UWTASP
tele-antimicrobial stewardship program

Penicillin Allergy

Joanne Huang, PharmD
UW Medicine | Valley Medical Center

Objectives

- Understand impacts inappropriately documented penicillin allergies.
- Review IgE and non-IgE drug allergies
- Evaluate patients appropriate for re-trialing beta-lactams.
- Identify challenges and potential roles of non-allergists.

citations

Penicillin allergy prevalence

JAMA | Review

Evaluation and Management of Penicillin Allergy
A Review

Erica S. Shenoy, MD, PhD; Eric Macy, MD, MS; Theresa Rowe, DO, MS; Kimberly G. Blumenthal, MD, MSc

- True prevalence of penicillin allergy is ~1%.
- Penicillin allergies fade over time.
- Patients receive suboptimal therapy when unable to use beta-lactams.
  - Cost (Macy et al.)
  - Poorer outcomes (Blumenthal et al.)
  - Increased resistance (Gray et al.)

Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019 Jan 15;321(2):188-199.
Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.
Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study. J Allergy Clin Immunol. 2014 Mar;133(3):790-6.
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. 2018 Jan 18;66(3):329-336.
Gray MP, Kellum JA, Kirisci L, Boyce RD, Kane-Gill SL. Long-Term Outcomes Associated With β-Lactam Allergies. JAMA Netw Open. 2024 May 1;7(5):e2412313.

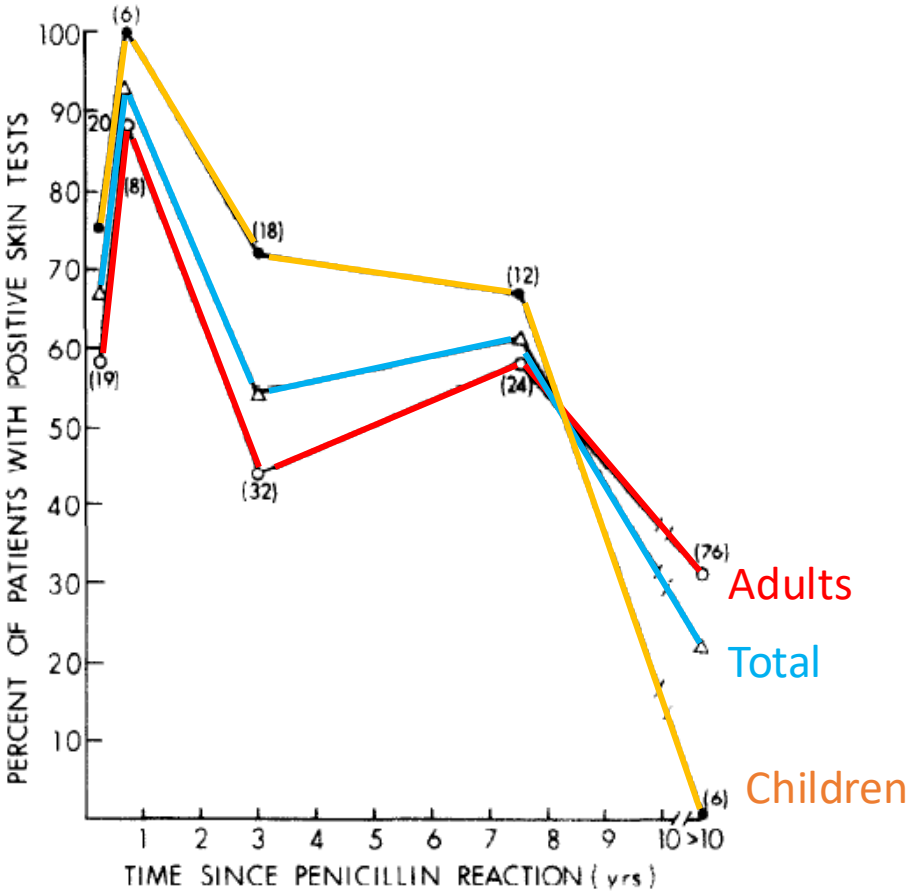
80% of patients with an IgE allergy will fade after 10 years

Original articles

Skin testing to detect penicillin allergy

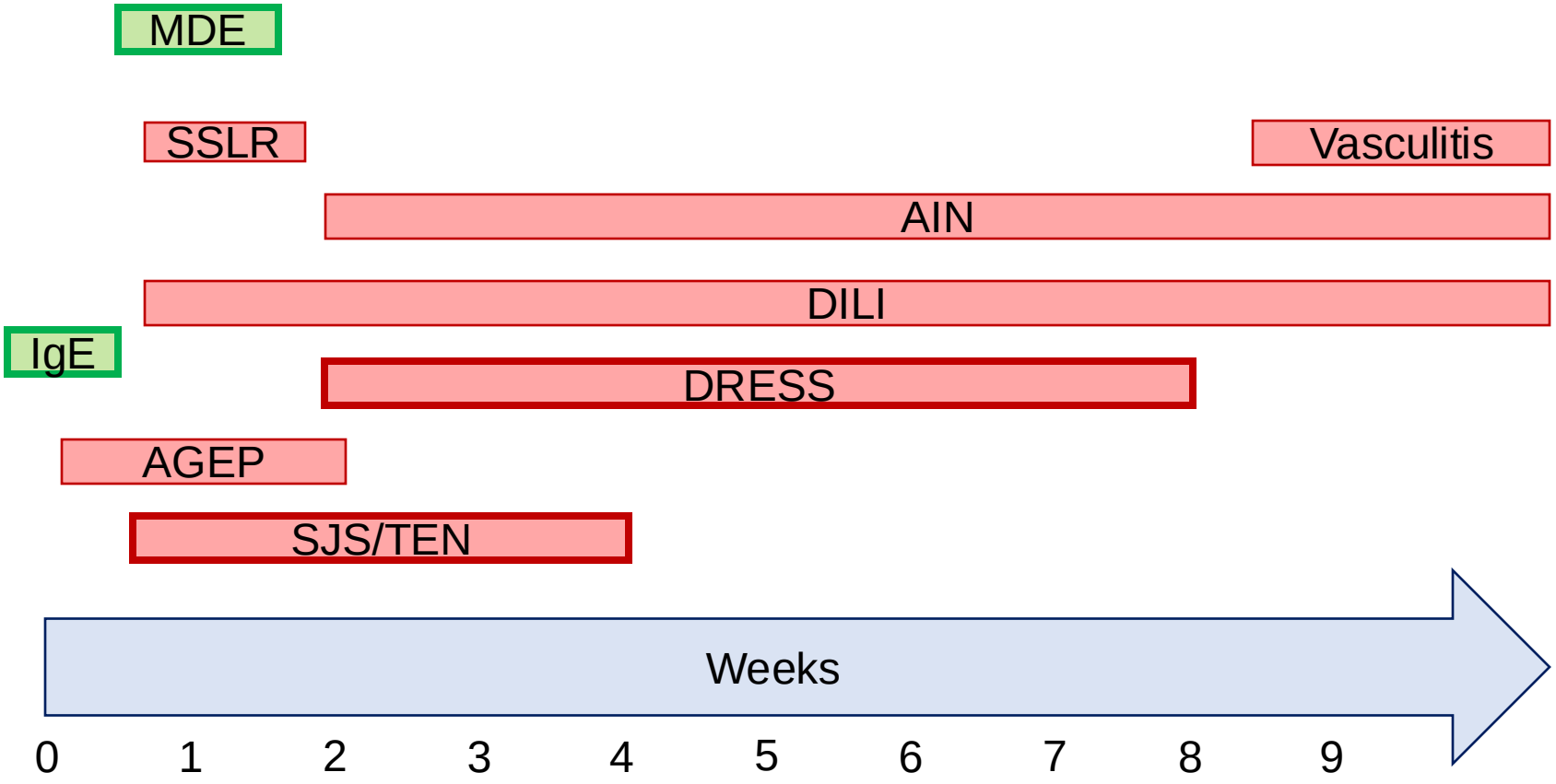
Timothy J. Sullivan, M.D., H. James Wedner, M.D., Gerald S. Shatz, M.D., Lewis D. Yecies, M.D., and Charles W. Parker, M.D.
Dallas, Texas, St. Louis, Mo., and Stony Brook, N.Y.

Prevalence of positive skin-test reactions decrease with increasing time after last known beta-lactam exposure.



Sullivan TJ, Wedner HJ, Shatz GS, Yecies LD, Parker CW. Skin testing to detect penicillin allergy. J Allergy Clin Immunol. 1981 Sep;68(3):171-80.
Solensky R, Earl HS, Gruchalla RS. Lack of penicillin resensitization in patients with a history of penicillin allergy after receiving repeated penicillin

Beta-lactam allergy onset



MDE – morbilliform drug eruption
AIN – acute interstitial nephritis
DRESS – Drug Reaction with Eosinophilia and Systemic Symptoms
SJS – Stevens Johnson Syndrome
TEN – toxic epidermal necrolysis
AGEP – acute generalized exanthematous pustulosis
SSLR – Serum sickness-like reactions

Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.

Beta-lactam allergy symptoms

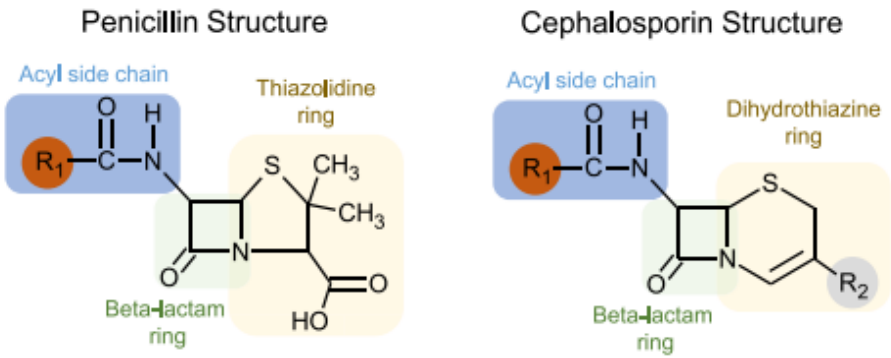
Chronology	Gell-Coombs classification	Descriptor/ mediators	Presentation
Immediate (1 to 6 hours)	Type I	IgE	Urticaria, angioedema, bronchospasm, anaphylaxis
Delayed (days to weeks)	Type IV	Cell-mediated Ab independent/ T cell	Benign: morbilliform drug eruption
			Severe: SCARs (DRESS, SJS, TEN, AGEP)
	Type II	Cytotoxic Ab dependent/ IgG, IgM	Organ-specific drug reactions (cytopenias, liver injury, interstitial nephritis, vasculitis)
	Type III	Immune complex/ IgG, IgM	SSLR (urticaria like lesions persisting >24 hours), erythema multiforme-like lesions, joint inflammation, fever

Ab – Antibody
SCAR – Severe Cutaneous Adverse Reaction
DRESS – Drug Reaction with Eosinophilia and Systemic Symptoms
SJS – Stevens Johnson Syndrome
TEN – Toxic Epidermal Necrolysis
AGEP – Acute Generalized Exanthematous Pustulosis
SSLR – Serum sickness-like reactions

Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.
Trubiano JA, Adkinson NF, Phillips EJ. Penicillin Allergy Is Not Necessarily Forever. JAMA. 2017 Jul 4;318(1):82-83.
Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010 Oct;105(4):259-273.
Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy Asthma Clin Immunol. 2018 Sep 12;14(Suppl 2):49.

AMS interventions should target IgE reactions

Chronology	Gell-Coombs classification	Descriptor/ mediators	Presentation
Immediate (1 to 6 hours)	Type I	IgE	Urticaria, angioedema, bronchospasm, anaphylaxis



- Cross-reactivity risk is highest with greater similarity of R1 side chains
- Cross reactivity via R2 side chains and beta-lactam ring are uncommon

Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.
Joint Task Force on Practice Parameters; American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; Joint

Cross-reactivity based on R1 side chain similarity

American Academy of Allergy Asthma & Immunology

AAAAI Guidelines 2022

A recent meta-analysis…found that the risk of cross-reactivity (based on skin testing) to cephalosporins in patients with proven penicillin allergy varied from 16.45% for aminocephalosporins (ie. cephalexin, cefadroxil, etc.) to 2.11% for low similarity-score cephalosporins (ie. cefazolin, ceftriaxone, etc.)…cefazolin notably has a unique side chain and appears to have very low cross-reactivity with penicillins.

Khan DA, Banerji A, Blumenthal KG, et al. Drug allergy: A 2022 practice parameter update. J Allergy Clin Immunol. 2022 Dec;150(6):1333-1393.

Similar/Identical side chains

ß-Lactam Side Chain Cross Reactivity Chart

		PEN					1st GEN			2nd GEN						3rd GEN								4th	5th		N	CARB		M
		Amoxicillin	Ampicillin	Nafcillin	Penicillin G/V	Piperacillin	Cefadroxil	**Cefazolin***	Cephalexin	Cefaclor	Cefamandole	Cefotetan	Cefoxitin	Cefprozil	Cefuroxime	Cefoperazone	Cefdinir	Cefixime	Cefotaxime	Cefpodxime	Ceftazidime	Ceftibuten	Ceftriaxone	Cefepime	Ceftaroline	Ceftolozane	Cefiderocol	Ertapenem	Meropenem	Aztreonam
PEN	Amoxicillin		X				X		X	X	X			X																
	Ampicillin	X				X	X		X	X	X			X																
	Nafcillin																													
	Penicillin G/V								X				X																	
	Piperacillin		X						X	X	X			X																
1st GEN	Cefadroxil	X	X			X			X	X	X			X																
	Cefazolin*																													
	Cephalexin	X	X		X	X	X			X	X			X																
2nd GEN	Cefaclor	X	X			X	X		X		X			X																
	Cefamandole	X	X			X	X		X	X		X		X		X														
	Cefotetan										X					X														
	Cefoxitin				X										X				X											
	Cefprozil	X	X			X	X		X	X	X																			
	Cefuroxime												X					X	X	X	X		X	X		X				
3rd GEN	Cefoperazone										X	X																		
	Cefdinir																	X												
	Cefixime														X		X		X	X	X		X	X		X				
	Cefotaxime														X			X		X	X		X	X		X				
	Cefpodxime														X			X	X		X		X	X		X				
	Ceftazidime														X			X	X	X			X	X		X	X			X
	Ceftibuten																													
	Ceftriaxone														X			X	X	X	X			X		X				
4th GEN	Cefepime														X			X	X	X	X		X			X				
5th GEN	Ceftaroline																													
	Ceftolozane														X			X	X	X	X		X	X						X
None	Cefiderocol																				X									X
CARB	Ertapenem																													
	Meropenem																													
MONO	Aztreonam																				X					X	X			

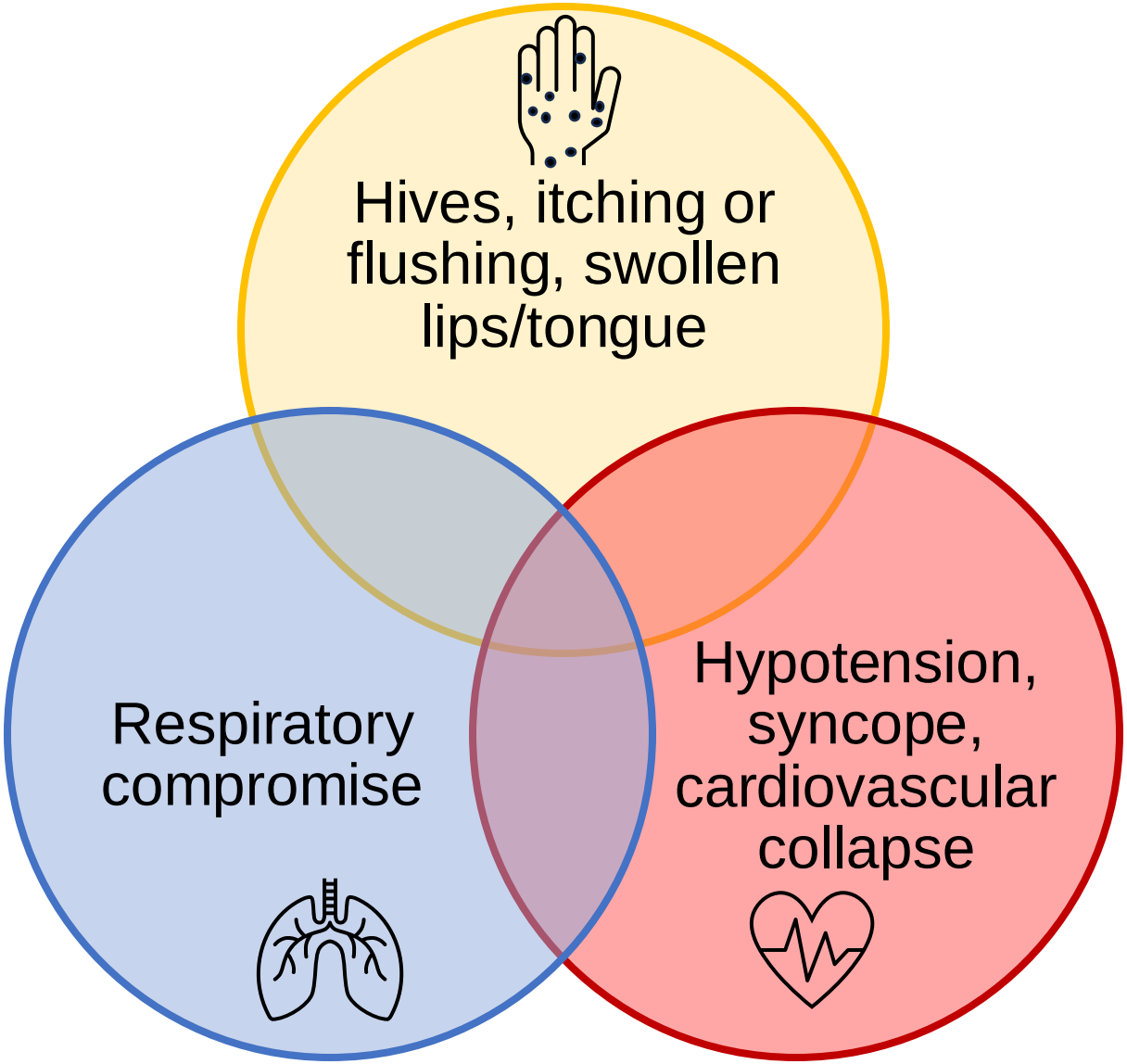
Date: 11/12/2020

Names: Vidya Atluri MD/PhD, Rupali Jain PharmD, Paul Pottiger MD, Lahari Rampur MD, David Coleman MD

Notable identical side chains:

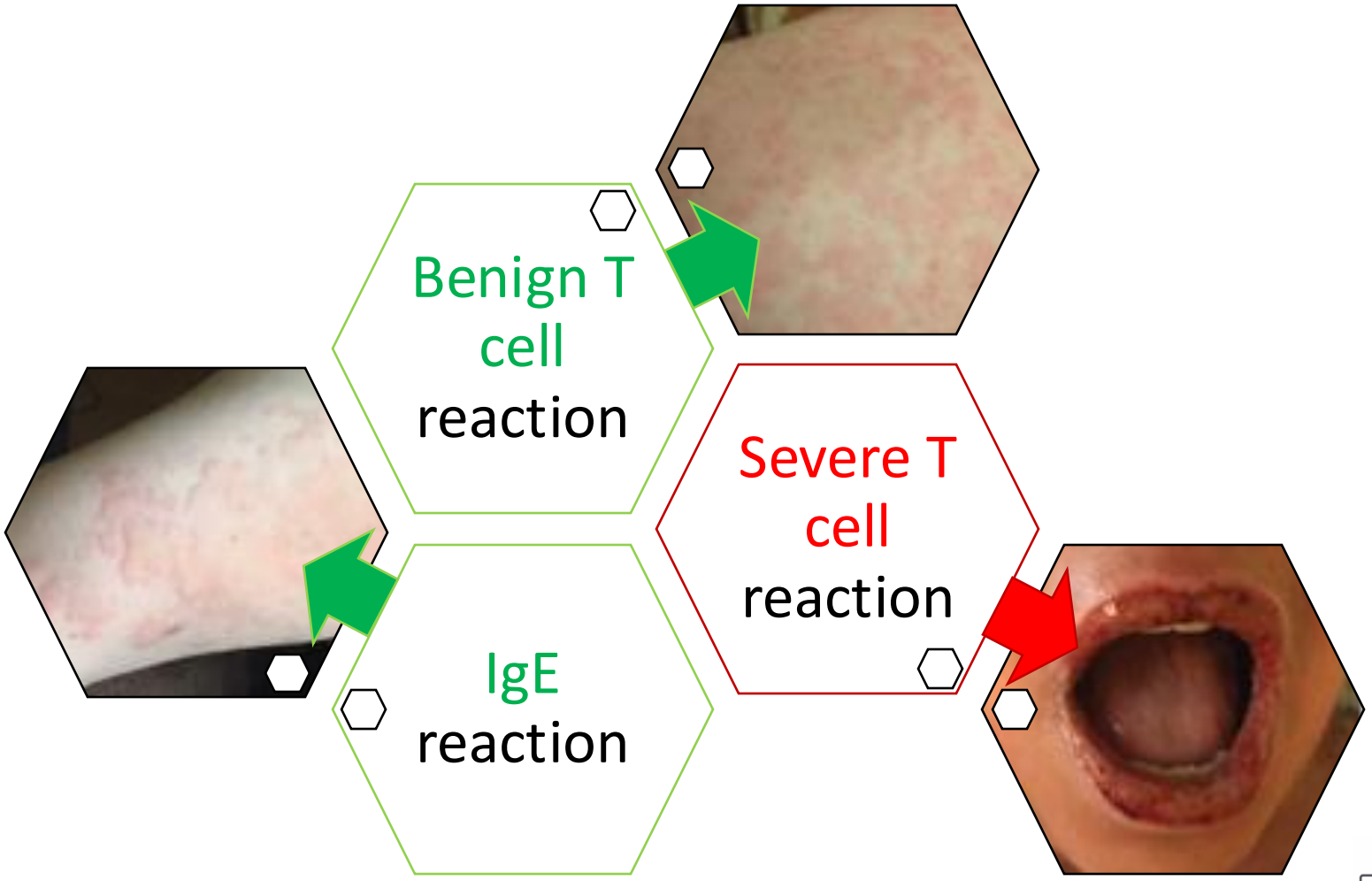
- Cephalexin/ cefadroxil and penicillins
- Cefepime and ceftriaxone
- Ceftazidime and aztreonam

Anaphylaxis defined (IgE mediated)



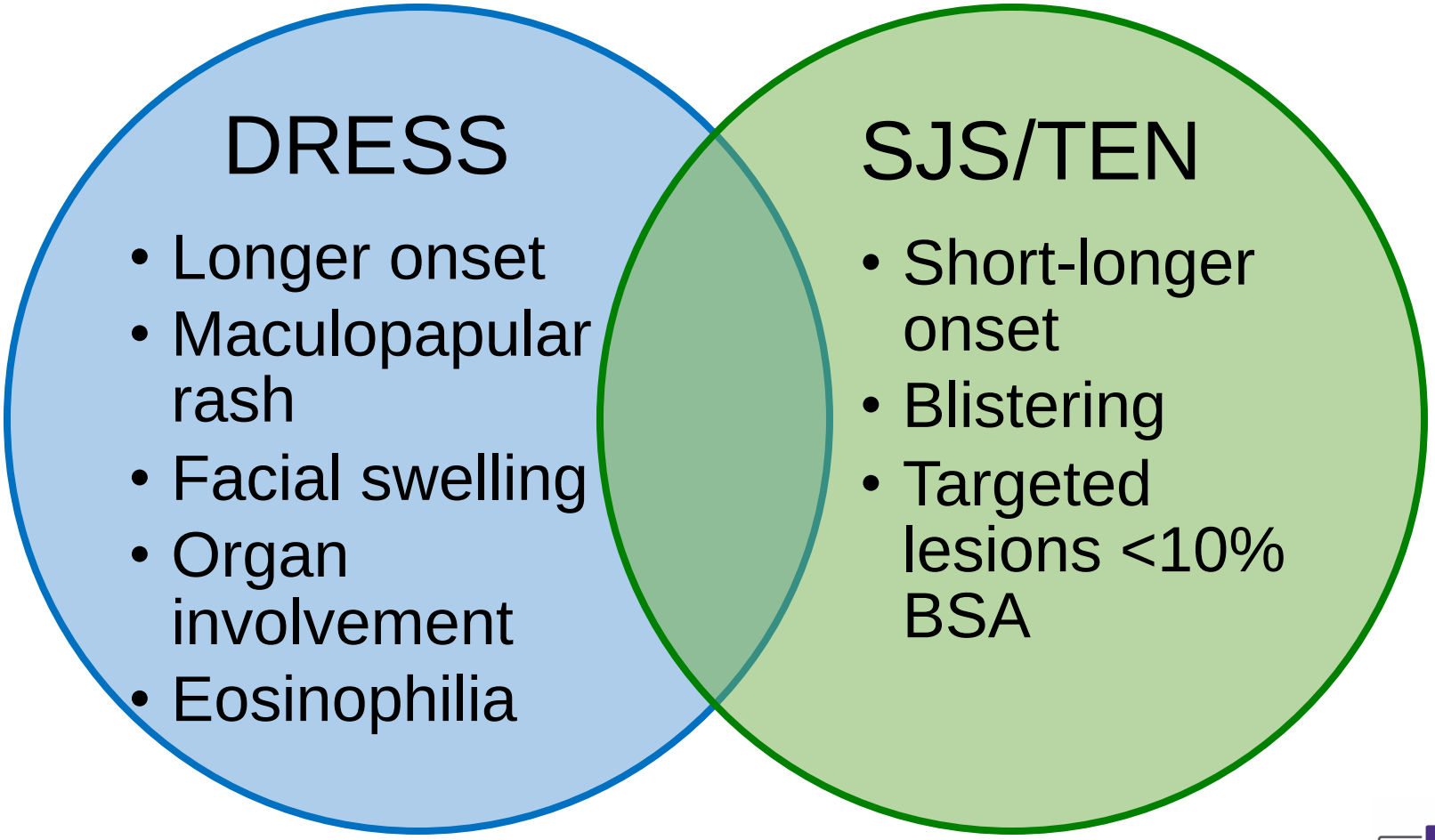
citations

Primary cutaneous drug reactions (IgE and T cell mediated)



Shenoy ES, Macy E, Rowe T, et al. Evaluation and Management of Penicillin Allergy: A Review. JAMA. 2019 Jan 15;321(2):188-199.

SCARs: DRESS vs SJS/TEN



Casagranda A, Suppa M, Dehavay F, et al. Overlapping DRESS and Stevens-Johnson Syndrome: Case Report and Review of the Literature. Case Rep Dermatol. 2017 May 8;9(2):1-7.

When to re-challenge: penicillin allergy

Low risk reaction

ADEs
Non-anaphylaxis

Test dose penicillin

Full dose cephalosporin

Higher risk reactions

Anaphylaxis
Recent Hives

Full dose cephalosporin*

Desensitization

Severe cutaneous reaction

Mucosal and/or organ involvement

non beta-lactam

*1st generation PO and select 2nd generation cephalosporins can cross react due to identical R1 sidechains

When to re-challenge: cephalosporin allergy

Low risk reaction

ADEs
Non-anaphylaxis

Test dose
cephalosporin with dissimilar side chain

Full dose
penicillin

Higher risk reactions

Anaphylaxis
Recent Hives

Full dose
carbapenem, aztreonam*

Desensitization

Severe cutaneous reaction

Mucosal and/or organ involvement

non beta-lactam

*Unless reaction was to ceftazidime or other cephalosporins with identical R1 side chains

Challenges and strategies for non-allergists

Identify what's mandatory → Allergy guidelines/ resources

+

Resource intensive → Prioritize patient groups

Time intensive → Antibiotic challenges

c

Poll

Beta lactam allergy guidelines/other hospital resources are available at my institution:

A. Yes

B. No

C. I’m not sure

citations

Poll

Beta lactam challenges are available at my institution

A. Yes

B. No

C. I’m not sure

citations

Poll

Penicillin allergy delabeling program is available at my institution

A. Yes

B. No

C. I’m not sure

citations

Hospital resources

Assessment of Patient Reported Penicillin Allergy

Minor risk reactions

Ex. Isolated GI upset (diarrhea, nausea, vomiting, abdominal pain), chills (rigors), headache, fatigue

(Includes "never took b/c whole family is allergic")

OK to use FULL dose:
Any penicillin

Low risk reactions

Any non-severe non-anaphylactic reaction

Ex.
Possible non-anaphylactic IgE mediated reaction >5 years ago

Maculopapular rash (type IV hypersensitivity reaction)

Medical record lists allergy but patient denies

Unknown reaction >10 years ago not requiring medical care (includes "mom told me that I had a reaction as a baby")

OK to administer after TEST dose:
Penicillin

OK to use FULL dose:
Cephalosporin
Aztreonam
Carbapenem
Non-beta-lactam antibiotics

Higher risk (IgE mediated reactions that were severe or recent)

Anaphylaxis (any time in the past)

Any of the following within 6 hours of dosing and <5 years ago:
- Angioedema /laryngeal edema
- Hives/itching/rash/flushing
- Wheezing
- Hypotension
- Severe GI symptoms

Any urticarial rash within the past 5 years.

Positive penicillin skin test with no prior reaction

Any unknown reaction <10 years or >10 years if required medical care

OK to use FULL dose:
Cephalosporin with dissimilar side chain (ie. cefazolin, ceftriaxone, cefepime)
Carbapenem
Aztreonam
Non-beta-lactam antibiotics

If penicillin or cephalosporin with similar side chain indicated, consult ID

Severe risk reactions (delayed severe cutaneous)

Steven Johnson syndrome/

Toxic epidermal necrolysis

Any severe/generalized rash with skin sloughing/skin peeling

Drug rash eosinophilia systemic symptoms (DRESS) syndrome

Serum Sickness - fever, rash, arthritis

Generalized bullous reactions

Acute interstitial nephritis

Drug induced hemolytic anemia/thrombocytopenia

Hepatitis

OK to use FULL dose:
Non-beta lactam antibiotics

Avoid
Penicillin, Cephalosporins, Carbapenem

If clinical indication for beta-lactam or aztreonam, consult ID and consider outpatient allergy referral

Table
1. S
2. A
3. C
4. T
5. V
6. A

citations

Decision support tools

Vidya Atluri, MD-PhD
Senior ID Fellow
Infectious Diseases

Paul Pottinger, MD
Professor
Infectious Diseases

Rupali Jain, PharmD
Clinical Associate Professor
Infectious Diseases

Ania Lang, MD-PhD
Assistant Professor
Allergy / Immunology
U of Washington

Try Me!

https://redcap.iths.org/surveys/?s=7HJ8HMY87A7C7NRJ

citations

Hospital resources, cont.

URINARY TRACT INFECTIONS

Do **NOT** culture or treat pyuria, increased urine odor, cloudy or discolored urine without *urologic procedure with bleeding.*

Treatment:

Culture directed therapy recommended if prior data available

Cystitis (includes male patients if prostatitis ruled out)

Diagnosis: dysuria, frequency, urgency, hematuria

Analgesia should be offered - Ibuprofen 200-400 mg PO once-three times daily PRN - P

Duration:

- **IV beta lactam, Fluoroquinolone (3 days)**
- **IV to PO beta lactam (3 to 5 days)**
- **Nitrofurantoin, PO beta lactam (5 days)**

First line	Nitrofurantoin 100 mg BID **OR** Ceftriaxone 1 g daily **OR** Tobramycin or gentamicin 5 mg/kg IV/IM once
Second line	Amoxicillin/Clavulanate 875/125 mg BID x5 days

2) cUTI (e.g. abnormal urinary tract, urinary obstruction)/Pyelonephritis/Catheter-a out)

Diagnosis: new onset fever, rigors, flank pain, CVA tenderness, AND ≥10^3 CFU of ≥1 ba malaise, lethargy with no other source.

Catheter Management

- Replace if indwelling >2 weeks
- Obtain urine culture from freshly placed catheter.

Duration:

- **IV beta lactam, Fluoroquinolone (7 days)**
- **PO beta lactam preceded with IV antibiotics (10 days)**

Outpatient	Levofloxacin 750 mg daily
Inpatient[1-5]	
First line	Ceftriaxone 1 g daily
Severe PCN Allergy[2]	Levofloxacin 750 mg daily
High risk for resistance or shock[3]	Ertapenem 1 g daily or Meropenem 1 g q 8h

Gram Negative Isolates URINE Only Percent susceptible *(Shading indicates not tested)*

Clinic

Organism	No. of Isolates	Amoxicillin/Clavulanate	Nitrofurantoin	Trimethoprim/Sulfa
Citrobacter spp.	**128**	48	94	95
Enterobacter spp.	**85**	2	54	80
Escherichia coli	**3652**	88	97	91
Klebsiella spp.	**640**	81	43	92
Morganella morganii	**22[1]**	4	0	81
Proteus spp.	**332**	99	2	82

(3) Clinical Laboratory Standards Institute (CLSI) recommends creating Antibiogram for those organisms with > 30 isolates. Information provided for historical perspective only and may not reflect accurate susceptibility trends.

Patient selection

- Who may benefit the most from an allergy assessment?
- What can be automated?
- Feasibility of allergy assessments vs. selective strategies?

citations

30% w/ a beta lactam allergy still get a beta lactam

Original Article

Beta-lactam antibiotics administration among adult inpatients with a beta-lactam allergy label: incidence, predictors, and outcomes

Naama Epstein-Rigbi MD[1,2], Sharon Ziv BS[2], Marina Bulanenkova MD[3], Ruth Bouganim MD[4], Ruthy Tal-Jasper MD[4] and Dror Marchaim MD[2,4]

Retrospective cohort study, Israel (N=3,571)

798 (68%) PCN
154 (13%) BLBLI
147 (12.5%) CPN
72 (6%) various BL

1,171 (33%) patients w/ BLA receiving BL

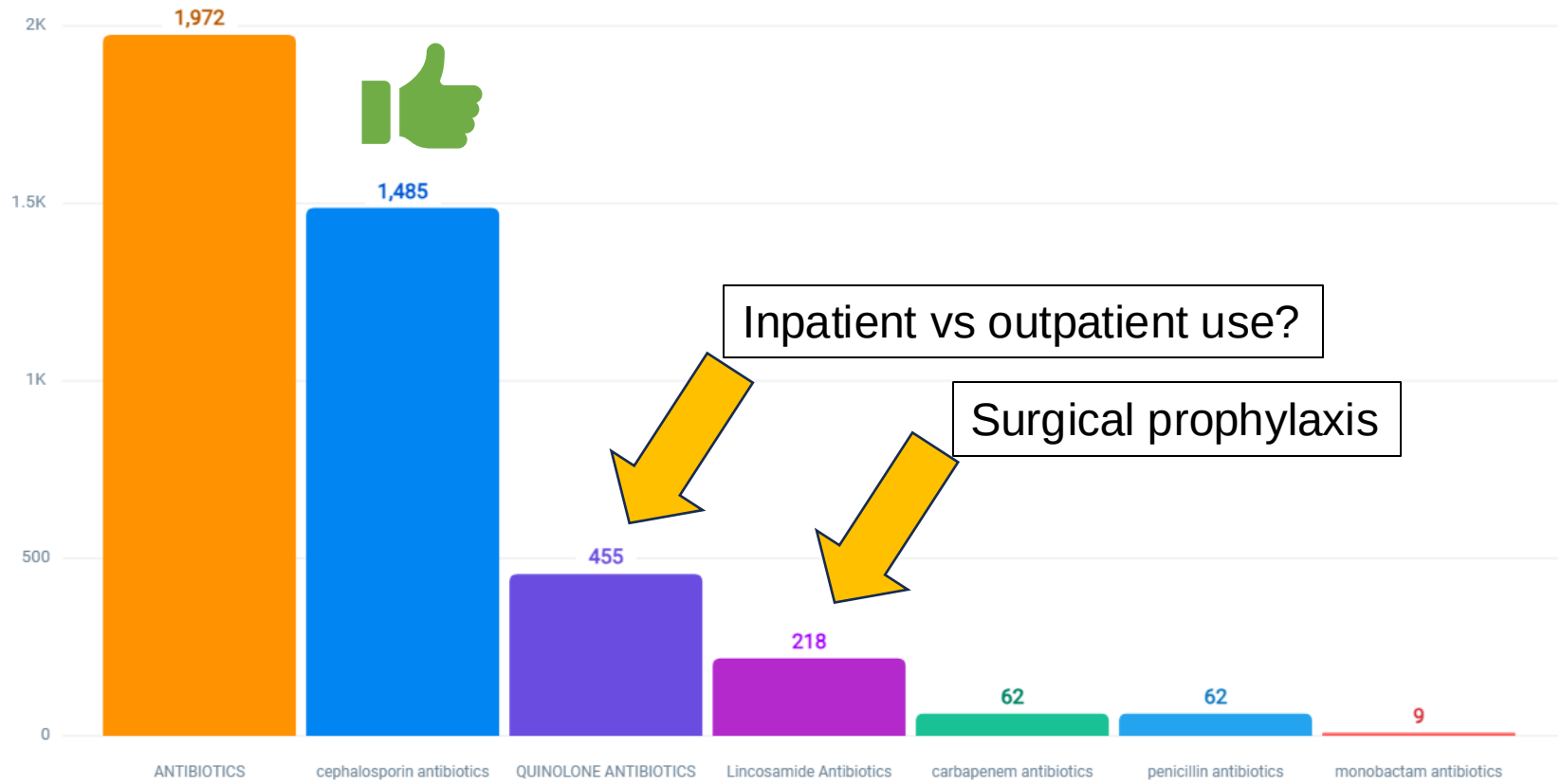
30 (2.6%) with mild reaction to BL

PCN – Penicillin
BL – Beta lactam
BLA – Beta lactam allergy
BLBLI – Beta lactam beta lactamase inhibitor
CPN – Cephalosporin

BLA – BL received	w/ reaction	w/o reaction
PCN-PCN	3 (13%)	42 (4.2%)
PCN-CPN	16 (54%)	846 (74.1%)
CPN-PCN	3 (13%)	65 (6.4%)
CPN-CPN	1 (4.3%)	67 (6.6%)
BL received same as BLA	6 (23%)	121 (11%)
BL received w/ high cross reactivity	12 (5.6%)	18 (1.9%)

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. 2018 Jan 18;66(3):329-336.

VMC: Patients w/ PCN allergy receiving antibiotics



citations

Patient selection at VMC

- Who may benefit the most from an allergy assessment?
  - Assess higher risk patients (ex. Multiple allergies, high risk for readmission)
- What can be automated?
  - Surgical prophylaxis
- Feasibility of allergy assessments vs. selective strategies?
  - Orders for non-beta lactams (ex. fluoroquinolones)

citations

Single dose challenges

JAMA Internal Medicine | Original Investigation

Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy
The PALACE Randomized Clinical Trial

Ana Maria Copaescu, MD; Sara Vogrin, MBiostat; Fiona James, BBiomedSci; Kyra Y. L. Chua, PhD; Morgan T. Rose, MBBS; Joseph De Luca, MBBS; Jamie Waldron, MD; Andrew Awad, MD; Jack Godsell, MBBS; Elise Mitri, BPharm; Belinda Lambros, MAdvNursPrac; Abby Douglas, PhD; Rabea Youcef Khoudja, MD; Ghislaine A. C. Isabwe, MD; Genevieve Genest, MD; Michael Fein, MD; Cristine Radojicic, MD; Ann Collier, MD; Patricia Lugar, MD; Cosby Stone, MD; Moshe Ben-Shoshan, MD; Nicholas A. Turner, MD; Natasha E. Holmes, PhD; Elizabeth J. Phillips, MD; Jason A. Trubiano, PhD

- PEN-FAST <3
- Amoxicillin 250mg x1
- Symptoms monitored for 60 minutes and day 5

DOI: 10.1111/acem.14893

ORIGINAL ARTICLE

Full-dose challenge of moderate, severe, and unknown beta-lactam allergies in the emergency department

Adam M. Anderson MD[1] | Stephanie Coallier MD[2] | Reid E. Mitchell DO[2] | Lisa E. Dumkow PharmD[3] | Lauren M. Wolf PharmD[3]

- Moderate (43%), severe (13%), unknown reaction (44%)
- Full dose challenge – monitoring parameters not defined

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. 2023 Sep 1;183(9):944-952.

Summary

- Incorrect penicillin allergies are associated with increased cost and poorer patient outcomes.
- Patients with non-anaphylactic beta-lactam reactions can likely be re-challenged.
- Allergy assessments are resource intensive. Tailor approaches to what is needed at your institution.

citations