Penicillin Allergy Edition

December 11th, 2018

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Statement of Disclosures

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Objectives

- Understand the clinical impact of penicillin allergy in patients for which a β-lactam is indicated
- Describe the most important elements of a thorough drug allergy history
- Discuss the opportunities and strategies for antimicrobial stewardship intervention for penicillin allergy
- Describe the processes and role of the pharmacist in penicillin skin testing

Case Presentation

- 55 year old healthy male with no prior past medical history presenting with shoulder pain
- Reports a fall ~3-4 weeks prior with worsening of pain
- Urgent care prescribed cyclobenzaprine, oxycodone, and a prednisone taper
- Progression of pain, now with chills/fevers → ED

Case Presentation

- Severe right shoulder pain, 10/10 despite multiple analgesics, limited range of motion
  - Sharp, radiating across the clavicle to the sternum and up the right side of his neck
- ROS: (+) fevers, chills
- Physical Examination
  - BP 125/82; HR 112; RR 18; temp 101.9F
  - Mildly diaphoretic, appeared uncomfortable
  - Sternoclavicular joint swollen, very tender, redness expanding across chest and up towards the neck

Case Presentation

- Past Medical History
  - Depression
  - Asthma
  - Morbid obesity
  - Sleep apnea
- Past Surgical History
  - Gastric banding 2010
  - Hernia repair 2007
- Allergies
  - **PCN as a child – anaphylaxis and hives; none since**
- Social History
  - Previous smoker
  - Denies alcohol use
  - No travel history
  - No pets
  - Lives with wife and foster children – 5 total (18 months to 19 years)
  - Manager at an insurance company
  - Sexually monogamous with wife
  - Recently had a cracked tooth

Case Presentation

- Pertinent Labs/Micro
  - WBC 10.9
  - LFTs normal
  - Scr/BUN 0.8/11
  - Troponin <0.01
  - Lactic acid 1.3
  - ESR/CRP: 63/295

  - Blood cultures x 2
  - Empiric vancomycin IV, aztreonam, and clindamycin started

- Imaging
  - MRI shoulder without contrast
    - Subcutaneous edema within the anterior shoulder and supraclavicular regions
    - No drainable fluid collection

Case Presentation

- Hospital day #3 – 2/4 blood culture bottles grow methicillin-susceptible *Staphylococcus aureus*

Penicillin allergy is lifelong

Penicillin Allergy

- Most frequently reported drug allergy
  - Up to 10% of the general population
  - Up to 20% of hospitalized patients
- Up to 90% of patients will tolerate penicillin

Drug Allergy Practice Guidelines. Ann Allergy Asthma Immunol 2010.105(4):259.

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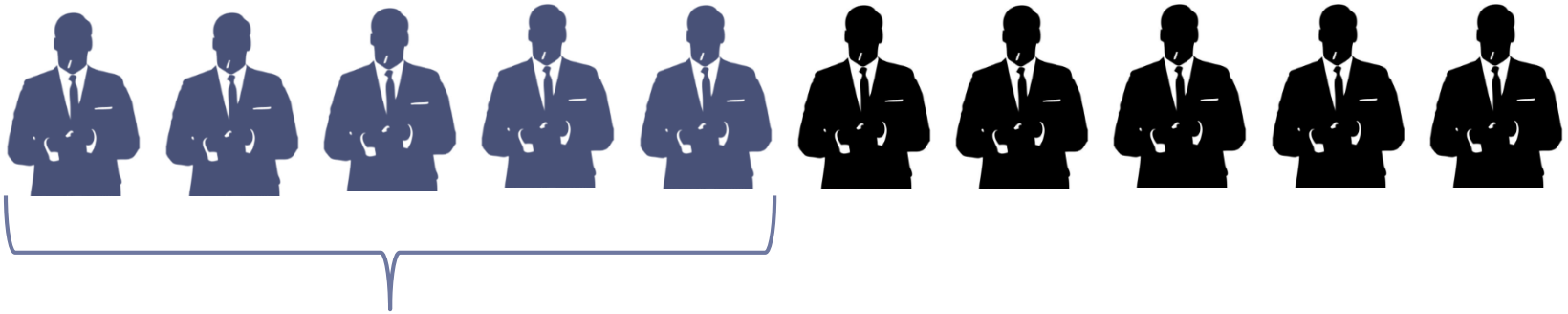

50% of patients outgrow their allergy within **5 years**

Drug Allergy Practice Guidelines. Ann Allergy Asthma Immunol 2010.105(4):259.

Penicillin Allergy

- Most frequently reported drug allergy
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- Up to 90% of patients will tolerate penicillin

80% of patients outgrow their allergy within **10 years**

Drug Allergy Practice Guidelines. Ann Allergy Asthma Immunol 2010.105(4):259.

Penicillin allergy is lifelong

The penicillin allergy label is harmless

Risks of the Penicillin Allergy Label

To determine health care use and infection prevalence associated with penicillin allergy in a retrospective, matched cohort study of subjects admitted from 2010 – 2012

Primary Objective

Total hospital days in hospitalized patients with and without a penicillin allergy

Secondary Objectives

Prevalence of *C.difficile*, MRSA, and VRE; top antibiotics prescribed

Macy E. J Allergy Clin Immunol 2014;133:790.

Risks of the Penicillin Allergy Label

Primary Objective

Total hospital days in hospitalized patients with and without a penicillin allergy

Secondary Objectives

Prevalence of *C.difficile*, MRSA, and VRE; top antibiotics prescribed

	Female		Male	
	Allergy n=36,583	No Allergy n=73,166	Allergy n=14,999	No Allergy n=29,998
Total Hospital Days† ± SD	6.3 ± 12.4	5.6 ±10.1	7.1 ±13.4	6.8 ±12.2
Total Admissions† ± SD	1.8 ± 1.8	1.7 ± 1.6	1.9 ± 1.9	1.9 ±1.8
C.difficile prevalence, no. (%)	1,071 (2.9)†	1,686 (2.3)	427 (2.9)	755 (2.5)
MRSA prevalence, no. (%)	960 (2.6) †	1,631 (2.2)	566 (3.8)	1,053 (3.5)
VRE prevalence, no. (%)	234 (0.6) †	337 (0.5)	68 (0.5)	128 (0.4)

† statistically significant

Macy E. J Allergy Clin Immunol 2014;133:790.

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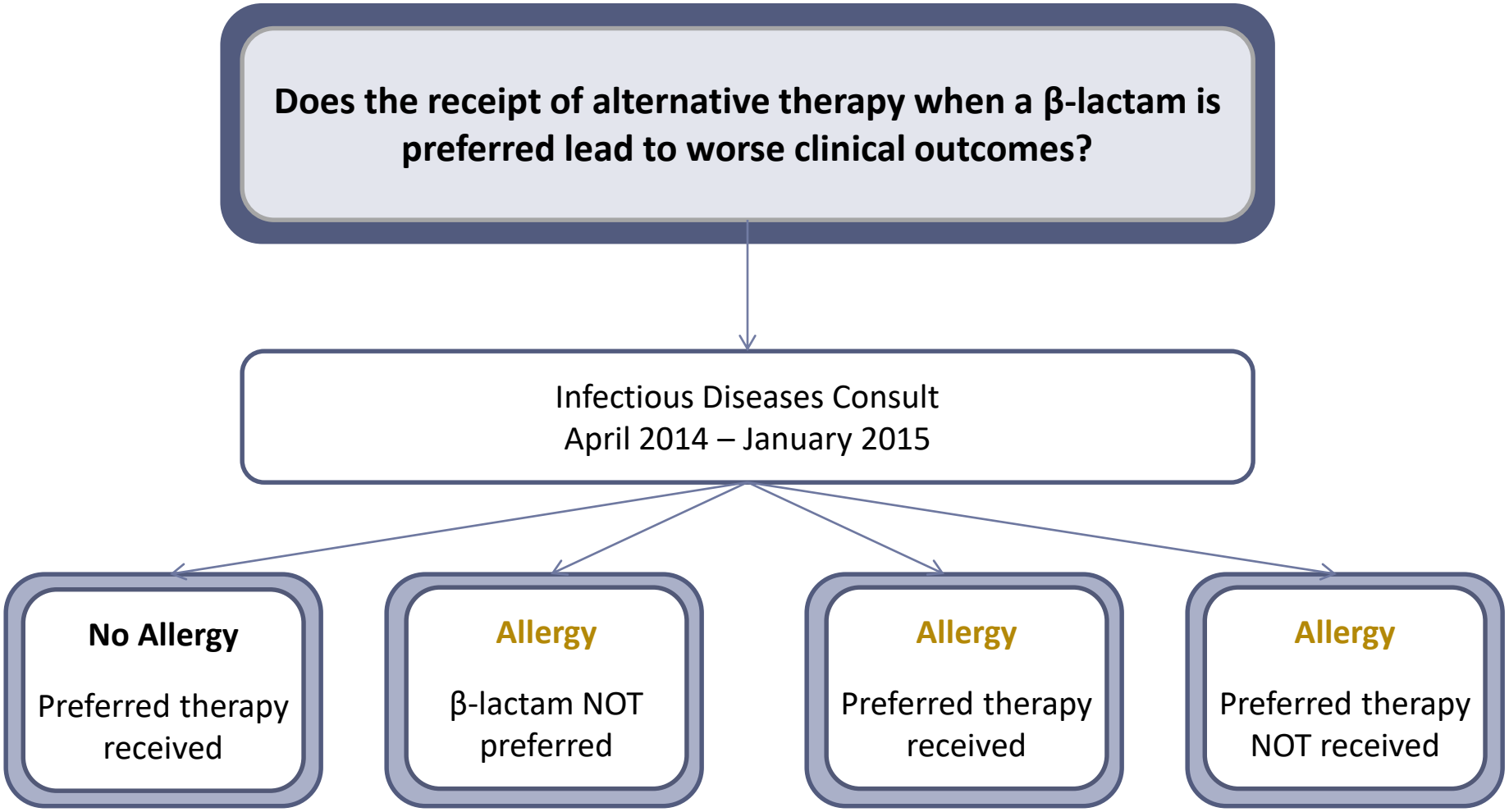
Rank	**Allergy n = 51,582**	**No Allergy n = 103,164**
1	Clindamycin† n = 12,579 (24.4%)	Cefazolin n = 32,614 (31.6%)
2	Ciprofloxacin† n = 10,888 (21.1%)	Ceftriaxone n = 21,726 (21.1%)
3	Vancomycin† n = 10,872 (21.2%)	Vancomycin n = 12,772 (12.4%)

† statistically significant

Macy E. J Allergy Clin Immunol 2014;133:790.

Risks of the Penicillin Allergy Label



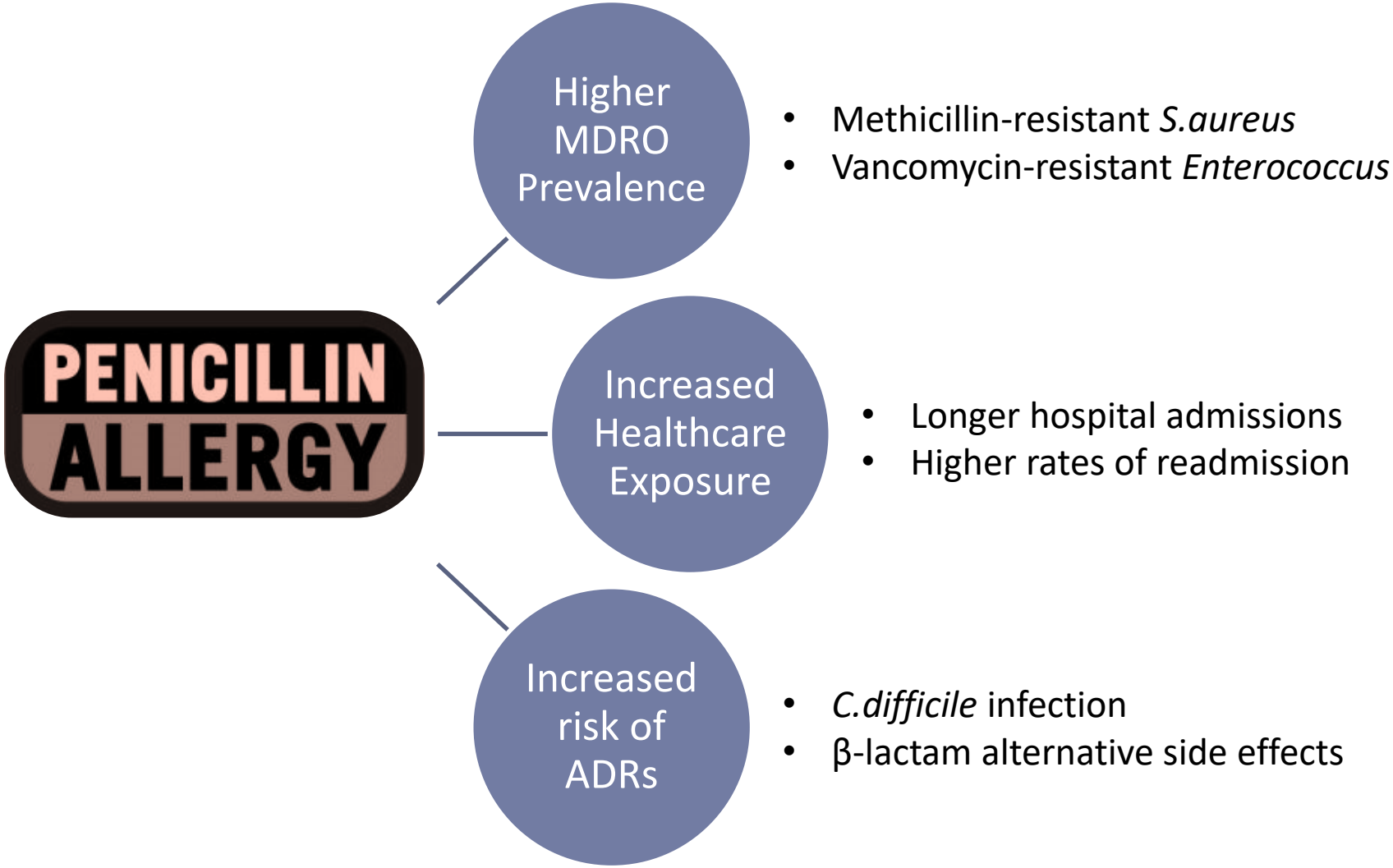
MacFadden D. Clin Infec Dis. 2016;63:904.

Risks of the Penicillin Allergy Label

	No Allergy Preferred therapy received	**Allergy** β-lactam NOT preferred	**Allergy** Preferred therapy received	**Allergy** Preferred therapy NOT received
	n = 412	**n = 23**	**n = 47**	**n = 25**
Readmission	**24 (6) †**	1 (4)	2 (4)	**6 (24) †**
C.difficile	18 (4)	1 (4)	0	0
Drug Reaction	**2 (0.5) †**	0	**4 (9) †**	**2 (8) †**
Kidney Injury	29 (7)	3 (13)	5 (11)	4 (16)

MacFadden D. Clin Infec Dis. 2016;63:904.

Summary of Risks

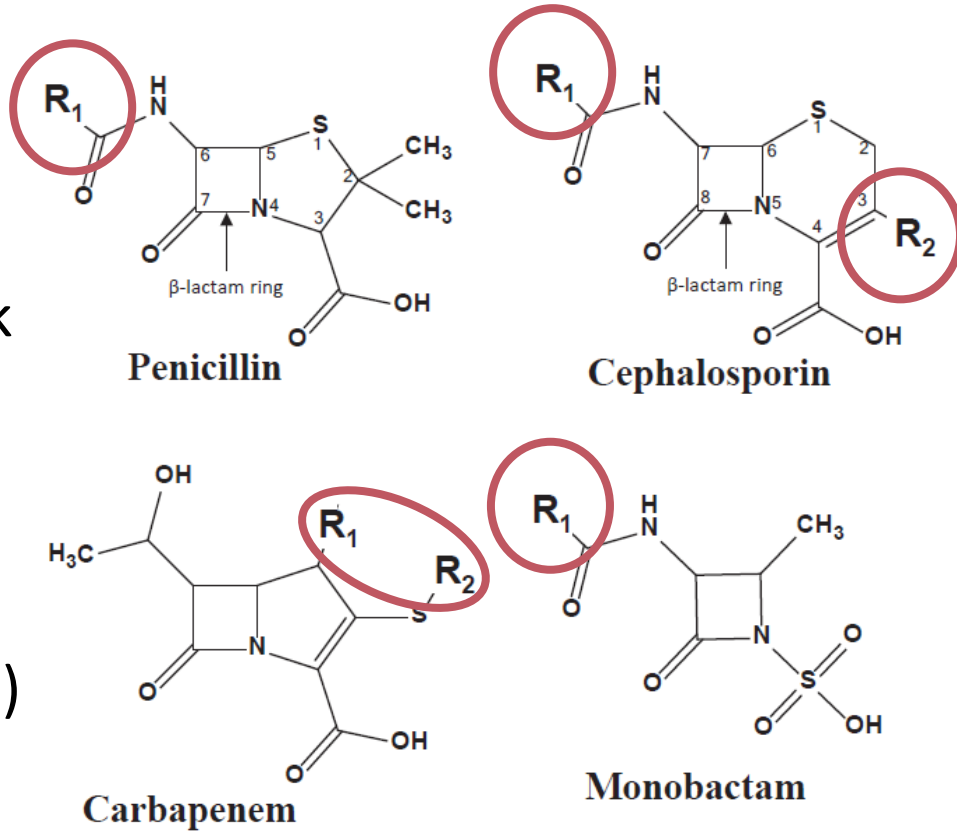


The penicillin allergy label is harmless

Cephalosporin antibiotics should be avoided in penicillin-allergic patients

Cross-reactivity of β-lactams

- Based on side-chain similarities
  - Cephalosporins
    - 1st generation highest risk
    - PST-positive, 2% cross-reactivity
  - Carbapenems
    - Low cross-reactivity (<1%)
  - Monobactams
    - No cross-reactivity



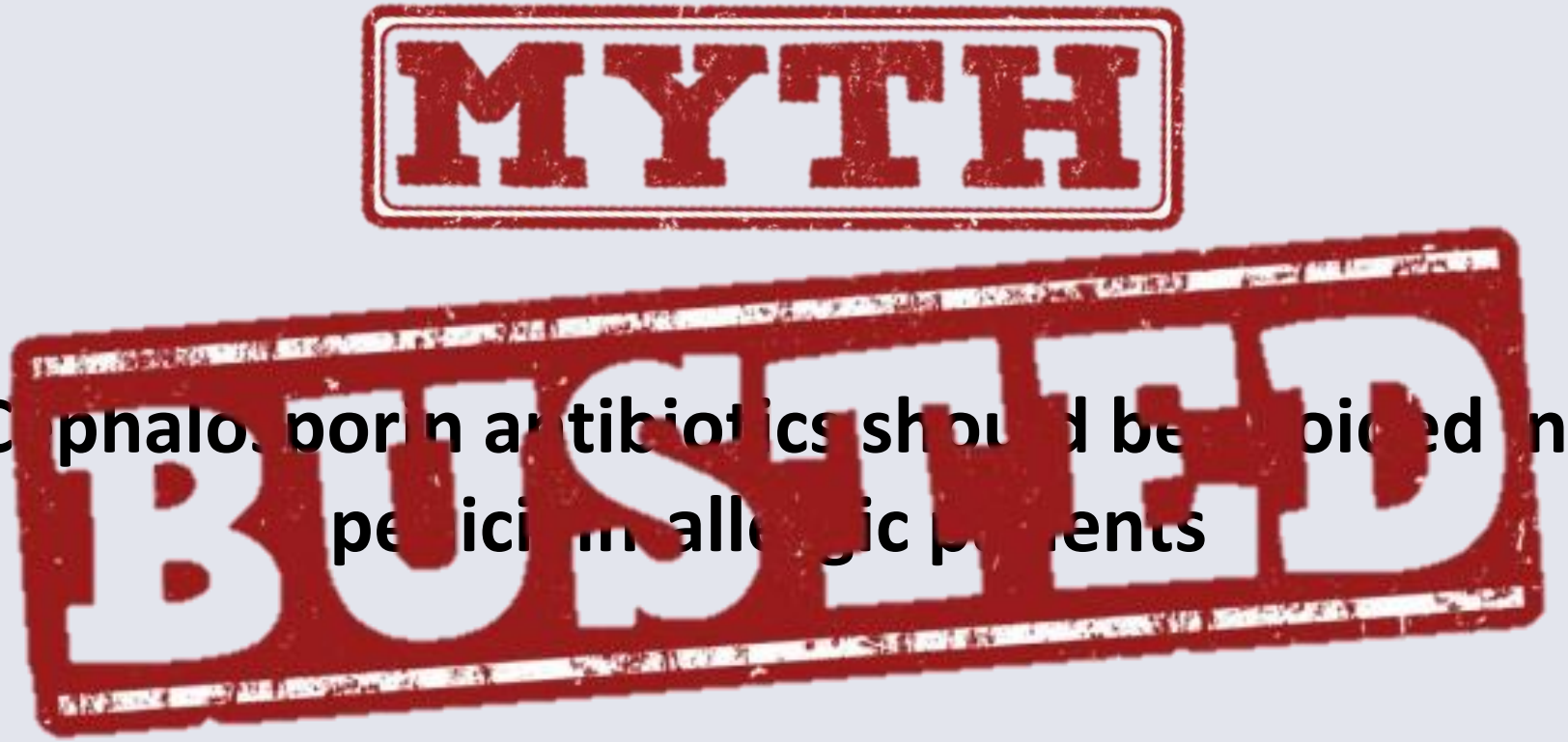
Zagursky. J Allergy Clin Immunol Pract 2018;6:72.
Drug Allergy Practice Guidelines. Ann Allergy Asthma Immunol 2010.105(4):259.

Penicillins and Cephalosporins with Similar Side-chain Structures

	Penicillin G	Amoxicillin	Ampicillin	Cephalexin	Cefazolin	Cefaclor	Cefprozil	Cefuroxime	Cefixime	Ceftibuten	Cefpodoxime	Cefdinir	Ceftriaxone
Penicillin G													
Amoxicillin			✓	✓		✓	✓						
Ampicillin		✓		✓		✓	✓						
Cephalexin		✓	✓			✓	✓						
Cefazolin													
Cefaclor		✓	✓	✓			✓						
Cefprozil		✓	✓	✓		✓							
Cefuroxime													
Cefixime												✓	
Ceftibuten													
Cefpodoxime													✓
Cefdinir									✓				
Ceftriaxone											✓		

Penicillins
1st Gen Ceph
2nd Gen Ceph
3rd Gen Ceph

Modified from DePestel. J Am Pharm Assoc 2008;48:530.

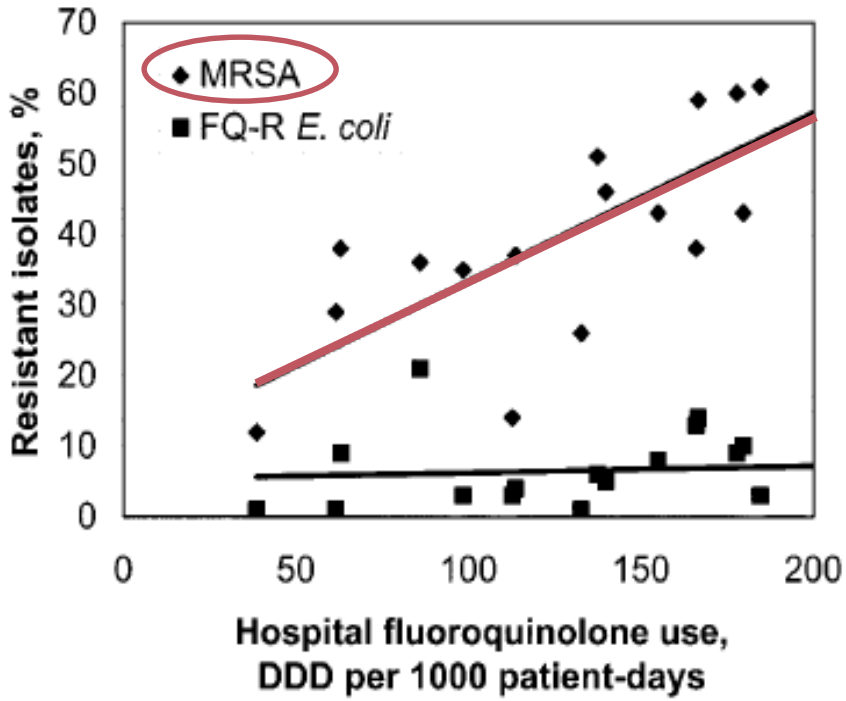


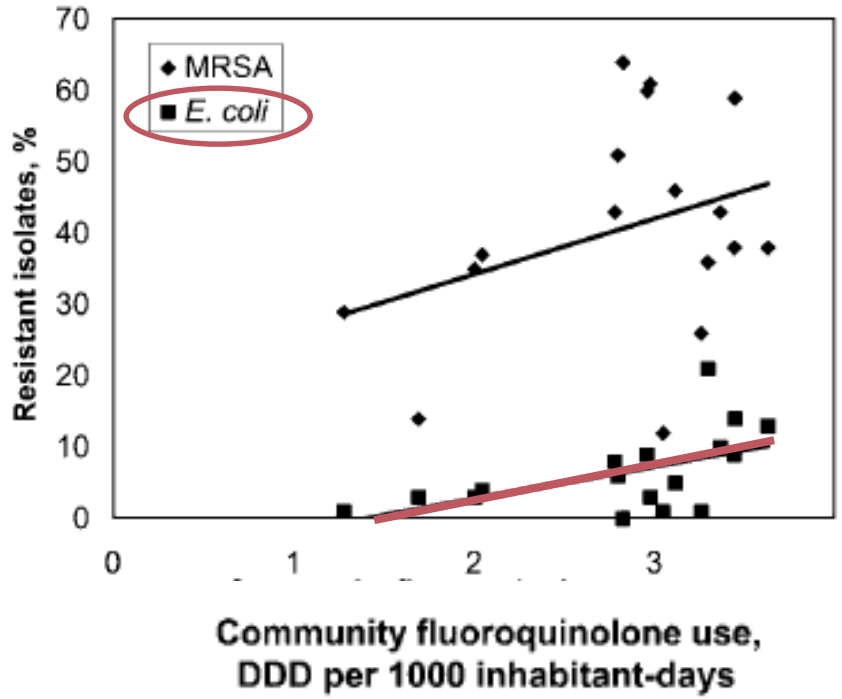
Cephalosporin antibiotics should be avoided in penicillin allergic patients

Alternatives to β-lactam antibiotics are safe

Risks of Alternative Antibiotics

Hospital and Community Fluoroquinolone Use and Resistance in *Staphylococcus aureus* and *Escherichia coli* in 17 US Hospitals





MacDougall C. Clin Infect Dis 2005;41:435.

Risks of Alternative Antibiotics

Comparison of Cumulative Antibiotic Exposures for Case and Non-case Hospitalizations			
Antibiotic Class	CDI positive n (%)	CDI negative n (%)	Adjusted hazard ratio (95%, CI)
Quinolones	132 (55)	3,471 (35)	4.0 (2.7, 5.9)
Third- and Fourth-gen cephalosporins	74 (31)	1,527 (15)	3.1 (1.9, 5.2)
Vancomycin	120 (50)	2,741 (28)	2.6 (1.7, 4.0)
First- and Second-gen cephalosporins	94 (39)	3,883 (39)	2.4 (1.4, 4.1)
β-Lactamase inhibitor combinations	120 (50)	3,013 (30)	2.3 (1.5, 3.5)
Clindamycin	34 (14)	876 (9)	1.9 (0.8, 4.4)
Penicillins	30 (12)	993 (10)	1.9 (0.9, 4.0)
Sulfas	33 (14)	1,158 (12)	1.9 (1.1, 3.4)
Macrolides	48 (20)	1,266 (13)	1.5 (0.7, 3.1)
Aminoglycosides	22 (9)	837 (8)	0.9 (0.3, 3.0)
Metronidazole	37 (15)	981 (10)	0.3 (0.1, 0.9)

CDI, *C.difficile* infection

Stevens V. Clin Infect Dis 2011;53:42.

Drugs

FDA reinforces safety information about serious low blood sugar levels and mental health side effects with fluoroquinolone antibiotics; requires label changes

Safety Announcement

[07-10-2018] The Food and Drug Administration (FDA) is strengthening the current warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects. The low blood sugar levels can result in serious problems, including coma, particularly in older people and patients with diabetes who are taking medicines to reduce blood sugar. We are making these changes because our recent review found reports of life-threatening low blood sugar side effects and reports of additional mental health side effects.

We are requiring these updates in the drug labels and to the patient Medication Guides for the entire class of fluoroquinolones (see List of FDA-Approved Fluoroquinolones for Systemic Use). This affects only the fluoroquinolone formulations taken by mouth or given by injection. Blood sugar disturbances, including high

https://www.fda.gov/Drugs/DrugSafety/ucm500143.htm

Alternatives to β-lactam antibiotics are safe

Penicillin allergy documentation in the medical record is usually accurate

Allergy Collection and Documentation

- A thorough medication allergy history is the first step to evaluating drug hypersensitivity

- Inaccurate reporting continues to be described across all platforms
  - Non-allergy trained personnel
  - Time constraints
  - Cumbersome documentation requirements

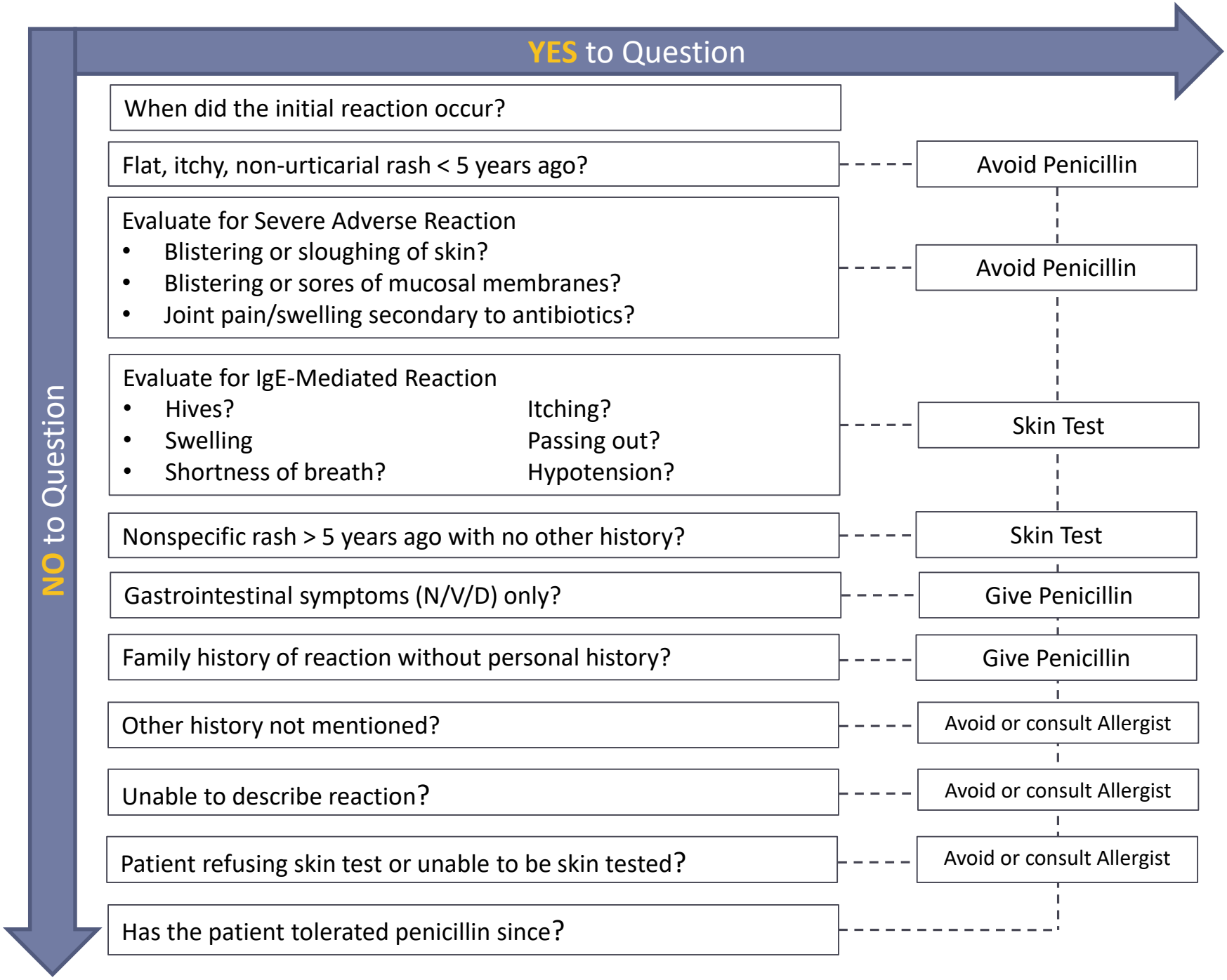
Characterization	No. of Patients (n=100)
Patient did not report a PCN allergy but was documented to have a PCN allergy in the EMR	0
Patient reported a PCN allergy reaction that was consistent with EMR documentation	32
Patient described a PCN allergy reaction that was different from EMR documentation	19
Patient described a PCN allergy reaction but the EMR reaction field was empty	13
Patient described a PCN allergy reaction but the EMR reaction field was incomplete	32
Patient described a history of a PCN allergy but had subsequently tolerated PCN-like antibiotics	1
The PCN allergy reaction was an intolerance incorrectly classified as an allergy	1
The PCN allergy reaction was documented as family history without a patient history	2

Staicu ML. Ann Allergy Asthma Immunol 2017;119:94.

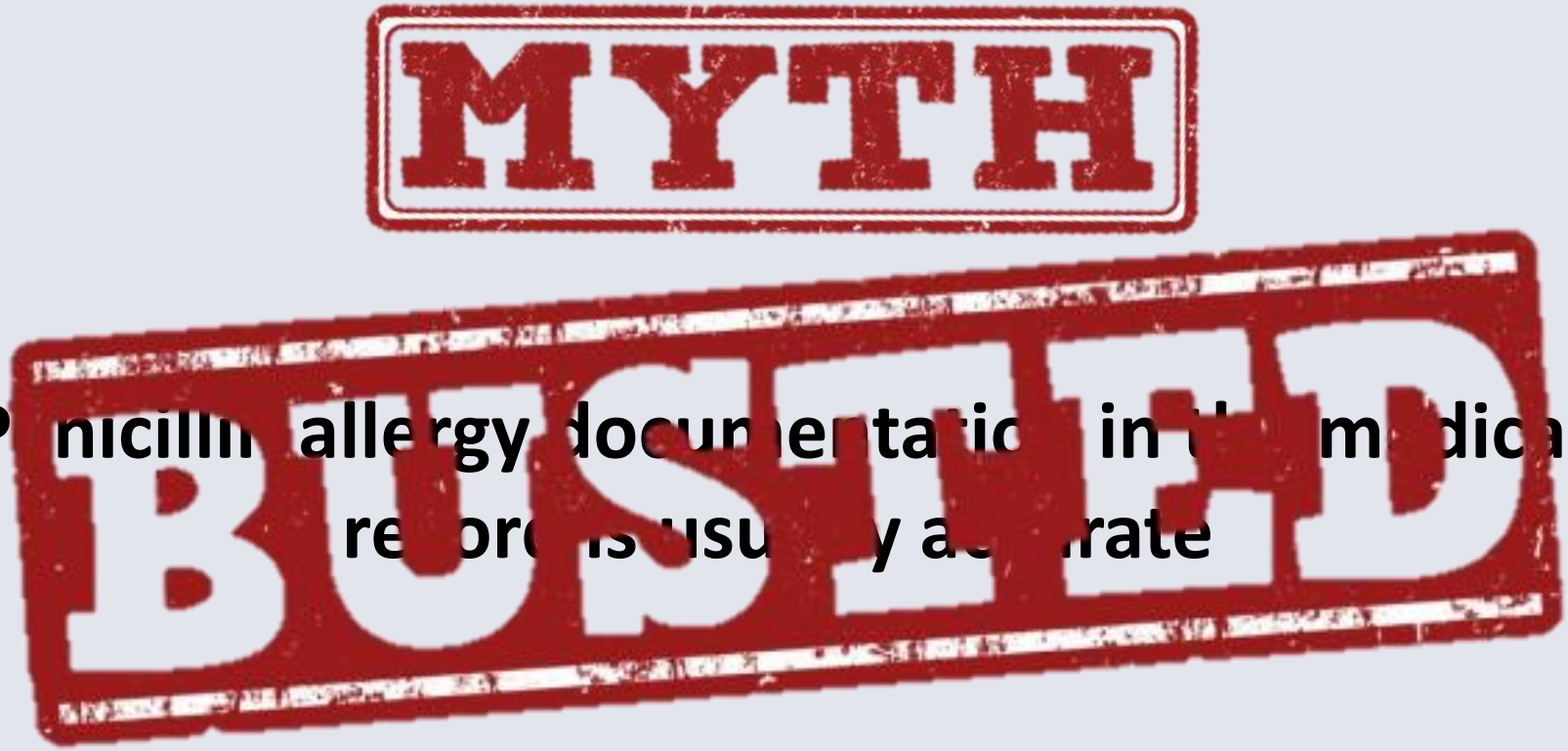
Gell and Coombs Classification Scheme

Reaction Type	Immunoglobulin Mediator	Typical Onset of Symptoms	Clinical Manifestation
Type I (IgE)	IgE antibodies leading to mast-cell/basophil degranulation	Immediate, minutes to hours	• Hives • Itching • Wheezing • Hypotension • Anaphylaxis • Angioedema
Type II (AIHA)	IgG/IgM-mediated cytotoxic reaction against cell surface	Days, >72 hours	• Cytopenias • Nephritis
Type III (serum sickness)	Immune complex reaction	1 – 3 weeks	• Rash • Urticaria • Lymphadenopathy • Joint pain
Type IV (T-cell)	Delayed T lymphocyte-mediated reaction	Variable (days to weeks)	• Blistering • Rash • Nephritis

Drug Allergy Practice Guidelines. Ann Allergy Asthma Immunol 2010.105(4):259.



Ramsey. J Allergy Clin Immun Pract 2018; 6:1349.



Penicillin allergy documentation in the medical record is usually accurate

Limited management options are available for penicillin-allergic patients

Management Strategies

Direct or Graded Challenges

- Controlled introduction of a drug in patients with a low likelihood of reacting

Penicillin Skin Testing (PST)

- Diagnostic tool which detects the presence of allergen-specific IgE on a patient's mast cells

Temporary Induction of Drug Tolerance

- Administration of incremental doses of a drug to temporarily induce immune tolerance

Direct or Graded Challenges

- Controlled introduction of a drug in patients with a low likelihood of reacting

Process

- Administration of progressively increasing doses until full dose is reached
  - Two to three doses
  - Given 30-60 minutes apart
- Do not pre-medicate
- Does not require ICU admission

Clinical Pearls

- Tolerability = no allergy
- Avoid if reaction history is severe non-IgE mediated
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
  - Interstitial nephritis
  - Hepatitis
  - Hemolytic anemia

AMOXICILLIN (PO) GRADED CHALLENGE PANEL (DOSES 1-3)

Accept

Amoxicillin (PO) graded challenge panel.
For antibiotic graded challenge in adults.

amoxicillin oral graded challenge DOSE #1 (8.75 mg)

Allergy/Contraindication: Penicillins **Reactions:** Unknown

8.75 mg (0.148 mg/kg), Oral, ONCE, Indications: Graded Challenge, Today at 1430, For 1 dose
Please administer graded challenge doses 30 minutes apart. If the patient experiences a reaction during the graded challenge, do not proceed with additional doses before discussing with Allergy/Immunology.

amoxicillin 8.75 mg

- Specific dosing guidelines are not available for this patient's level of renal impairment. The ordered dose is within the limits that do not consider renal impairment but otherwise match the patient's conditions.
- See details for additional information on adjusting the dose for renal impairment

amoxicillin oral graded challenge DOSE #2 (87.5 mg)

Allergy/Contraindication: Penicillins **Reactions:** Unknown

87.5 mg (1.48 mg/kg), Oral, ONCE, Indications: Graded Challenge, Today at 1500, For 1 dose
Please administer graded challenge doses 30 minutes apart. If the patient experiences a reaction during the graded challenge, do not proceed with additional doses before discussing with Allergy/Immunology.

amoxilcillin 87.5 mg

- Specific dosing guidelines are not available for this patient's level of renal impairment. The ordered dose is within the limits that do not consider renal impairment but otherwise match the patient's conditions.
- See details for additional information on adjusting the dose for renal impairment

AMOXICILLIN GRADED CHALLENGE DOSE # 3 (FINAL DOSE)

Antibiotic graded challenge in adults.

amoxicillin oral graded challenge DOSE #3 (AMOXIL) 400 mg/5 mL SUSPENSION

400 mg, Oral, ONCE, Starting H+120 Minutes, Please administer graded challenge doses 30 minutes apart. If the patient experiences a reaction during the graded challenge, do not proceed with additional doses before discussing with Allergy/Immunology.

amoxicillin oral graded challenge DOSE #3 (AMOXIL) CAPSULE

Oral, ONCE, Starting H+120 Minutes, Please administer graded challenge doses 30 minutes apart. If the patient experiences a reaction during the graded challenge, do not proceed with additional doses before discussing with Allergy/Immunology.

Direct or Graded Challenges

- Controlled introduction of a drug in patients with a low likelihood of reacting
  - Confino-Cohen R. J Allergy Clin Immunol Pract 2017;5:669-75.
    - 617 patients with a nonimmediate β-lactam reaction were directly challenged with 1/10th of therapeutic PCN dose followed by full dose x 5 days
    - Immediate reactions observed in 9 patients (1.5%); late reactions observed in 24 patients (4%)
  - Tucker MH. J Allergy Clin Immunol Pract 2017;3:813-815.
    - 328 penicillin-allergic Marine recruits were directly challenged with amoxicillin
    - Excluded if history of SJS, hepatitis, hemolytic anemia, nephritis
    - 5 patients (1.5%) had an acute objective challenge reaction, all cutaneous
  - Mill C. JAMA Pediatr 2016 Jun 6;170(6):e160033.
    - 818 children with an amoxicillin allergy (rash) underwent direct challenge
    - 770 patients (94.1%) tolerated challenge; 17 (2.1%) developed mild immediate reactions; 31 (3.8%) developed nonimmediate reactions
    - Specificity 100%; NPV 89.1%; PPV 100%

Penicillin Skin Testing (PST)

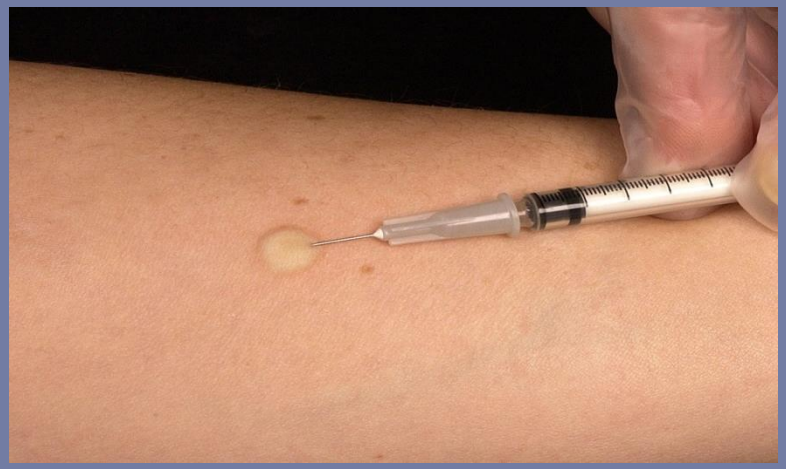
- Diagnostic tool which detects the presence of allergen-specific IgE on a patient's mast cells

Process

- Skin prick testing followed by intradermal testing
  - Controls (NS 0.9%, histamine)
  - Major determinant (PRE-PEN)
  - Minor determinant (PCN G)
- Amoxicillin test dose if skin test negative
- Application and results usually available within 1 hour

Clinical Pearls

- Most reliable method for evaluating IgE-mediated allergy
  - NPV 97 – 99%
- Results
  - Negative: risk same as general population
  - Positive: 50/50 chance of reaction
- Medications with anti-histiminic properties may interfere




5
6
7
8
4
3
2
1

Penicillin Skin Testing (PST)

- Diagnostic tool which detects the presence of allergen-specific IgE on a patient's mast cells
  - Macy E. J Allergy Clin Immunol Pract 2017;5:705-10.
    - 308 PST cases matched to 1251 penicillin allergic unique controls
    - Followed for an average of ~4 years
    - PST was associated with 0.09 fewer outpatient visits and 0.55 fewer hospital days per year; greater use of narrow-spectrum antibiotics
  - Chen JR. J Allergy Clin Immunol Pract 2017;5:686-93.
    - 252 inpatient penicillin allergy evaluations over 18 months
    - 228 (90.5%) had penicillin allergy removed (223 via PST; 5 via prior tolerance)
    - 85 patients transitioned to β-lactam preventing 504 inpatient and 648 outpatient days of alternative agents
  - Ramsey A. J Allergy Clin Immunol Pract 2018. In Press.
    - 50 patients identified for PST via a penicillin allergy history algorithm
    - 47 patients (94%) PST-negative and transitioned to first-line antibiotics
    - 982 days of second-line antibiotic therapy and 23 hospital days to administer antibiotics were avoided

Temporary Induction of Drug Tolerance

- Administration of incremental doses of a drug to temporarily induce immune tolerance

Process

- Incremental doses given approximately 20 – 30 minutes apart
  - Approximately 10 – 14 doses
- Do not pre-medicate
- Traditionally conducted in an ICU setting
- Process must be restarted if doses are missed*

*Process varies based on which dose

Clinical Pearls

- Previously regarded as "desensitization"
- Intended for agents that induce IgE-mediated reactions
- Contraindicated for serious non-IgE mediated reactions
- Tolerance is temporary

AMPICILLIN IV DESENSITIZATION PANEL (DOSES 1-8)

Accept

Ampicillin IV desensitization panel.
For antibiotic desensitization in adults.

ampicillin IV desensitization DOSE #1 (0.0002mg)

Remove

Allergy/Contraindication: Penicillins **Reactions:** Unknown

0.0002 mg (0.00000339 mg/kg), Intravenous, Administer over 20 Minutes, EVERY 20 MIN, First Dose Today at 1415, For 1 dose
Total volume (with overfill)= 44.11 ml. See order for "hold parameters" & see order for "Management of systemic reaction"
Indications: desensitization to allergen

Followed by

ampicillin IV desensitization DOSE #2 (0.002mg)

Remove

Allergy/Contraindication: Penicillins **Reactions:** Unknown

0.002 mg (0.0000339 mg/kg), Intravenous, Administer over 20 Minutes, EVERY 20 MIN, First Dose Today at 1435, For 1 dose
Total volume (with overfill)= 34.11 ml. See order for "hold parameters" & see order for "Management of systemic reaction"
Indications: desensitization to allergen

Followed by

ampicillin IV desensitization DOSE #3 (0.02 mg)

Remove

Allergy/Contraindication: Penicillins **Reactions:** Unknown

0.02 mg (0.000339 mg/kg), Intravenous, Administer over 20 Minutes, EVERY 20 MIN, First Dose Today at 1455, For 1 dose
Total volume (with overfill)= 44.11 ml. See order for "hold parameters" & see order for "Management of systemic reaction"
Indications: desensitization to allergen

Followed by

ampicillin IV desensitization DOSE #4 (0.2 mg)

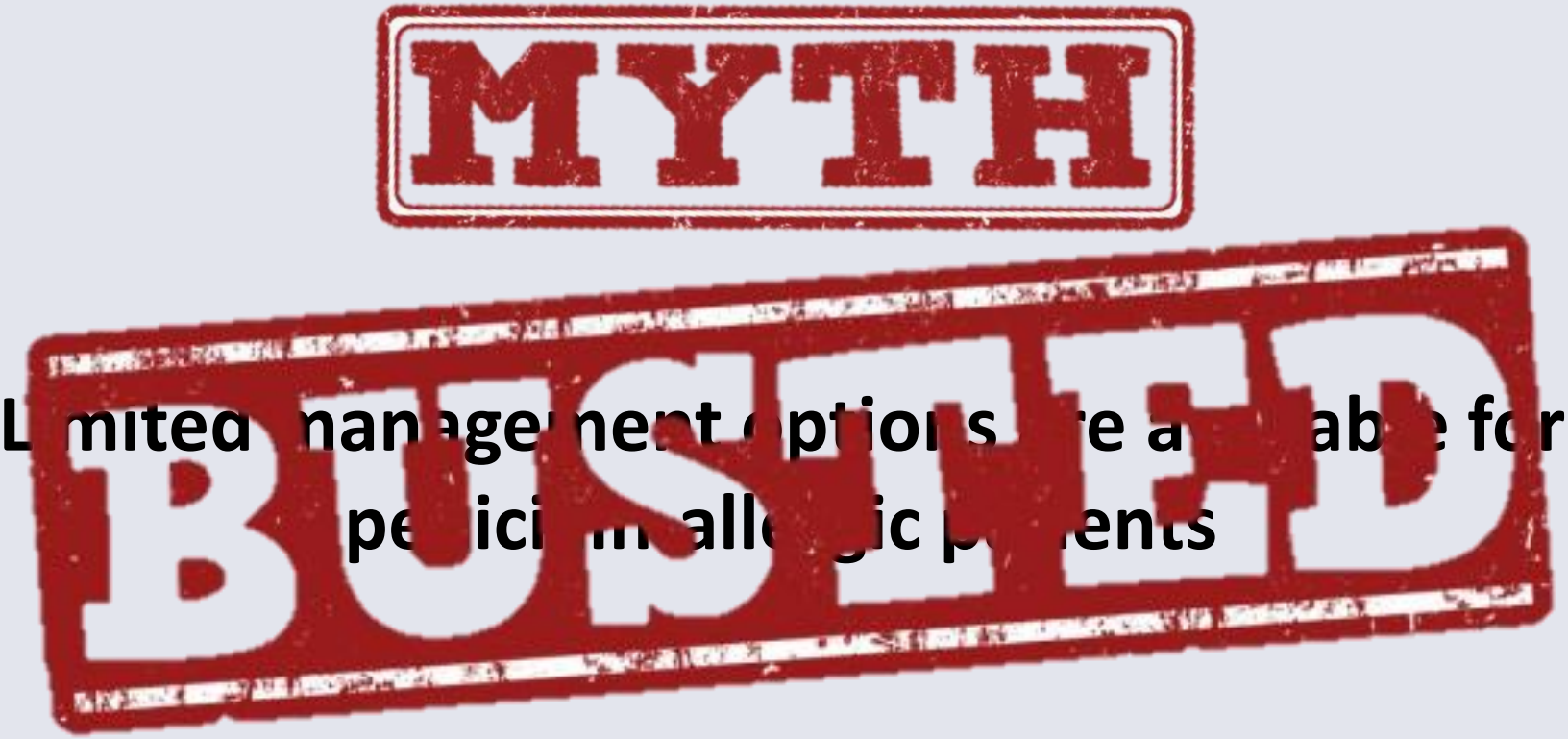
Remove

Allergy/Contraindication: Penicillins **Reactions:** Unknown

0.2 mg (0.00339 mg/kg), Intravenous, Administer over 20 Minutes, EVERY 20 MIN, First Dose Today at 1515, For 1 dose
Total volume (with overfill)= 34.11 ml. See order for "hold parameters" & see order for "Management of systemic reaction"
Indications: desensitization to allergen

Temporary Induction of Drug Tolerance

- Administration of incremental doses of a drug to temporarily induce immune tolerance
  - Sullivan TJ. J Allergy Clin Immunol 1982;69:275-282.
    - Case series of 30 PST-positive patients
    - Progressively increasing doses were administered every 15 minutes
    - No immediate reactions; 9 (30%) developed pruritic cutaneous reactions within 2 days; 1 (3%) developed reversible nephritis 3 weeks into therapy
  - Wendel GD. N Engl J Med 1985;312:1229-1232.
    - Case series of 15 PST-positive pregnant women
    - Each 'desensitized' over 4-6 hours via PO administration of PCN VK
    - 3 patients (20%) experienced pruritis, 2 (13%) urticaria – no interruption of oral 'desensitization' was necessary
  - Stark BJ. J Allergy Clin Immunol 1987;79:523-532.
    - 24 adults and 2 children were 'desensitized' to a β-lactam
    - Increasing oral doses of PCN were administered at 15-minute intervals
    - Immunologic reactions during 'desensitization' occurred in 12 patients (50%); interruption of procedure occurred in 1 (4%)



Limited management options are available for penicillin allergic patients

Where to Start

Collaborate

- Team up with allergists, nurses, ID fellows, pharmacy technicians

Collate

- Collect (and document) thorough allergy histories

Educate

- Inform patients of the risks and their options
- Review penicillin allergy and skin testing data with colleagues

Initiate

- Quality improvement initiatives

Allergy Services

Not available

- β-lactam usage guidelines for β-lactam allergic patients
- Update order sets to include cephalosporin alternatives
- Patient education
- Referral to Allergist as outpatient

Available

- Penicillin skin testing
  - Inferior second-line antibiotic therapy
  - Frequent non-β-lactam antibiotic use
  - Multiple antibiotic allergies
  - Prior to anticipated neutropenia
- Desensitization and graded challenge panels

Back to the Case

- 55 yo man with MSSA bacteremia complicated by sternoclavicular septic arthritis and chest cellulitis.
- TEE negative
- ID recommended antibiotics x 4 weeks

- **PCN allergy – childhood anaphylaxis and hives; no penicillin since**

Conclusions

- The penicillin allergy is associated with significant clinical and financial risks
  - Higher MRSA, VRE, *C.difficile* prevalence
  - Increased healthcare exposure, costs, and ADRs
- A thorough penicillin allergy history is the first step to evaluating management options
  - Various management strategies based on history
  - Antibiotic therapy optimization

Penicillin Allergy Edition

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