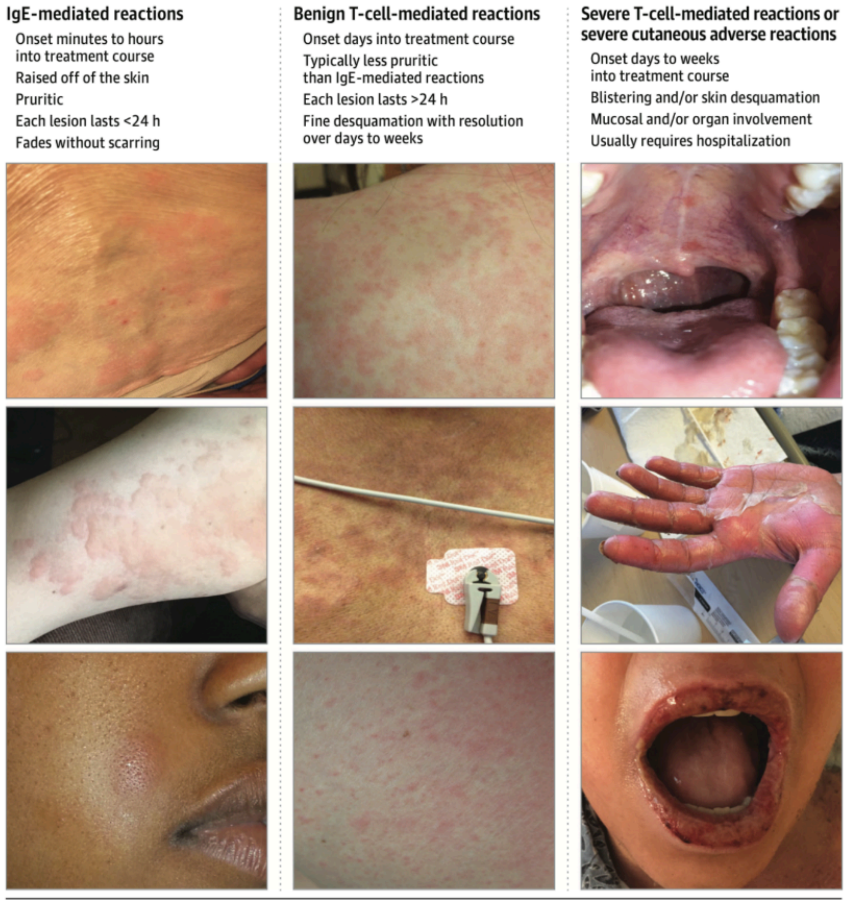
☐ Subsequent use of a penicillin or beta-lactam (after the course that caused a reaction)

If yes, please list drugs:

History taken by

Print name: _____ Signature: _____ Date: _____

Timing and clinical presentation of reaction



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.

How to assess patient risk

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).

PENFAST score

PEN	*Penicillin allergy reported by patient*	☐ *If yes, proceed with assessment*
F	*Five years or less since reaction*[a]	☐ **2 points**
A	*Anaphylaxis or angioedema*	
	OR	☐ **2 points**
S	*Severe cutaneous adverse reaction*[b]	
T	*Treatment required for reaction*[a]	☐ **1 point**
		☐ **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 epidermalnecrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalizedexanthematous 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.

PENFAST performance

Table 4. Validation of PEN-FAST in Predicting a Positive Penicillin Allergy Test Result in All Derivation and Validation Cohorts

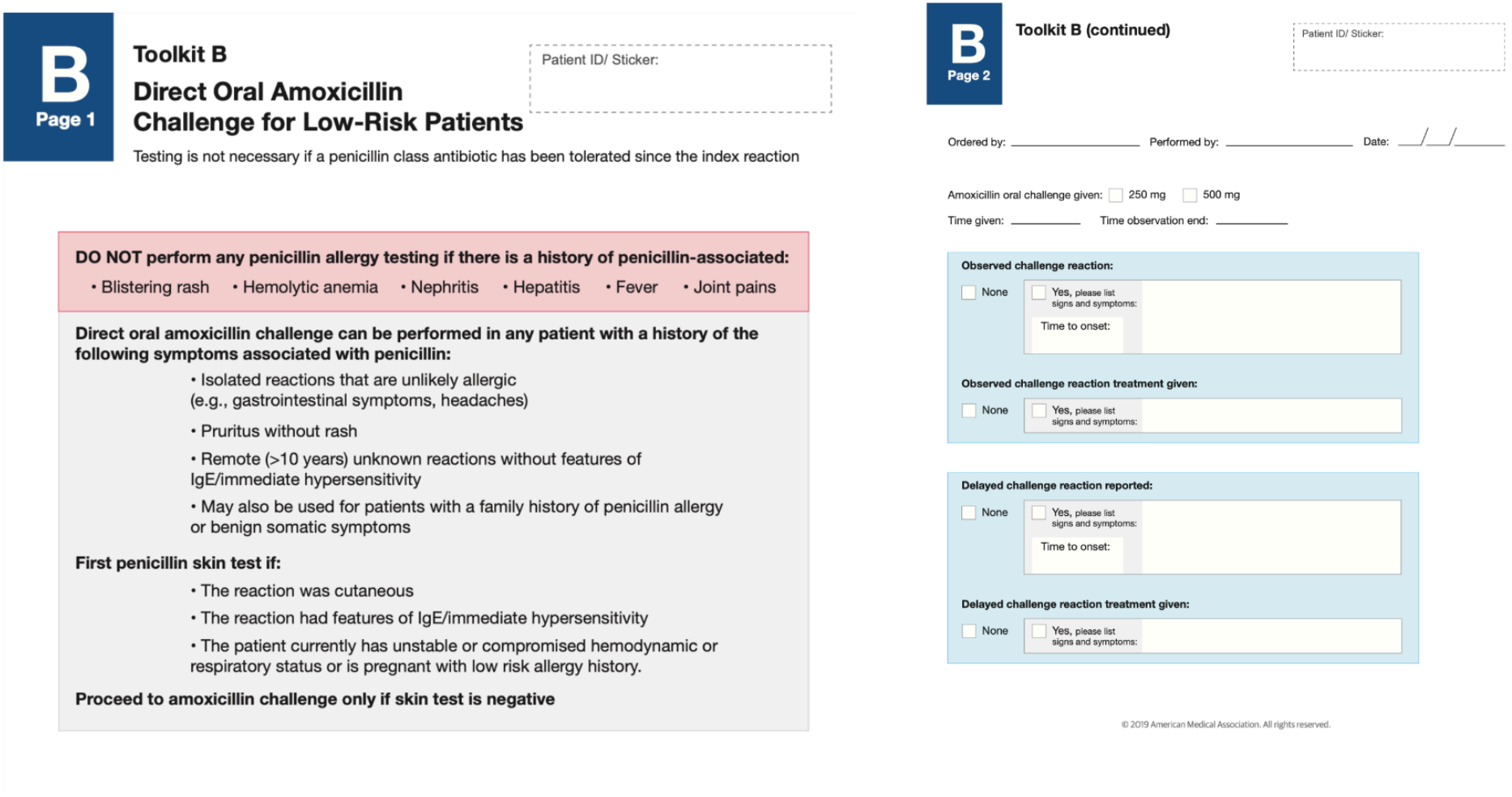
Cohort	No. of patients	No. (%) with positive finding[a]	Validation[b]				
			AUC (95% CI)	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI),%	NPV (95% CI), %
Melbourne, Australia	622	58 (9.3)	0.75 (0.68-0.81)	70.7 (57.3-81.9)	78.5 (74.9-81.9)	25.3 (18.8-32.7)	96.3 (94.1-97.8)
Perth, Australia	334	48 (14.4)	0.73 (0.66-0.81)	87.5 (74.8-95.3)	39.9 (34.1-45.8)	19.6 (14.5-25.6)	95.0 (89.4-98.1)
Sydney, Australia	80	27 (33.8)	0.78 (0.68-0.88)	70.4 (49.8-86.2)	84.9 (72.4-93.3)	70.4 (49.8-86.2)	84.9 (72.4-93.3)
Nashville, Tennessee	531	19 (3.6)	0.74 (0.62-0.86)	73.7 (4.8-90.9)	59.8 (55.4-64.0)	6.4 (3.5-10.4)	98.4 (96.3-99.5)

Abbreviations: AUC, area under the receiver operating characteristics curve; NPV, negative predictive value; PPV, positive predictive value.

[a] Indicates any penicillin allergy test with a positive finding.

[b] Based on a PEN-FAST score of at least 3.

Direct oral amoxicillin challenge



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

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:

Rationale behind oral amoxicillin challenge

- Only ~2% of penicillin “allergic” individuals develop an acute hypersensitivity reaction with an oral challenge of a therapeutic dose and 1 hour of observation.
  - An additional approximately 2% will have a delayed onset, typically benign, rash within the next 5 days.
  - The requirement for viral costimulation of T cells likely explains the low reproducibility of drug exanthems.
- Hence, a direct oral challenge with a single therapeutic dose of amoxicillin is an important step to avoid unnecessary penicillin allergy labels, and indicated in low-risk phenotypes and nonanaphylactic symptoms, such as those with benign delayed-onset rashes without systemic symptoms or SCAR features

Palace study

JAMA Internal Medicine

RCT: Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy

POPULATION

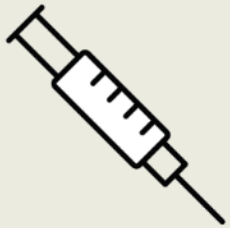
130 Men, 247 Women

Adults ≥18 y old with a low-risk penicillin allergy

Median age, 51 y

INTERVENTION

377 Participants analyzed



190 Control
Skin prick and intradermal penicillin testing, followed by oral challenge if skin testing results are negative

187 Intervention
Direct oral penicillin drug challenge

SETTINGS / LOCATIONS

6 Hospitals in North America and Australia

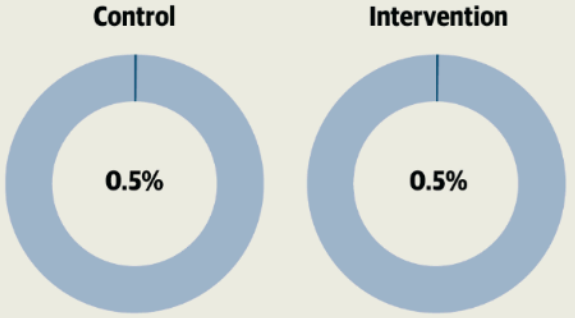
PRIMARY OUTCOME

Between-group difference in the proportion of participants with a physician-verified immune-mediated positive oral penicillin challenge (percentage points); noninferiority margin was set at 5 percentage points

FINDINGS

The intervention was found to be noninferior to the control for the primary outcome in adults with low-risk penicillin allergy

Proportion of participants with a positive oral penicillin challenge



1 of 190 participants **1 of 187 participants**

Risk difference, 0.0084 (90% CI, −1.22 to 1.24) percentage points, which is less than the noninferiority margin

Two step oral amoxicillin challenge

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)

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:

Anaphylaxis medications

Toolkit E

Sample Anaphylaxis and Adjunctive Medications for Ambulatory Environments

	Drug	Pediatric dosing	Adult dosing
Intramuscular (IM) epinephrine	Epinephrine 1 mg/mL (1: 1000)	**<10 kg**: 0.1 mg **10-25 kg**: 0.15 mg **Children >25 kg:** use Adult dosing	0.30 mg
Antihistamines	Diphenhydramine	1 to 2 mg/kg/dose (IM or PO); **Maximum:** 50mg/dose	25-50 mg
	Cetirizine	**6m to <2 years:** 2.5 mg **2 to 5 years:** 2.5-5 mg **Children ≥6 years:** use Adult dosing	10-20 mg
	Fexofenadine	**2 to 11 years:** 30-60 mg **Children ≥12 years:** use Adult dosing	90-360 mg
	Ranitidine[a]	4 to 8 mg/kg; **Maximum:** 300 mg/day	150-300 mg/day
Glucocorticoids	Prednisone	1-2 mg/kg	20-60 mg
Bronchodilators	Albuterol inhaler	1 inhalation **Anaphylaxis:** 4-8 inhalations every 20 minutes for 3 doses	2 inhalations **Anaphylaxis:** 4-8 inhalations every 20 minutes for up to 4 hrs
	Albuterol nebulized	0.15 mg/kg (minimum dose: 2.5 mg) in 3 mL saline, inhaled via nebulizer **>12 years old:** use Adult dosing	2.5-5 mg every 20 minutes for 3 doses

Footnote: [a] H2 blocker

How to assess patient risk

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.

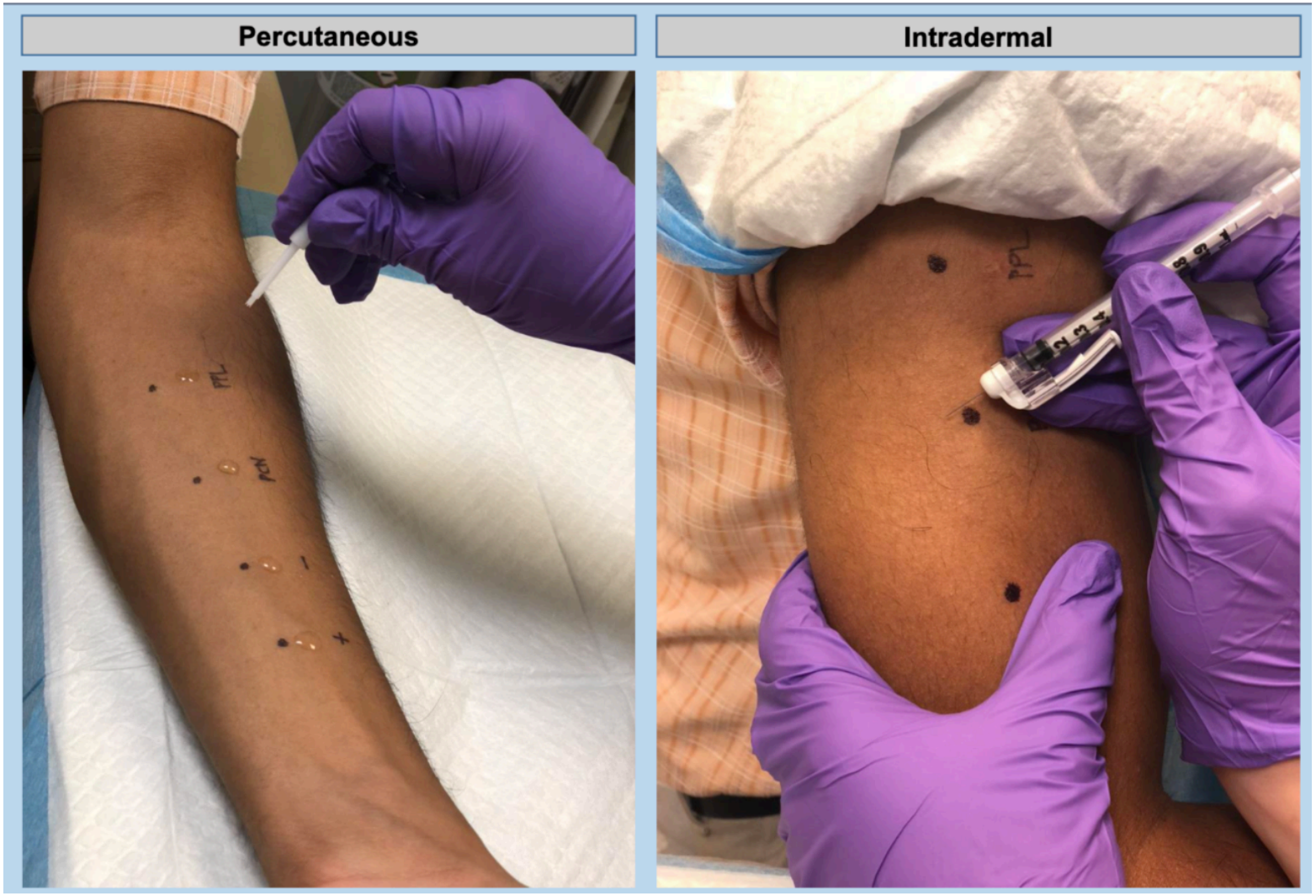
[b] IgE features classically include cutaneous symptoms, such as itching, flushing, urticaria, and angioedema, but also involve respiratory system (rhinitis, wheezing, shortness of breath, bronchospasm), cardiovascular system (arrhythmia, syncope, chest tightness), and gastrointestinal system (abdominal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

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

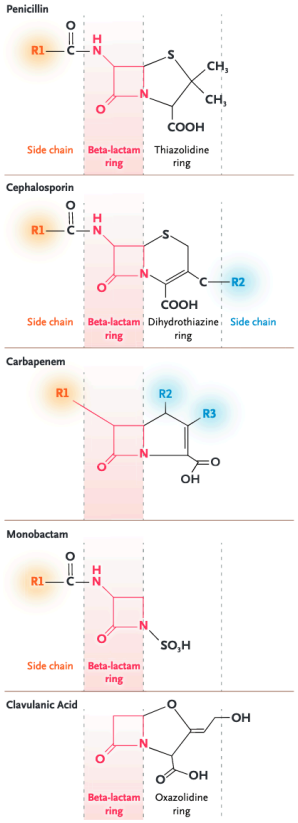
[d] Considering patient comfort level with trying penicillin again and whether resources exist for observation.

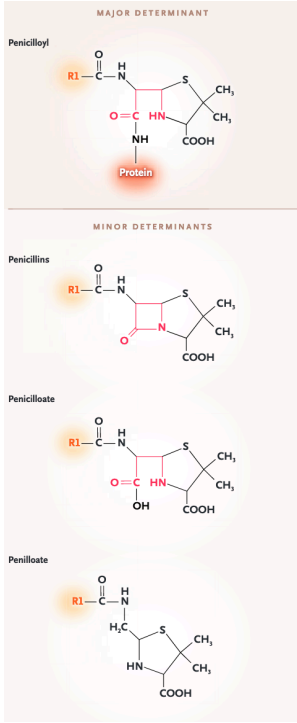
[e] If skin testing is not possible, a graded amoxicillin challenge can be considered for medium-risk histories. A graded challenge often requires administration of a one-tenth to one-fourth full dose of the desired drug and a 30- to 60-minute period of monitoring followed by administration of a full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

Skin testing



Allergic determinates

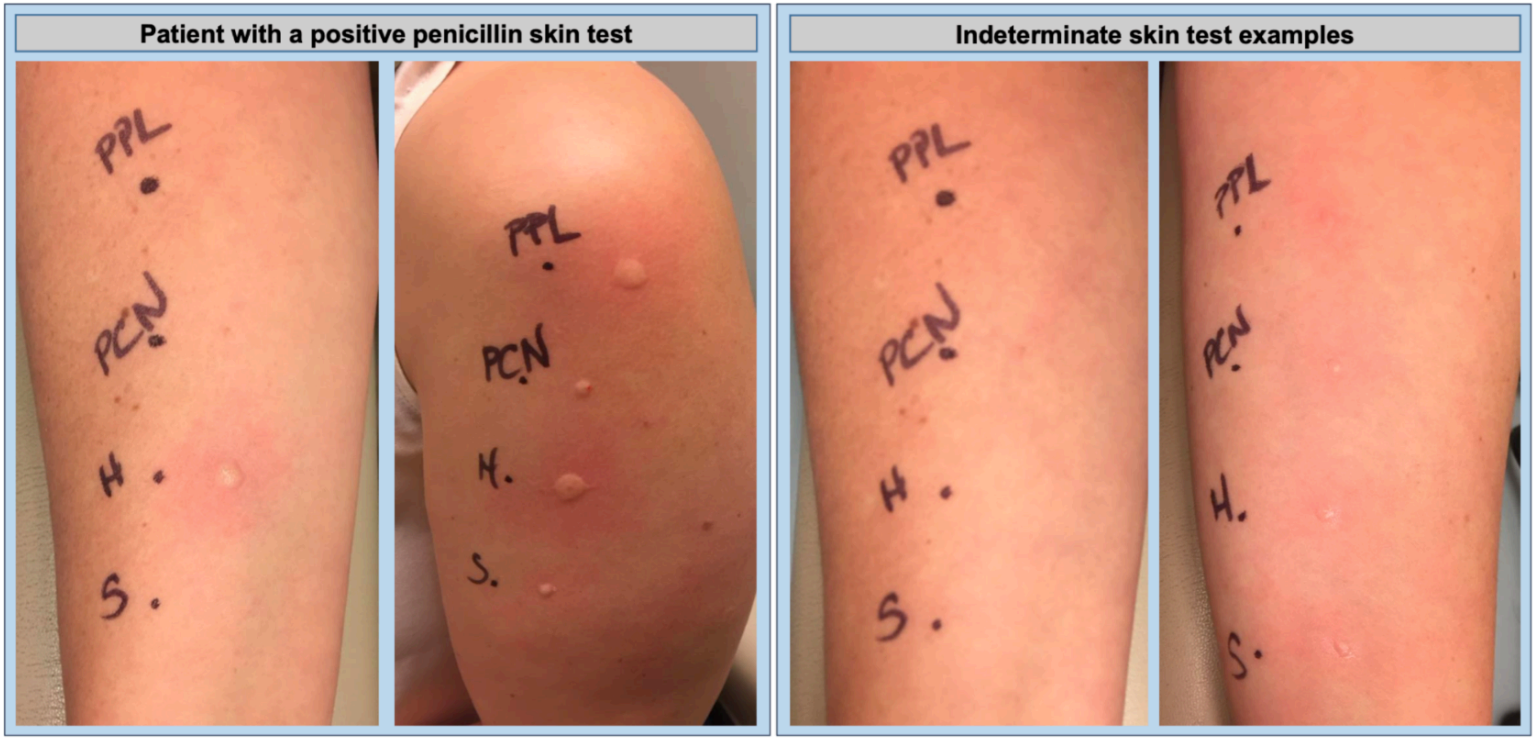




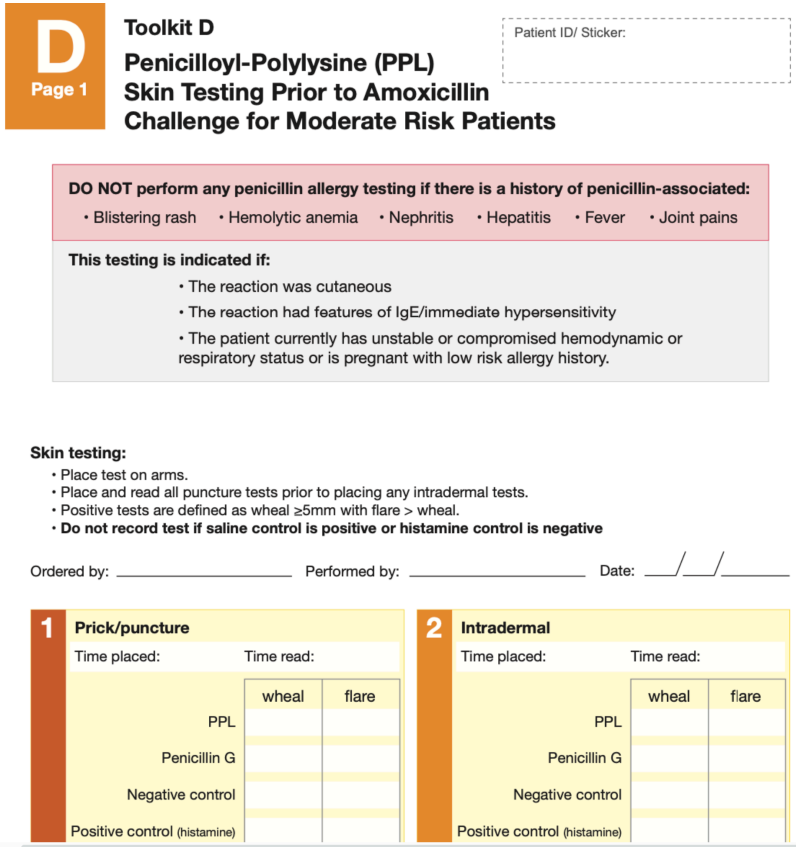
Penicillin skin test assessment

- High negative predictive value (NPV) ~95% for IgE-mediated reactions
- Poor positive-predictive value- Possible false positive diagnosis if used in patient with low pre-test probability
- Amoxicillin is commonly used to challenge after negative penicillin skin tests as it addresses the core β-lactam of penicillin and also side-chain–specific reactions, which may not be detected through skin testing with penicillin itself (NPV 100% if both are negative)
- Traditional penicillin skin testing or amoxicillin challenge may be negative in patients with historical reactivity to piperacillin-tazobactam. Skin testing to piperacillin-tazobactam may help to establish this selective sensitization, and these patients are often able to tolerate other penicillins
- Penicillin skin testing has no value in delayed reactions, including SJS/TEN, DRESS, and other noncutaneous organ-based reactions

Penicillin skin test assessment



Penicillin skin test assessment -Medium risk history



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

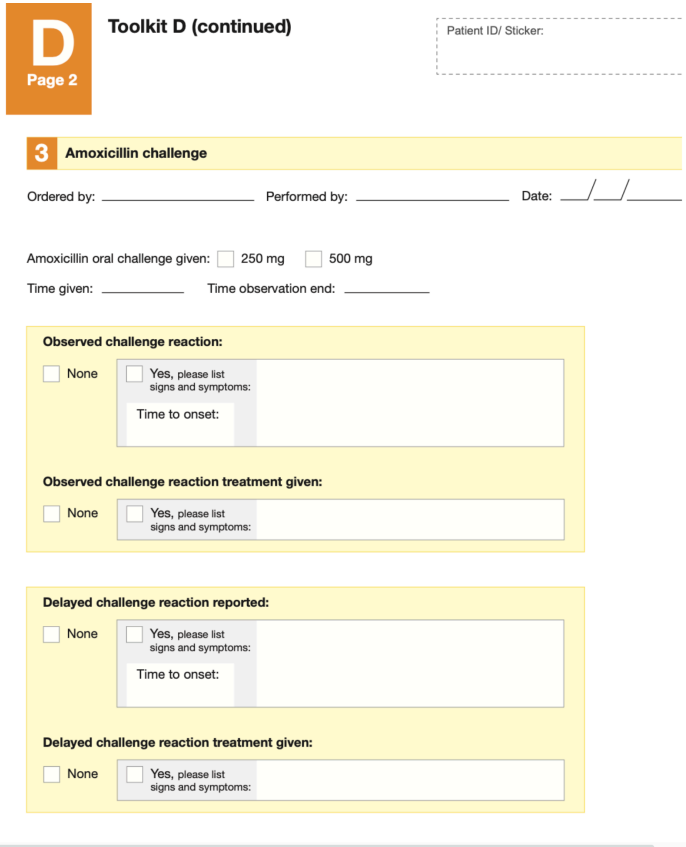
Time placed: Time read:

	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)		



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:

Impact “medium risk” patients?

- A negative skin test is associated 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 referred to an allergy/immunologist or desensitization considered

Desensitization

- Progressive, graded de-granulation of mast cells (histamine release) and internalization of high-affinity IgE receptors by administering graded doses of antibiotic
- Desensitization is 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

Sample desensitization protocol

* 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

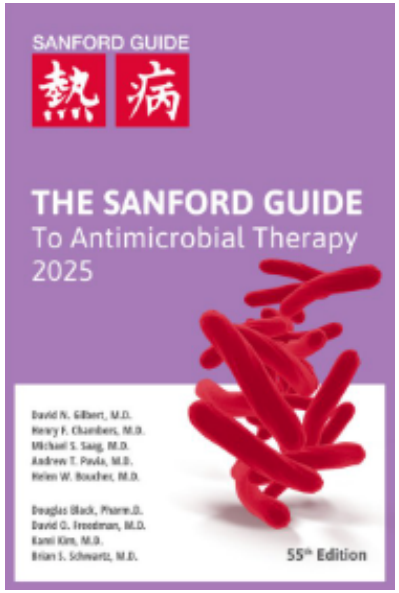
Dose Number	Dose Strength (mg)	Preparation Instructions	Volume of dose (mL)
1	0.004 mg	Add 2 mL from **dose #3** to 50 ml 0.9% NaCl minibag	50 mL
2	0.02 mg	Add 1.5 mL from **dose #4** to 50 ml 0.9% NaCl minibag	50 mL
3	0.1 mg	Add 1.5 mL from **dose #6** to 50 ml 0.9% NaCl minibag	50 mL
4	0.6 mg	Add 1 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

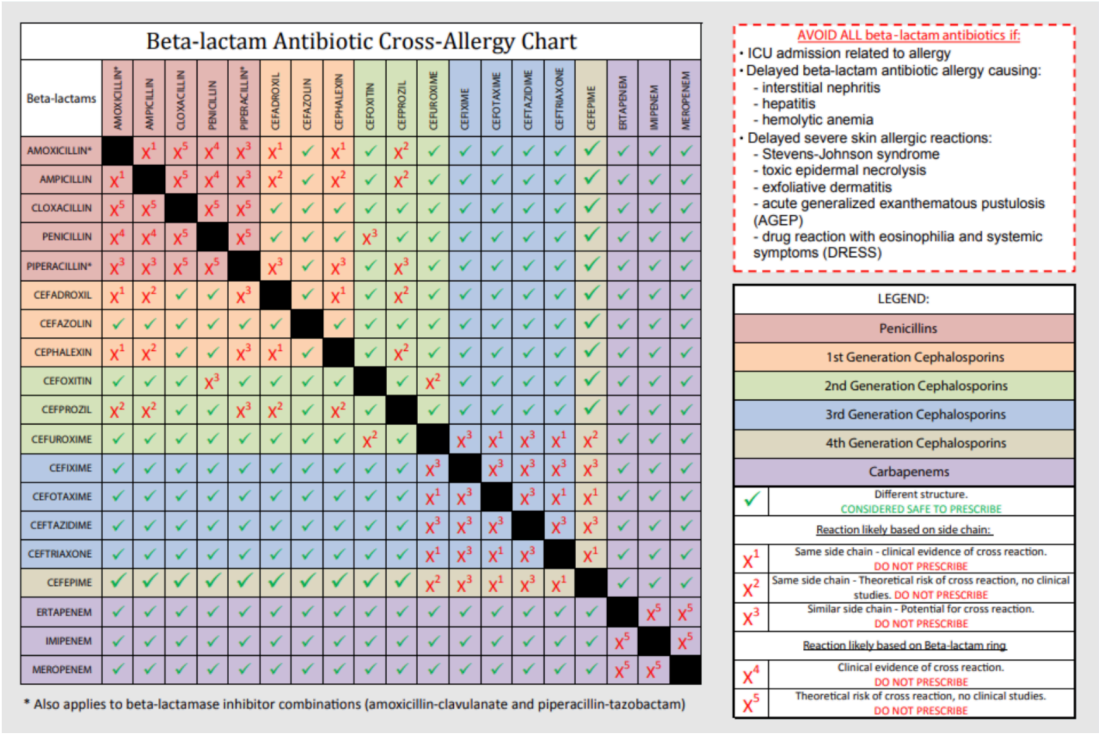
Other desensitization protocols



Cross-reactivity: Infectious diseases dogma

- Common teaching: If a patient has a documented PCN allergy, the risk of cross reactions with cephalosporins is 10%
- **THIS IS FALSE,** the actual cross reactivity is more likely 2%-3%
  - A subset of patients with history of anaphylaxis may have cross-reactivity determined by the R1 sidechain of the molecule
  - Cefazolin as a unique side chain and and very low risk for cross-reactivity

Risk of cross-reactivity related to cephalosporin sidechain



Beta-lactam Antibiotic Cross-Allergy Chart

Beta-lactams	AMOXICILLIN*	AMPICILLIN	CLOXACILLIN	PENICILLIN	PIPERACILLIN*	CEFADROXIL	CEFAZOLIN	CEPHALEXIN	CEFOXITIN	CEFPROZIL	CEFUROXIME	CEFIXIME	CEFOTAXIME	CEFTAZIDIME	CEFTRIAXONE	CEFEPIME	ERTAPENEM	IMIPENEM	MEROPENEM
AMOXICILLIN*		X^1	X^5	X^4	X^3	X^1	✓	X^1	✓	X^2	✓	✓	✓	✓	✓	✓	✓	✓	✓
AMPICILLIN	X^1		X^5	X^4	X^3	X^2	✓	X^2	✓	X^2	✓	✓	✓	✓	✓	✓	✓	✓	✓
CLOXACILLIN	X^5	X^5		X^5	X^5	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PENICILLIN	X^4	X^4	X^5		X^5	✓	✓	✓	X^3	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PIPERACILLIN*	X^3	X^3	X^5	X^5		X^3	✓	X^3	✓	X^3	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEFADROXIL	X^1	X^2	✓	✓	X^3		✓	X^1	✓	X^2	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEFAZOLIN	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEPHALEXIN	X^1	X^2	✓	✓	X^3	X^1	✓		✓	X^2	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEFOXITIN	✓	✓	✓	X^3	✓	✓	✓	✓		✓	X^2	✓	✓	✓	✓	✓	✓	✓	✓
CEFPROZIL	X^2	X^2	✓	✓	X^3	X^2	✓	X^2	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
CEFUROXIME	✓	✓	✓	✓	✓	✓	✓	✓	X^2	✓		X^3	X^1	X^3	X^1	X^2	✓	✓	✓
CEFIXIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X^3		X^3	X^3	X^3	X^3	✓	✓	✓
CEFOTAXIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X^1	X^3		X^3	X^1	X^1	✓	✓	✓
CEFTAZIDIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X^3	X^3	X^3		X^3	X^3	✓	✓	✓
CEFTRIAXONE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X^1	X^3	X^1	X^3		X^1	✓	✓	✓
CEFEPIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X^2	X^3	X^1	X^3	X^1		✓	✓	✓
ERTAPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		X^5	X^5
IMIPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X^5		X^5
MEROPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X^5	X^5	

* Also applies to beta-lactamase inhibitor combinations (amoxicillin-clavulanate and piperacillin-tazobactam)

AVOID ALL beta-lactam antibiotics if:

- ICU admission related to allergy
- Delayed beta-lactam antibiotic allergy causing:
  - interstitial nephritis
  - hepatitis
  - hemolytic anemia
- Delayed severe skin allergic reactions:
  - Stevens-Johnson syndrome
  - toxic epidermal necrolysis
  - exfoliative dermatitis
  - acute generalized exanthematous pustulosis (AGEP)
  - drug reaction with eosinophilia and systemic symptoms (DRESS)

LEGEND:	
Penicillins	
1st Generation Cephalosporins	
2nd Generation Cephalosporins	
3rd Generation Cephalosporins	
4th Generation Cephalosporins	
Carbapenems	
✓	Different structure. CONSIDERED SAFE TO PRESCRIBE
Reaction likely based on side chain:	
X^1	Same side chain - clinical evidence of cross reaction. DO NOT PRESCRIBE
X^2	Same side chain - Theoretical risk of cross reaction, no clinical studies. DO NOT PRESCRIBE
X^3	Similar side chain - Potential for cross reaction. DO NOT PRESCRIBE
Reaction likely based on Beta-lactam ring	
X^4	Clinical evidence of cross reaction. DO NOT PRESCRIBE
X^5	Theoretical risk of cross reaction, no clinical studies. DO NOT PRESCRIBE

β-lactams with common side chains

β-Lactams With Common Side Chains

FIVE GROUPS OF β-LACTAMS WITH COMMON R1 SIDE CHAINS		
Common Aminobenzyl Group	**Common Aminobenzyl Group**	**Common Methylene Group**
Amoxicillin	Ampicillin	Benzyl penicillin
Cefadroxil	Cephalexin	Cephalothin
Cefatrizine	Cefaclor	
Cefprozil	Cephradine	
	Cephaloglycin	
	Loracarbef	

β-Lactams With Common Side Chains

Common Methoxyimino Group	Common Aminothiazole Group	
Ceftriaxone	Ceftazidime	
Cefuroxime	Cefiderocol	
Cefotaxime	Aztreonam	
Cefepime		

SIX GROUPS OF β-LACTAMS WITH COMMON R2 SIDE CHAINS		
Cephalexin	Cefotaxime	Cefuroxime
Cefadroxil	Cephalothin	Cefoxitin
Cephradine	Cephaloglycin	
Cefotetan	Cefaclor	Ceftibuten
Cefamandole	Loracarbef	Ceftizoxime
Cefmetazole		
Cefpiramide		

Skin testing has not been well studied in carbapenem allergy, and thus the negative predictive value is unknown. Successful desensitization regimens to both imipenem and meropenem have been described, mostly as case reports, where carbapenems were the only antibiotic indicated.

CEPHTEST: Application of PENFAST score to cephalosporin allergies

Validation of CEPH-FAST in predicting a positive cephalosporin allergy test result for cross-reactive cephalosporin cohort and implicated cephalosporin cohort in Australia and 0North America.

		Cross-reactive cephalosporin cohort		Implicated cephalosporin cohort	
		Australian cohort	North American cohort	Australian cohort	North American cohort
No of patients		228	167	191	130
No (%) of positive cephalosporin test		91 (39.9%)	30 (18.0%)	88 (46.1%)	26 (20.0%)
AUROC (95% CI)		0.921 (0.887, 0.955)	0.847 (0.779, 0.914)	0.929 (0.893, 0.965)	0.842 (0.773, 0.911)
Validation of low-risk (CEPH-FAST <3)	Sensitivity (95% CI)	93.4% (86.2, 97.5)	70.0% (50.6, 85.3)	93.2% (85.7, 97.5)	73.1% (52.2, 88.4)
	Specificity (95% CI)	72.3% (64.0, 79.6)	83.9% (76.7, 89.7)	77.7% (68.4, 85.6)	83.7% (75.1, 90.2)
	PPV (95% CI)	69.1% (60.1, 77.1)	48.8% (33.3, 64.5)	78.1% (69.0, 85.6)	52.8% (35.5, 69.6)
	NPV (95% CI)	94.3% (88.0, 97.9)	92.7% (86.7, 96.6)	93.0% (85.4, 97.4)	92.6% (85.3, 97.0)

Abbreviations: AUROC: area under receiver-operating characteristics curve, CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

What is the cross-reactivity with carbapenems?

- Cross reactivity with penicillin allergy and carbapenems is less than 1%
- No cross reactivity between penicillins and monobactams (aztreonam)
- A graded challenge or test dose can be considered:
  - i.e. Infuse 5-10% of dose and observe patient, then progress to full dose if not reaction
  - Skin testing (if available) could also rule out allergies

Special populations that should be considered for testing

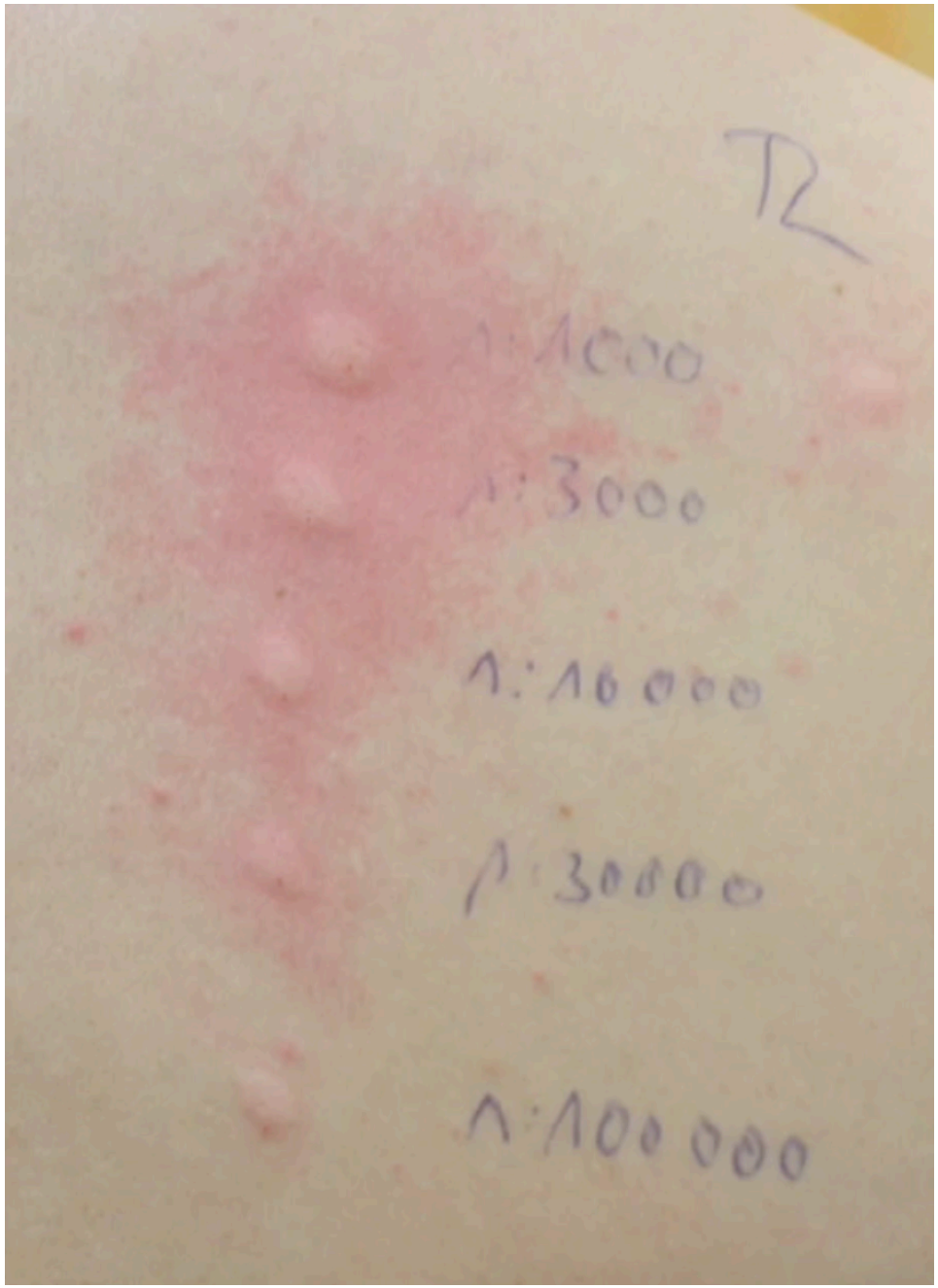
- **Peri-procedure before elective surgery**
  - Importance of antibiotic timing/tissue levels at time of incision-less optimal with vancomycin that requires longer infusion
- **Pregnancy**
  - PCN allergy associated with increased risk of cesarean delivery, post-cesarean wound complications, and longer length of stay
  - Consider third trimester referral for testing in patients with planned cesarean delivery, group B streptococcus colonization
- **Long term care facilities**
  - Non-beta-lactam based therapies have higher risk for drug interactions
  - Higher risk for adverse effects
- **Hematology-oncology**
  - Consider testing before chemotherapy or transplant (onset of of immunosuppression)
- **STD clinics**
- **ICU patients?**

Non-penicillin allergies

Similar principles- patient history is key

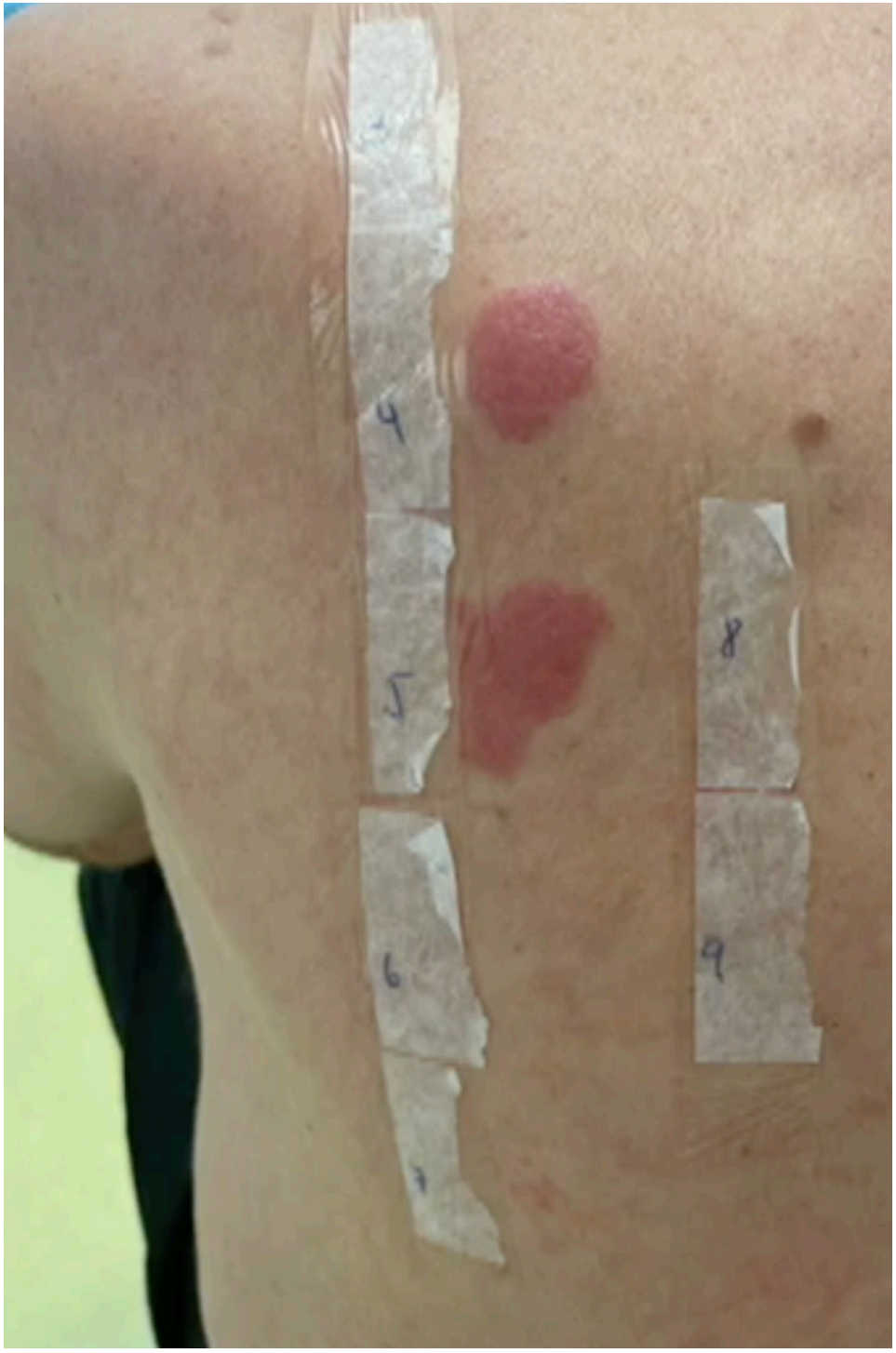
- Which drugs was the patient taking?
- Dates of intake
- Exact sequence of events
- Underlying disease/Concomitant infections
- Other drug administered at the same time/concomitant infections
- Clinical morphology (at several time points)of rash
- Histology of eosinophilia?

Intradermal testing-Non beta-lactams



- Skin tests for most antimicrobial agents lack high negative predictive values, and skin test positivity is often a function of the time elapsed since the index reaction
- Prick and intradermal tests less well standardized- non-irritating formulations required
- Some antibiotics are irritating even at low concentrations, making testing difficult
- Special cellular activation tests may be available in some centers for some drugs
    - e.g., The BAT (flow cytometry) detects the upregulation of activation markers CD63 and CD203c on the surface of basophils after incubation with the implicated drug

Approach to delayed-type hypersensitivity testing

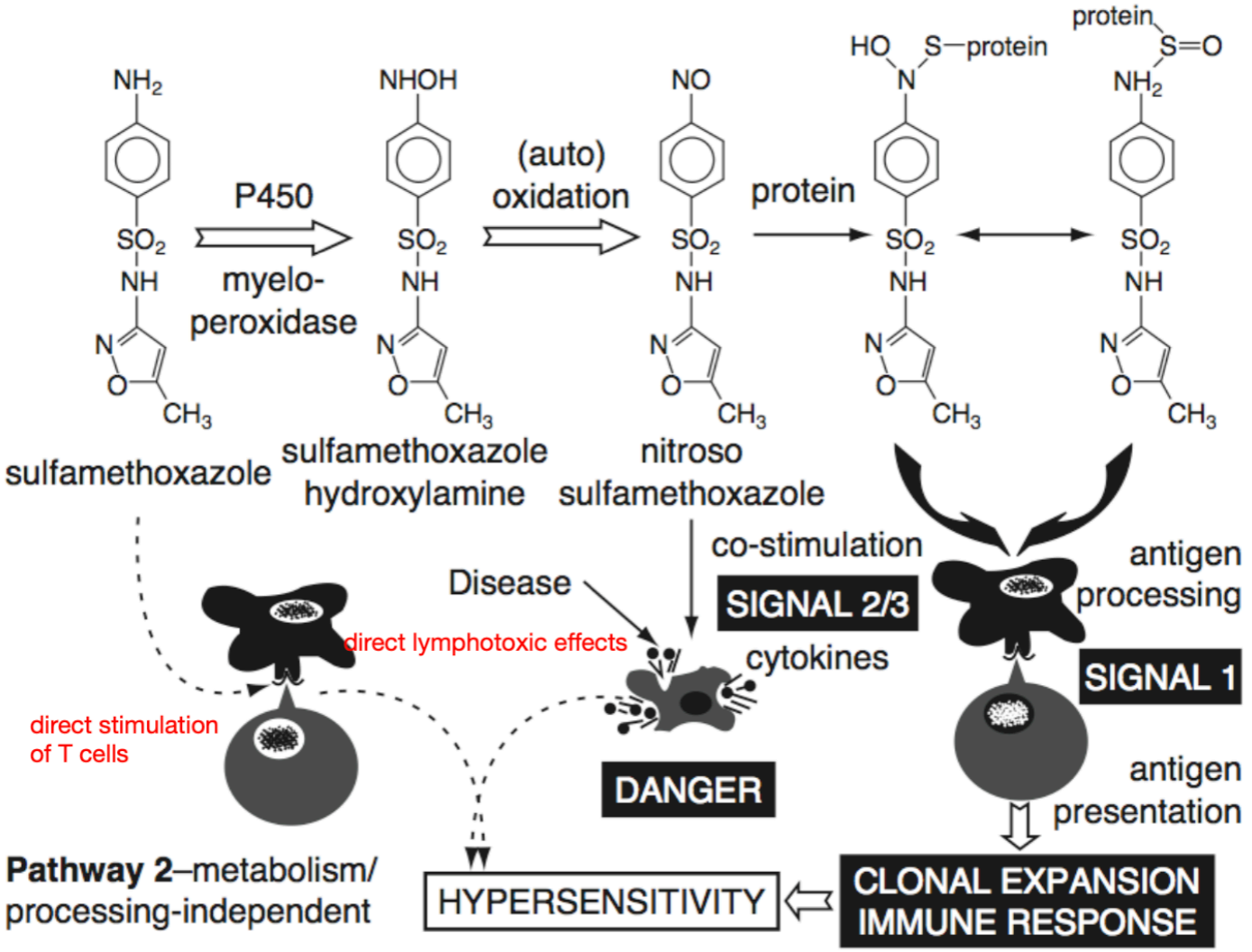


- Intradermal or patch testing with reading 24-72 hours
  - Low sensitivity, high specificity
- Lymphocyte transformation testing
  - Available in specialized laboratories
  - Haptenization to become an antigen in vivo (hard to imitate in lab)

Sulfonamide hypersensitivity

- Incidence 8%
- Primarily cutaneous and GI tract
- Only 3% are considered true hypersensitivity reactions.
  - Most common presentations are limited exanthems and fixed drug eruptions
  - However…sulfonamides are disproportionately associated with infrequent 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
- Higher incidence of reactions in patients with HIV/AIDS, tuberculosis

Mechanism of sulfonamide hypersensitivity



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

PENFAST score applied to sulfa allergies

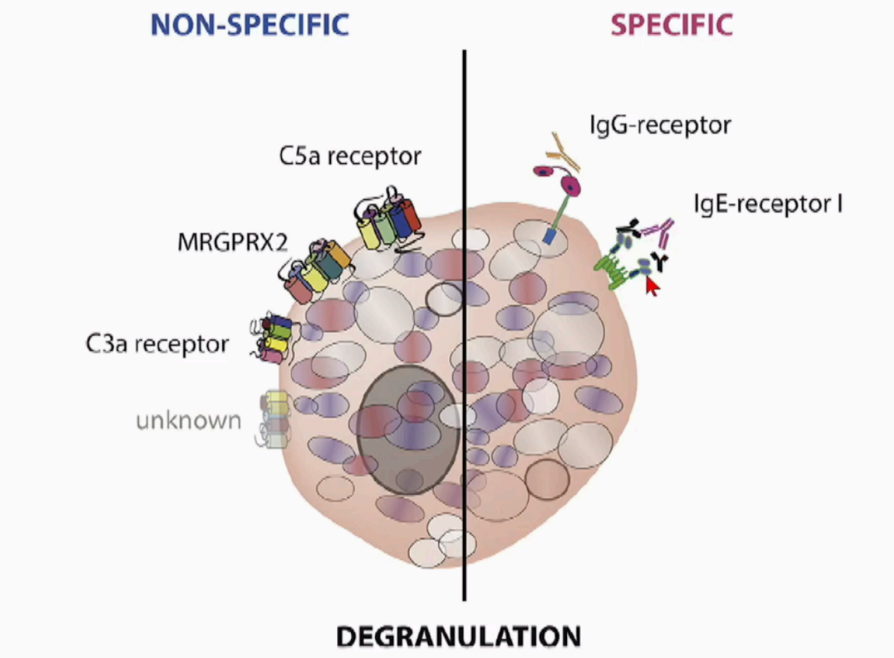
Table 2. Validation of SULF-FAST in All Validation Cohorts (Overall) With Subgroup Analysis Performed on Allergy Phenotype[a]

Characteristic	Melbourne, Australia				Nashville, Tennessee			
	Overall (N = 116)	Immediate (n = 32)	Delayed (n = 41)	Unknown (n = 43)	Overall (N = 204)	Immediate (n = 23)	Delayed (n = 106)	Unknown (n = 75)
No. (%) with SULF-FAST score ≥3	8 (6.9)	0	8 (19.5)	0	25 (12.3)	7 (30.5)	14 (13.2)	4 (5.3)
No./total No. (%) with SULF-FAST score ≥3 with positive test result	4/8 (50)	NA	4/8 (50)	NA	5/25 (20)	2/7 (28.6)	3/14 (21.4)	0/4 (0)
Validation AUC (95% CI)	0.82 (0.61-1.00)	NA	0.78 (0.56-0.99)	NA	0.64 (0.5-0.78)	0.71 (0.37-1.00)	0.61 (0.44-0.78)	0.47 (n/a)
Sensitivity, % (95% CI)	66.7 (22.3-95.7)	NA	66.7 (22.3-95.7)	NA	38.5 (13.9-68.4)	66.7 (9.4-99.2)	33.3 (7.5-70.1)	0 (0-97.5)
Specificity, % (95% CI)	96.4 (91.0-99.0)	NA	88.6 (73.3-96.8)	NA	89.5 (84.3-93.5)	75 (50.9-91.3)	88.7 (80.6-94.2)	94.6 (86.7-98.5)
PPV, % (95% CI)	50.0 (15.7-84.3)	NA	50 (15.7-84.3)	NA	20.0 (6.8-40.7)	28.6 (3.7-71.0)	21.4 (4.7-50.8)	0 (0-60.2)
NPV, % (95% CI)	98.1 (93.5-99.8)	NA	93.9 (79.8-99.3)	NA	95.5 (91.4-98.1)	93.8 (69.8-99.8)	93.5 (86.3-97.6)	98.6 (92.4-100)

Abbreviations: AUC, area under the curve for S-FAST score 3 or higher; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value.

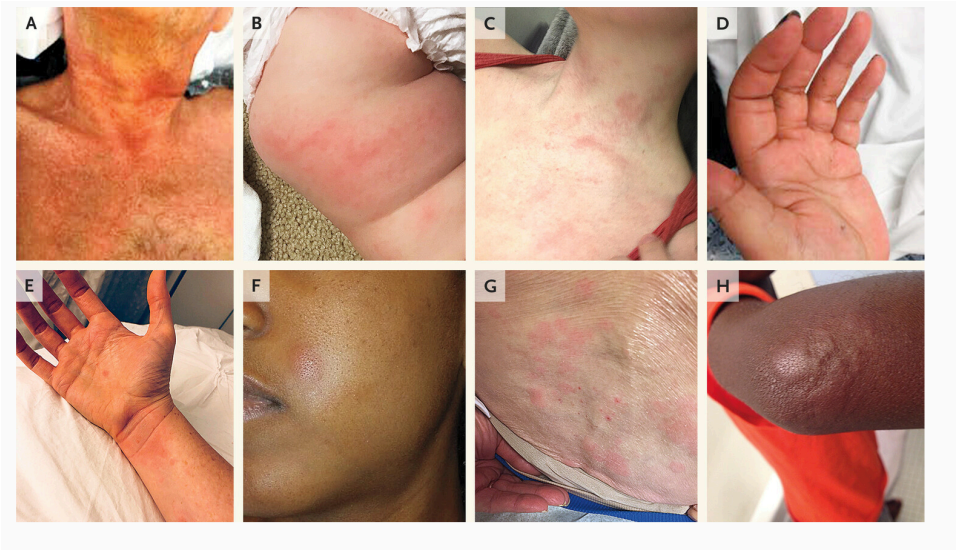
[a] Immediate phenotype was defined as any reaction that occurred within 1 hour after exposure to initial medication dose, whereas delayed phenotype was defined as any reaction occurring beyond 1 hour, including those after multiple medication doses. Unknown phenotype includes any reaction that was nonimmune mediated and reactions with unknown timeline.

Non-sensitizing allergic reactions



- Mas-related G protein coupled receptor (MRGPRX2)
- Neuromuscular blocking agents
- Opioids
- Radiocontrast media
- Vancomycin, glycopeptides, fluoroquinolones
- Complement-activation-related pseudoallergy (CARPA)
- Liposomes, drug carriers

Vancomycin infusion reaction “red man syndrome”



- Vancomycin can also cause:
  - Hypotension, anaphylaxis
  - Maculopapular exanthems
  - Vasculitis E
  - Eosinophilia Exfoliative dermatitis/DRESS/Stephens-Johnson

Take home messages

- Penicillin allergies are the most common “contraindication” to antibiotic therapy, but most histories do not represent true allergies
- A systematic approach can be used to evaluate and potentially “de-label” patients with penicillin allergy
- Cross-reactivity rates are low with current cephalosporins and carbapenems, but can alternatively be addressed through antibiotic challenges and skin testing
- Desensitization can be attempted in specific cases when a particular antibiotic is needed for IgE-mediated reactions
- Some antibiotics cause non-immune-related hypersensitivity reactions that can be managed by slowing infusions and administering antihistamines

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