

Penicillin Allergy Management Across Care Settings: A Case Based Approach



Antimicrobial Stewardship Collaborative
of South Carolina

Hana R. Winders,
PharmD, BCIDP

Prisma Health-Midlands,
Columbia, SC

Objectives



Describe the prevalence and clinical impact of penicillin allergy labels.



Compare evidence-based penicillin allergy de-labeling strategies and their feasibility and safety considerations.



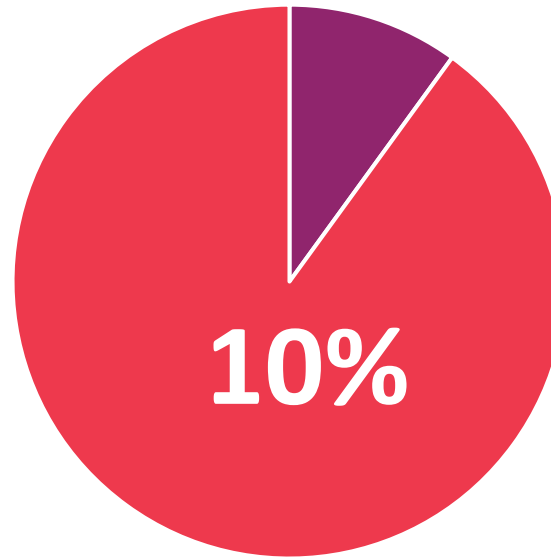
Choose appropriate penicillin allergy management strategies for patients across care settings using patient case examples.

Disclosures

- None

Penicillin allergy

Most reported
medication allergy



of patients in the US
report penicillin allergy

9/10 people with
penicillin allergy labels
are NOT truly allergic



Penicillin allergy

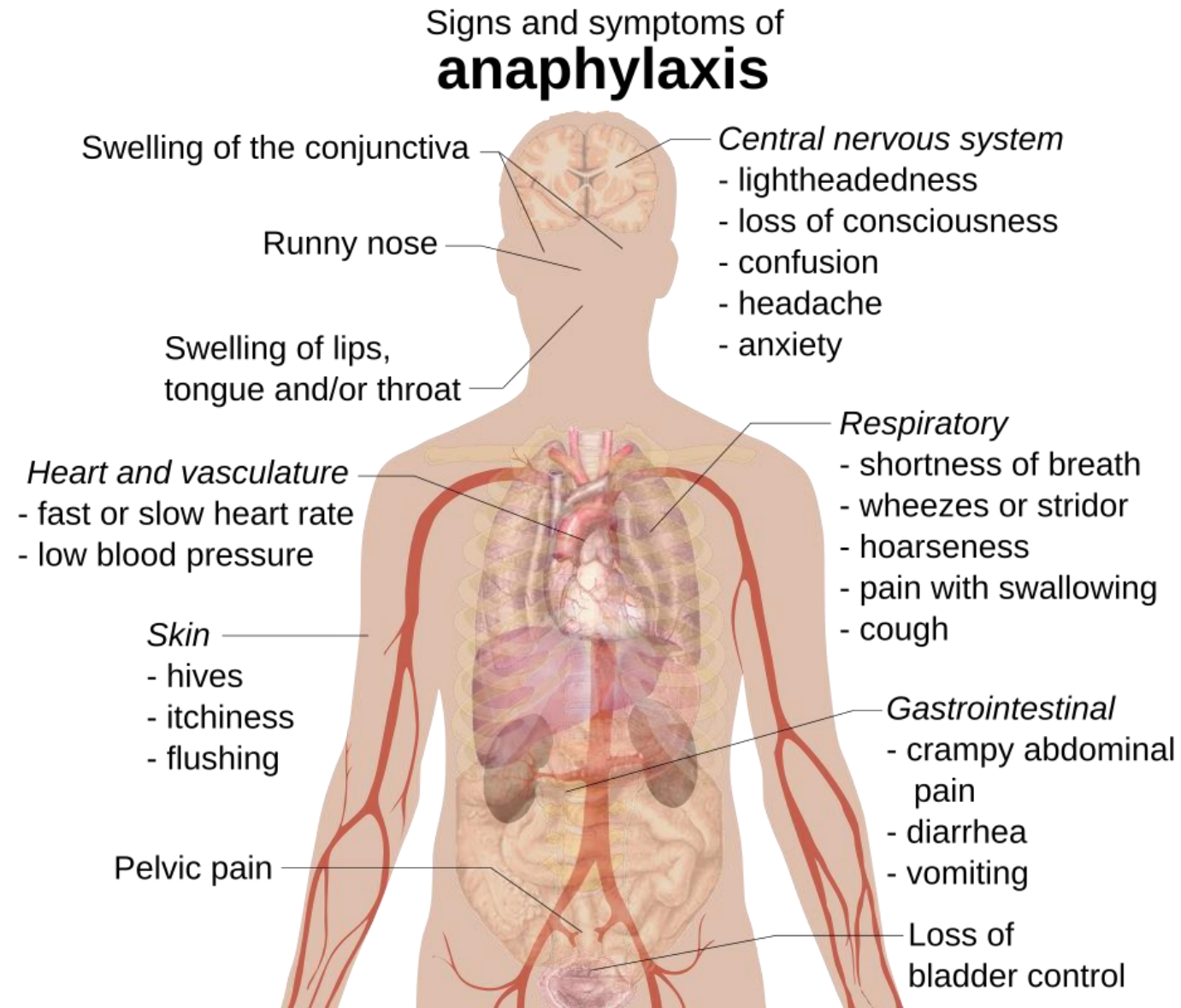
- IgE-mediated reactions wane over time

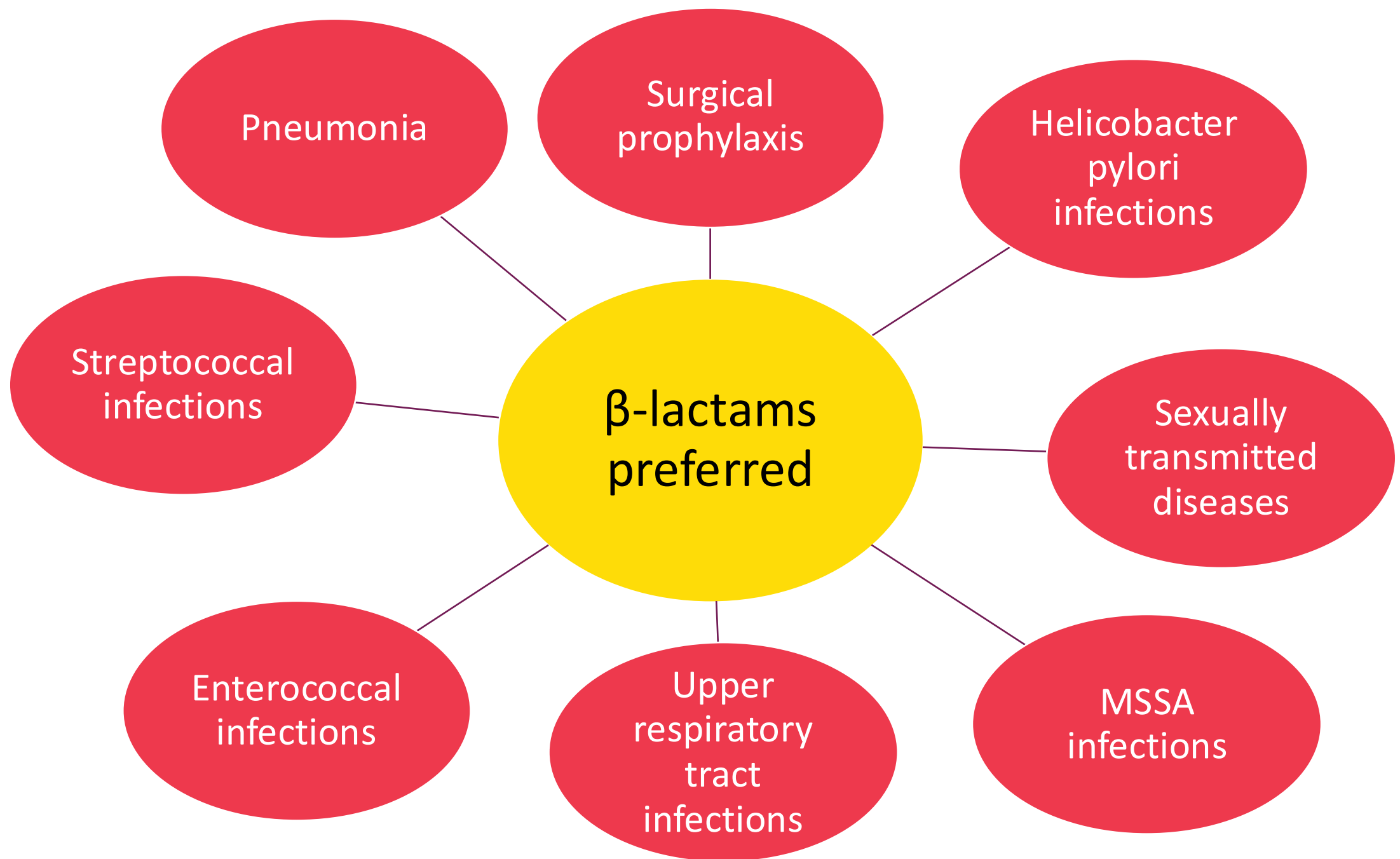


- Many patients were never allergic (intolerance/side effect/effect of infection)

Penicillin Allergy

- Anaphylaxis is rare
 - 0.001% of IV exposures
 - 0.0005% of oral exposures
- Most common reaction: delayed rash (type IV hypersensitivity)
 - May or may not recur with re-exposure





Penicillin Allergy Label (PAL)

```
graph TD; A[Penicillin Allergy Label (PAL)] --> B[Antibiotic Selection]; B --> C[Impact]; C --> D[Adverse Effects]; C --> E[Clinical Outcomes]; C --> F[Cost];
```

Antibiotic Selection

Impact

Adverse Effects

Clinical Outcomes

Cost

Antibiotic Selection

- ↑ Use of 2nd line antibiotics

Antibiotics	Antibiotic use rate (events/1000 person yrs)		Incidence rate ratio – Multivariate adjusted
	Penicillin allergy (n=64,141)	No penicillin allergy (n=237,258)	
β-lactams			
Penicillins	248.23	751.12	0.30 (0.30-0.31)
Cephalosporins, 1 st gen	165.67	81.16	1.82 (1.81-1.84)
β-lactam alternatives			
Macrolides	596.32	134.93	4.15 (4.12-4.17)
Clindamycin	6.35	1.45	3.89 (3.66-4.12)
Fluoroquinolones	118.44	49.55	2.10 (2.08-2.13)
Tetracyclines	228.20	119.59	1.75 (1.73-1.76)
Sulfonamides	193.10	146.66	1.26 (1.25-1.27)

Adjusted for age, sex, BMI, socioeconomic status, smoking status, alcohol status, CCI, dialysis, antibiotic prescriptions, PPI use, steroid use, other antibiotic allergies, nursing home resident, visits to GP, and admissions to hospital

Antibiotic Selection

-  Use of 2nd line antibiotics in surgical prophylaxis
 - Clindamycin (49% vs 3%, $p < 0.001$)
 - Vancomycin (35% vs 3%, $p < 0.001$)
 - Gentamicin (24% vs 3%, $p < 0.001$)
 - Cefazolin (12% vs 92%, $p < 0.001$)

Impact

Adverse Effects

↑ Incidence of MRSA

↑ Antibiotic days

↑ Incidence of VRE

↑ Adverse drug reactions
requiring
discontinuation

↑ Incidence of
Clostridioides difficile
infection (CDI)

Impact

Clinical Outcomes

↑ Hospital length of stay

↑ Surgical site infections

↑ Mortality

↑ Clinical failure

↑ Hospital readmissions

↑ Mean time to first dose

Impact

Cost

- ↑ Direct antibiotic expenditures
- ↑ Direct hospital costs
- ↑ Indirect costs (OR time, physician time, therapeutic drug monitoring, PICC line costs)
- ↑ Future costs (adverse drug reactions, hospital readmissions, bacterial resistant infections)

Strategies to optimize care in penicillin-allergic patients

- Intensive allergy assessment
- Education on risks of cross reactivity with cephalosporins and related antibiotics
- Implement treatment pathways addressing penicillin allergies
- Penicillin allergy skin testing (PAST) and/or oral challenges

Management strategies

Detailed
allergy history

Name of medication

How long ago was the reaction

Immediate vs delayed

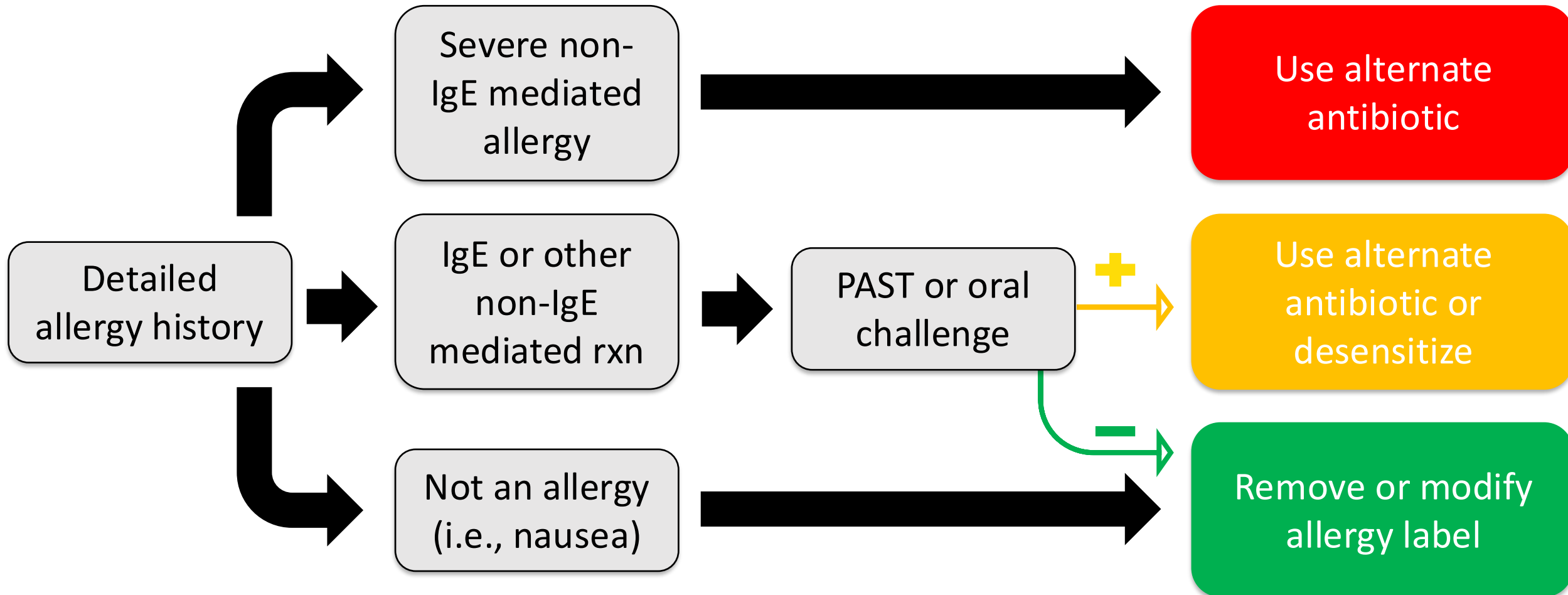
What happened (e.g., rash, hives, SOB, swelling, nausea, diarrhea)

Did they seek medical attention (e.g., doctor vs. hospitalization)

Resolution of reaction (e.g., medication as treatment vs. went away after stopping penicillin; how long reaction lasted)

Previously tolerated beta-lactams, especially after reaction

Management strategies



PAST

- More expensive
- Involves specialized training
- More difficult to obtain materials
- Decreased likelihood of systemic reaction if positive
- Only for IgE-mediated reactions

Oral Challenge

- Cheap
- Anyone can do it with minor training
- Oral amoxicillin readily available via prescription
- Increased likelihood of systemic reaction if positive
- Not limited to IgE-mediated reactions

PEN-FAST score

<u>P</u>EN icillin allergy reported by patient	If yes, proceed
<u>F</u> ive years or less since reaction	2 points
<u>A</u> naphylaxis or angioedema OR <u>S</u> evere cutaneous adverse reaction	2 points
<u>T</u> reatment required for reaction (or unknown)	1 points

Points	Interpretation
0	Very low risk (<1%)
1-2	Low risk (5%)
3	Moderate risk (20%)
4-5	High risk (50%)

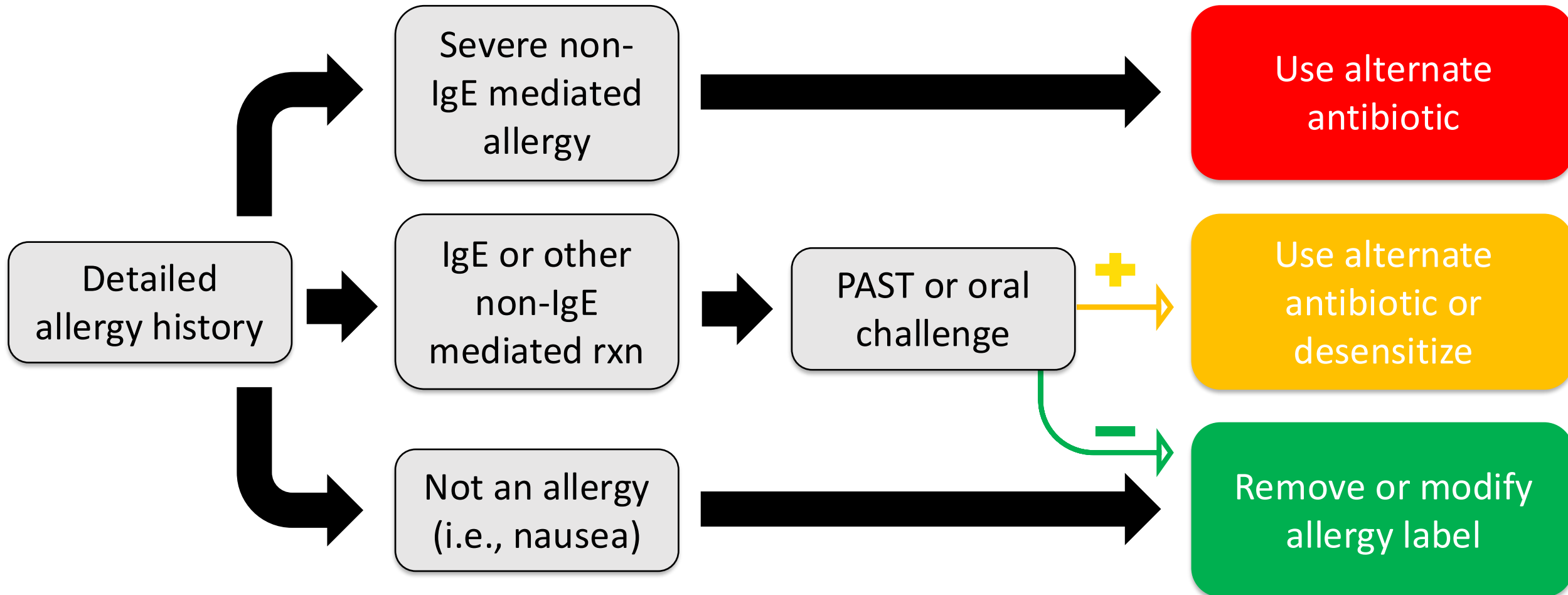
Patient Case 1

- 30-year-old female, 14-weeks pregnant, is referred by OBGYN for management of latent syphilis in setting of penicillin allergy
- Was told by OBGYN she may need admission for desensitization

Patient Case 1

- Penicillin allergy details
 - Occurred as a child
 - Hives and possible shortness of breath
 - Treated at emergency department with unknown medications
 - Occurred after first dose of amoxicillin although believes she tolerated it prior to that episode at least once
 - Has not taken penicillins or beta-lactams since

Management strategies



Considerations for testing in pregnancy

- Pregnancy-specific clinical implications of PAL
 - Higher rate of surgical site infections in C sections
 - Education on cross-reactivity may help
 - Inadequate GBS prophylaxis leading to worse neonatal outcomes
 - Status often unknown until end of pregnancy
 - No recommended alternatives for some indications (e.g., syphilis)

Considerations for testing in pregnancy

- Pregnancy-specific concerns
 - Pregnant patients may be less likely to consent due to concern about fetus
 - Anaphylaxis may lead to fetal morbidity or mortality if uterine perfusion and maternal oxygenation are compromised
 - Fetal monitoring is not available in most outpatient settings (outside of OBGYN clinics)

RCT Comparing Direct Challenges to PAST for Outpatient Low-Risk Penicillin Allergy in Pregnancy

- Low risk: history of cutaneous-only reaction (e.g., hives, nonspecific rash) or unknown reaction >5 years prior to evaluation
- Excluded reactions suspicious for severe cutaneous adverse reactions (e.g., angioedema, oral lesions, blistering, skin peeling)
- Testing could occur during any trimester
- Randomization 1:1

PAST with or without single-step oral challenge
(400mg amoxicillin monitored for 30 min)

Two-step oral challenge
(40mg amoxicillin monitored for 30 min followed by 400mg monitored for 30 min)

RCT Comparing Direct Challenges to PAST for Outpatient Low-Risk Penicillin Allergy in Pregnancy

- Low risk: history of cutaneous-only reaction (e.g., hives, nonspecific rash) or unknown reaction >5 years prior to evaluation
- Excluded reactions suspicious for severe cutaneous adverse reactions (e.g., angioedema, oral lesions, blistering, skin peeling)
- Testing could occur during any trimester

• Randomization

All would have PEN-FAST 0 or 1

**PAST with or
step oral
(400mg amoxi
for 3**

PENicillin allergy reported by patient

Five years or less since reaction

2

Anaphylaxis or angioedema

2

OR

Severe cutaneous adverse reaction

Treatment required for reaction (or unknown) 1

enge

monitored

400mg

in)

Characteristic	PAST	Direct Challenge (DC)	Total
Patients	73	71	144
Time since reaction, y (median [IQR])*	21 (18-28)	25 (21-30)	23.5 (18-29)
Weeks of gestation (median [IQR])	25 (20-35)	25 (16-35)	25 (18-35)
Index reaction, n (%)			
Rash	29 (39.7)	31 (52.1)	66 (45.5)
Urticaria	28 (38.4)	29 (40.8)	57 (39.6)
Unknown	12 (16.4)	6 (8.5)	18 (12.5)

*p≤0.05

Outcome	PAST	DC	Difference	P
PAST positive/DC fail, n (%)	5 (6.8)	0	6.8%	
PAST negative/DC pass, n (%)	68 (93.2)	70 (100)	−6.8%	.058
Time, min (median [IQR])	75 (70-80)	65 (65-70)	5.0	<.0001

1 patient with DC developed generalized pruritus and decided to prematurely stopped the study and ended up returning outside the study for PAST followed by oral challenge, which was negative

Of the 5 positive PAST, 2 had a previous history of hives, and 3 had a previous history of rash

According to the Revenue Integrity fee schedule at Rochester Regional Health

	PAST	DC	Difference
Cost/test	\$685.36	\$422.61	\$262.75

Summary of other studies in pregnancy

- Many studies show the safety and efficacy of PAST in pregnancy
- Safety of direct challenges (DC) in low-risk pregnant patients has also been shown with various low-risk definitions
- Validation of low-risk scores
 - One study showed PEN-FAST ≤ 2 with sensitivity 33.3%, specificity 92.68%, NPV 99.3% in pregnancy
 - Another study of 181 pregnant females (97.2% of which had negative allergy testing) showed multiple stratification tools labeled most patients as low risk (PEN-FAST 0-2 88.4%, JAMA low risk 60.2%, and FIRSTLINE very low risk 86.7%)

Implementation Models in the Literature in Outpatient Clinics

Wang, et al.	• Education and BPA to increase referrals to allergists or other clinics
Linn, et al.	• Pharmacist-led outpatient penicillin allergy testing clinics
Madapoosi, et al.	• Testing during scheduled visit at primary care offices by PCP and clinic staff

Considerations for Outpatient Feasibility

- While anyone eligible may be tested, consider limiting to specific criteria for feasibility
 - Patients that regularly get non-preferred antibiotics
 - Patients with multiple antibiotic allergies
 - Patients at higher risk of negative outcomes of PALs
 - Patients that would acutely benefit from penicillins or beta-lactams
- Availability of materials
 - Hospital pharmacy affiliated with outpatient practices could prepare PAST materials
 - Oral amoxicillin could be stocked or a prescription can be provided to the patient to bring with them

Patient Case 1

- 30-year-old female, 14-weeks pregnant, is referred to ID for management of latent syphilis due to having a penicillin allergy
- Was told by OBGYN she may need admission for desensitization
- Allergy details
 - Occurred as a child
 - Hives and possible shortness of breath
 - Treated at emergency department with unknown medications
 - Occurred after first dose of amoxicillin although believes she tolerated it prior to that episode at least once
 - Has not taken penicillins or beta-lactams since

Taking into consideration true prevalence of allergy, safety, feasibility, and clinical impact, which penicillin allergy management would be best to recommend?

- a) Admit for penicillin allergy de-sensitization
- b) Perform a penicillin allergy skin test followed by an oral challenge
- c) Perform a graded oral challenge
- d) Prescribe an alternative: doxycycline 100mg q12h x 28 days

Patient Case

PEN-FAST Assessment

Allergy details

- Occurred as a child
- Hives and possible shortness of breath (SOB)
- Treated at ED

PEN	<u>PEN</u> icillin allergy reported by patient	☒ proceed
F	<u>F</u> ive years or less since reaction	☐ 2 points
A	<u>A</u> naphylaxis or angioedema	
	<u>OR</u>	
S	<u>S</u> evere cutaneous adverse reaction	☒ 2 points
T	<u>T</u> reatment required for reaction (or unknown)	☒ 1 point

Better to assume SOB along with hives if patient thinks it might be the case

Patient Case PEN-FAST Assessment

Points	Interpretation
0	Very low risk (<1%)
1-2	Low risk (5%)
3	Moderate risk (20%)
4-5	High risk (50%)

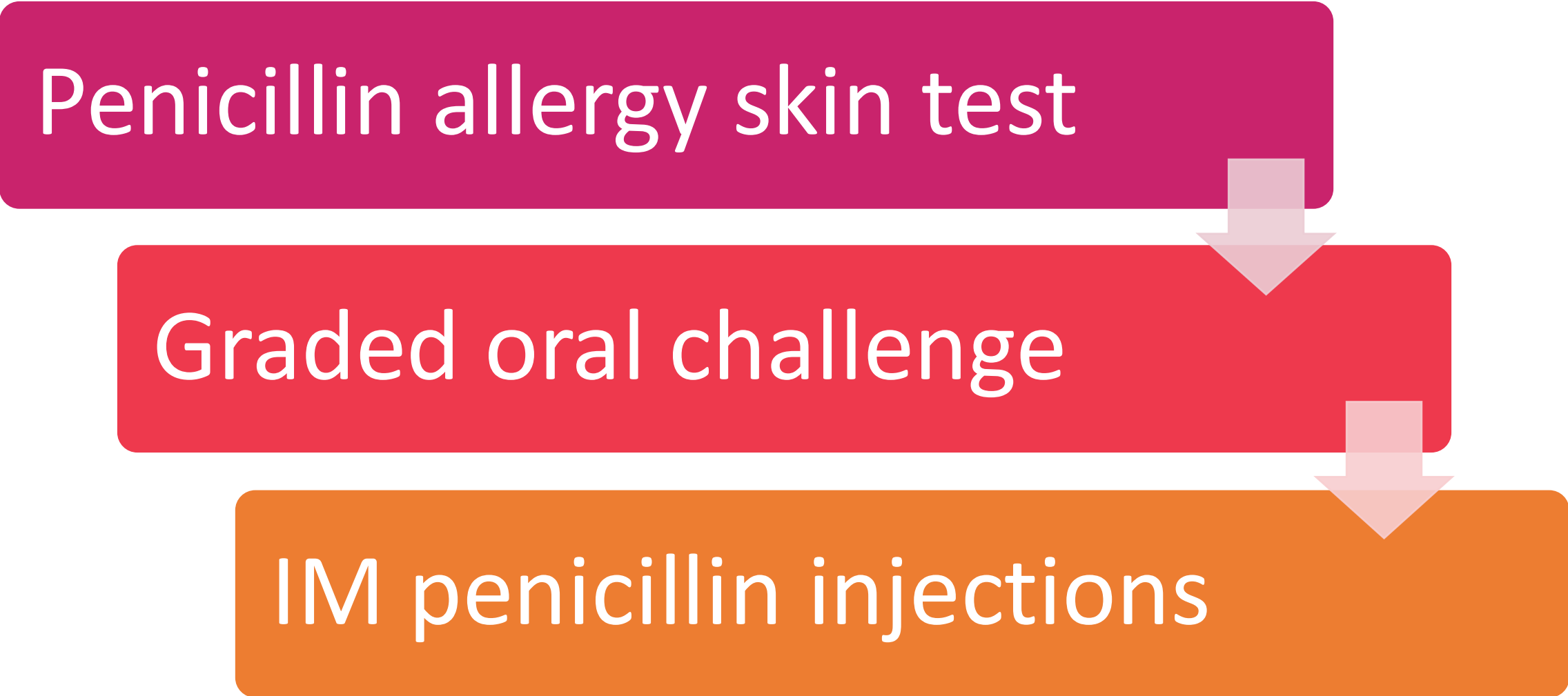


Taking into consideration true prevalence of allergy, safety, feasibility, and clinical impact, which penicillin allergy management would be best to recommend?

- a) Admit for penicillin allergy de-sensitization
- b) Perform a penicillin allergy skin test followed by an oral challenge
- c) Perform a graded oral challenge
- d) Prescribe an alternative: doxycycline 100mg q12h x 28 days

Patient Case Recommendations

Penicillin allergy skin test



```
graph TD; A[Penicillin allergy skin test] --> B[Graded oral challenge]; B --> C[IM penicillin injections];
```

Graded oral challenge

IM penicillin injections

Unexpected challenge

- DPH will not (*at this time*) treat anyone with any history of penicillin allergies including in patients that had negative allergy tests and have since tolerated first doses of IM penicillin
- Challenge for patients that live far from our institution
- Same challenge occurs for patients that are de-sensitized and need continuation of IM penicillin

Patient Case 2

- Patient SW is a 9-year-old girl with a penicillin allergy who presents to the pediatric emergency department with acute bacterial sinusitis.

Detailed
allergy history

- Penicillin allergy details:
 - Rash to amoxicillin at 8 months old
 - Has since tolerated cefdinir

Risk Stratification in Pediatrics

PEN-FAST

- Conflicting in studies
 - Yagmur: PEN-FAST ≥ 3 sensitivity 100%; specificity 35%; PPV 8%; NPV 100%
 - Guvenir: PEN-FAST ≥ 3 sensitivity 100%; specificity 45%; PPV 15%; NPV 100%
 - Copaescu: PEN-FAST ≥ 3 sensitivity 57%; specificity 46%; PPV $\sim 3\%$; NPV 95%
 - Possibly lower discriminatory power than in adults as having a reaction within 5 years automatically gives 2 points in the score

Many studies/centers use their own criteria for defining low risk patients eligible for direct oral challenge

Allergy Testing in Children with Low-Risk Penicillin Allergies in the Emergency Department

Inclusion	• Children 4-18 years • Low-risk symptom of penicillin allergy (e.g., rash, itching, diarrhea, vomiting, runny nose, nausea, cough, reported family history)
Exclusion	• High-risk symptom of penicillin allergy (e.g., respiratory or cardiovascular involvement, severe cutaneous reaction, angioedema, anaphylaxis, DRESS syndrome)
Testing	• Patients were screened in the emergency department but tested in the translational research unit by emergency medicine or allergy/immunology fellows • Testing was a tier 3 process (2 step skin test + oral challenge) • If skin test was positive, children were allowed to proceed to a graduated oral challenge if no high-risk symptom occurred during skin test

Allergy Symptoms

Low-Risk Symptom	N (100 patients included)
Nonhive rash	73
Itching	63
Hive rash	17
Diarrhea	7
Other	4
Vomiting	2
Nausea	2
Runny nose	1
Cough	1
Headache	1
Dizziness	1
Cannot remember	7

Results

- 3 children were initially positive on percutaneous testing
 - Original symptoms were rash +/- itching
- All were found to have negative results for penicillin allergy after oral challenge

Allergy Testing in Children with Low-Risk Penicillin Allergies in the Emergency Department

- Authors concluded that patients with low-risk symptoms do not correspond to true allergy
- Low PPV of PAST can lead to overdiagnosis of allergy
- Acknowledge utilization of PAST in pediatric ED is time-consuming, costly, labor-intensive, and likely impractical for real-world application however utilization of comprehensive allergy questionnaires +/- direct challenge for low-risk patients in the ED may facilitate increased use of first-line penicillin antibiotics
- Data agrees with prior studies that show PAST is unnecessary in low-risk patients

Alternate peds implementation example: primary care group visits

- After referral and a phone call with a pharmacist, patients were scheduled for an amoxicillin challenge group visit held monthly in an education room located in the general pediatric clinics
- Only excluded severe type IV adverse reactions
- Median group size was 2 patients
- 2-step graded challenge performed by pharmacist (50mg with 5 min observation and 200mg followed by 60 min observation)
- 58/61 were negative, and the 3 reactions (itching, rash) resolved with oral antihistamine or topical steroid

Patient Case 2

- Patient SW is a 9-year-old girl with a penicillin allergy who presents to the pediatric emergency department with acute bacterial sinusitis.

Detailed
allergy history

- Penicillin allergy details:
 - Rash to amoxicillin at 8 months old
 - Has since tolerated cefdinir

Taking into consideration true prevalence of allergy, safety, feasibility, and clinical impact, which penicillin allergy management would be best to recommend?

- a) Perform a penicillin allergy skin test followed by an oral challenge
- b) Perform an oral challenge of amoxicillin
- c) Prescribe amoxicillin without giving first dose in the ED
- d) Prescribe an alternative (e.g., levofloxacin)

Taking into consideration true prevalence of allergy, safety, feasibility, and clinical impact, which penicillin allergy management would be best to recommend?

- a) Perform a penicillin allergy skin test followed by an oral challenge
- b) Perform an oral challenge of amoxicillin
- c) Prescribe amoxicillin without giving first dose in the ED
- d) Prescribe an alternative (e.g., levofloxacin)

Patient Case 3

- A nursing home is currently experiencing a Group A *Streptococcus* (GAS) outbreak. So far 3 GAS infections have been identified, with 1 being bacteremia.
- Upon screening all residents, patient DL, an 85-year-old male, is found to be an asymptomatic carrier.
- PMH: DM-2, HTN, GERD, CKD, CDI (1 episodes 5 months prior)
- Antibiotic allergies: penicillins, clarithromycin

CDC recommended treatment for GAS carriers in long-term care (LTC) facilities

Universally susceptible antibiotic regimens

- IM benzathine penicillin x 1 + oral rifampin x 4 days
- First generation cephalosporins, such as cephalexin x 10 days

Alternatives needing susceptibility testing

- Azithromycin x 5 days
- Clindamycin x 10 days

Prevalence of PALs in Older Adults

Higher prevalence than other populations (up to 35%)

- Driven by cumulative antibiotic exposure and low rates of allergy reassessment
- Early penicillin formulations with protein contaminants increased sensitization risk

Despite higher PAL prevalence, true allergy appears to decline with age

- Possibly explained by immunosenescence, the gradual decline in immune system function that occurs with age

Clinical Impact of PALs in Older Adults

- Antibiotics are prescribed more frequently
 - Increased susceptibility to bacterial infections
 - 50-75% of LTC residents receive ≥ 1 antibiotic each year
 - β -lactams account for approximately half of antibiotics among LTC residents
- PALs result in reliance on second-line antibiotics leading to increased MDR infections, healthcare associated infections, and higher healthcare costs
- More vulnerable to the detriments associated with PALs
 - Higher infection-related mortality rates
 - Already at a higher risk of CDI and PALs are associated with an ~25% increased risk of CDI in addition to that

Penicillin Allergy Management Strategies

- Risk stratification and procedures including direct oral challenges have been shown to be safe with minimal adverse reactions in older adults
- Many low-risk histories have been shown to be de-labeled by history alone, reducing the need for specialized allergy evaluation and testing

Barriers



**Time
Constraints**



**Lack of Skills/
Expertise**



**Fear of
Reactions**



**Communication
Challenges**



**EHR
Barriers**



**Limited Access
to Allergists**

Facilitators



**Multidisciplinary
Collaboration**



**Education and
Training**



**Safety profile of
Penicillin allergy
De-labeling**



**Algorithms and
Toolkits**



**Risk Stratification
and Scoring of
Allergy History**



**Leadership
Support**

Barriers



Time Constraints



Lack of Skills/ Expertise



Fear of Reactions



Communication Challenges



EHR Barriers



Limited Access to Allergists

Facilitators



Multidisciplinary Collaboration



Education and Training



Safety profile of Penicillin allergy De-labeling



Algorithms and Toolkits



Risk Stratification and Scoring of Allergy History



Leadership Support

Integration of efforts among geriatricians or other PCPs, pharmacists, ID or allergy specialists

Targeted training for providers along with patient education to improve understanding of penicillin allergy evaluation and de-labeling processes

Abundance of safety/efficacy data with history-based and testing-based de-labeling processes

Standardized protocols and clinical decision support tools to guide risk stratification, testing, and documentation

Utilization of validated scoring systems to identify low-risk patients

Institutional support to promote initiatives, allocate resources, and drive culture change for adoption of penicillin allergy de-labeling

RISK ASSESSMENT IN PENICILLIN ALLERGY DE-LABELING

KEY COMPONENTS OF ALLERGY HISTORY

1. **What was the reaction?** (symptoms, timing, severity)
2. **When did it happen?** (context of the exposure, how long ago)
3. **What happened after?** (treatment and outcome)

DE-LABEL BASED ON HISTORY

- Family history of penicillin allergy only
- Fear of allergy only without prior reaction
- Known tolerance of penicillin since original reaction occurred
- Non-allergic symptoms (headache, fatigue, GI upset)

"I had a headache when given penicillin to treat my infection"

De-Label

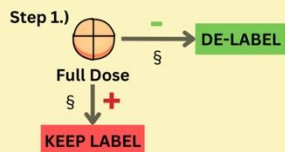
CONDUCT DIRECT ORAL CHALLENGE

- Isolated skin rash without warning signs*
- Remote childhood reaction with limited details

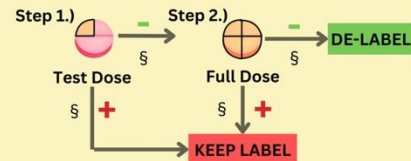
"As a kid I had hives after receiving amoxicillin"

Conduct Oral Challenge

EXAMPLE 1-STEP ORAL CHALLENGE PROCEDURE*



EXAMPLE 2-STEP ORAL CHALLENGE PROCEDURE*



REQUIRES FURTHER EVALUATION BY ALLERGIST IF CLINICALLY INDICATED

- History of anaphylaxis
- Development of allergic symptoms** within 1 hour of penicillin administration
- Severe delayed immunologic reactions
- SJS, TEN, DRESS, AGEP, DILI, AIN
- Hemolytic anemia
- Recurrent reaction with re-exposure

"I went into anaphylaxis 15 minutes after taking ampicillin and needed epinephrine"

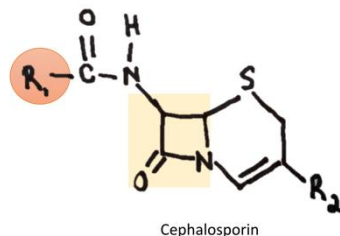
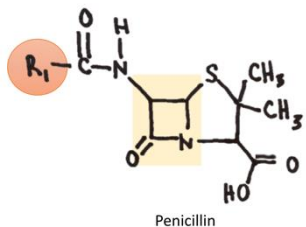
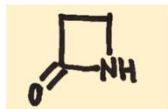
Do Not De-Label

Example of penicillin allergy de-labeling flowchart for risk stratification and management

Cross Reactivity

- Cross reactivity between beta-lactam antibiotics due to identical/similar side chains (R1)

Common Core:
Beta Lactam Ring



Beta-lactam Antibiotic Cross-Allergy Chart																
Beta-lactams	AMOXICILLIN*	AMPICILLIN	CLOXACILLIN	PENICILLIN	PIPERACILLIN*	CEFADROXIL	CEFAZOLIN	CEPHALEXIN	CEFOXITIN	CEFPROZIL	CEFUROXIME	CEFIXIME	CEFOTAXIME	CEFTAZIDIME	CEFTIRAXONE	CEFEPIME
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
CEFTIRAXONE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X ¹	X ³	X ¹	X ³		X ¹
CEFEPIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X ²	X ³	X ¹	X ³	X ¹	
ERTAPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X ⁵
IMIPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X ⁵
MEROPENEM	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	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

Patient Case 3

- A nursing home is currently experiencing a Group A *Streptococcus* (GAS) outbreak. So far 3 GAS infections have been identified, with 1 being bacteremia.
- Upon screening all residents, patient DL, an 85-year-old male, is found to be an asymptomatic carrier.
- PMH: DM-2, HTN, GERD, CKD, CDI (1 episodes 5 months prior)
- Antibiotic allergies: penicillins, clarithromycin

Patient Case 3

Penicillin allergy details:

- Hives to amoxicillin as an adult, around 15 years ago
- Denies shortness of breath or swelling
- Does not recall additional details or if he received treatment
- Records show receipt of cefazolin ~4 years ago, but does not recall any other beta-lactam use

Clarithromycin allergy details:

- Anaphylaxis (SOB, throat swelling, itching) around 25 years ago
- Does not recall receiving azithromycin

Taking into consideration true prevalence of allergy, safety, feasibility, and clinical impact, which penicillin allergy management would be best to recommend?

- a) Prescribe full course of cephalexin with no additional monitoring
- b) Perform a penicillin allergy skin test followed by an oral amoxicillin challenge prior to treating
- c) Perform an oral challenge with amoxicillin or cephalexin prior to treating
- d) Prescribe an alternative: clindamycin x 10 days

Patient Case

PEN-FAST Assessment

Allergy details

- Occurred ~15 years ago
- Hives
- Unknown if treated

PEN PENicillin allergy reported by patient

☒ proceed

F Five years or less since reaction

☐ 2 points

A Anaphylaxis or angioedema

☐ 2 points

OR

S Severe cutaneous adverse reaction

T Treatment required for reaction (or unknown)

☒ 1 point

Patient Case PEN-FAST Assessment

Points	Interpretation
0	Very low risk (<1%)
1-2	Low risk (5%)
3	Moderate risk (20%)
4-5	High risk (50%)



Taking into consideration true prevalence of allergy, safety, feasibility, and clinical impact, which penicillin allergy management would be best to recommend?

- a) Prescribe full course of cephalexin with no additional monitoring
- b) Perform a penicillin allergy skin test followed by an oral amoxicillin challenge prior to treating
- c) Perform an oral challenge with amoxicillin or cephalexin prior to treating
- d) Prescribe an alternative: clindamycin x 10 days

Patient Case 4

- 91-year-old woman diagnosed with *Enterococcus faecalis* native tricuspid valve endocarditis secondary to possible urinary source. The patient is not a candidate for surgery. She is currently on day 3 of vancomycin due to a reported anaphylactic reaction to penicillin.

Thanks to Brandon Bookstaver
for the inpatient slides!

Inpatient management of penicillin allergies: What's different?

- 40-70% of hospitalized patients have incomplete allergy reconciliation
- Acuity is greater impacting not only antibiotic selection, but potentially morbidity/mortality, transitions of care therapeutics, and even patient placement post-discharge
- Most institutions do not have a readily available allergist to manage inpatient allergies, so various models have been used (e.g., pharmacist driven, nurse driven, mixed model among physicians, nurses, pharmacists)

Passive model example: Implementation of education plus side-chain guided therapy for inpatients with CAP/HAP

- Increased use of beta-lactams post-intervention (89% vs. 70%, $p < 0.001$)
- Decreased use of alternative therapies (36% vs. 58%, $p < 0.001$)
- No increase in allergic reactions or in reactions thought to be due to β -lactams (0.9% vs. 1.3%, $p = 0.703$)

Beta-lactams	AMOXICILLIN*	AMPICILLIN	CLOXACILLIN	PENICILLIN	PIPERACILLIN*	CEFADROXIL	CEFAZOLIN	CEPHELEXIN	CEFOXITIN	CEFTAZIDIME	CEFPROZIL	CEFUROXIME	CEFTRIAZONE	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	✓	✓	✓	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CEPHELEXIN	X ¹	X ²	✓	✓	X ³	X ¹	✓		✓	X ²	✓	✓	✓	✓	✓	✓	✓
CEFOXITIN	✓	✓	✓	X ³	✓	✓	✓	✓		X ²	✓	✓	✓	✓	✓	✓	✓
CEFTAZIDIME	X ²	X ²	✓	✓	X ³	X ²	✓	X ²	✓		✓	✓	✓	✓	✓	✓	✓
CEFPROZIL	✓	✓	✓	✓	✓	✓	✓	✓	X ²	✓		✓	✓	✓	✓	✓	✓
CEFUROXIME	✓	✓	✓	✓	✓	✓	✓	✓	✓	X ³	X ¹	X ³	X ¹	X ²	✓	✓	✓
CEFTRIAZONE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	X ³	X ³	X ³	X ³	✓	✓	✓
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)

Active model example: Success utilizing pharmacists to drive allergy reconciliation and de-labeling

- **Prisma Health** (*Palmetto Health at the time*) launched **pharmacist-driven penicillin allergy assessment and skin testing in September 2017**
- Approximately 450 skin tests have been performed with TNTC allergy reconciliations and challenges
 - 1% positive rate (indeterminates slightly more common)
- Creating an inpatient culture of allergy reconciliation has significantly decreased the need for PAST and increased comfort in utilizing evidence of lack of cross reactivity vs. challenges
 - **Key challenge** is to prevent re-labeling...easier in certain EHRs combined with active follow-up with outside providers (e.g., dentists, pharmacies, PCPs)

Patient Case 4

- 91-year-old woman diagnosed with *Enterococcus faecalis* native tricuspid valve endocarditis secondary to possible urinary source. The patient is not a candidate for surgery. She is currently on day 3 of vancomycin due to a reported anaphylactic reaction to penicillin.
- The penicillin allergy is not reconciled in the EHR, so you proceed with evaluation at the bedside.

Patient Case

PEN-FAST Assessment

Allergy details

- Occurred as a young teen approximately 75-80 years ago
- Throat swelling on 1st dose
- Went to ED and received treatment

PEN PENicillin allergy reported by patient

☒ proceed

F Five years or less since reaction

☐ 2 points

A Anaphylaxis or angioedema

☒ 2 points

OR

S Severe cutaneous adverse reaction

T Treatment required for reaction (or unknown)

☒ 1 point

Patient Case PEN-FAST Assessment

Points	Interpretation
0	Very low risk (<1%)
1-2	Low risk (5%)
3	Moderate risk (20%)
4-5	High risk (50%)



Taking into consideration true prevalence of allergy, safety, feasibility, and clinical impact, which penicillin allergy management would be best to recommend?

- a) Perform a penicillin allergy skin test followed by full dose IV ampicillin
- b) Perform a penicillin allergy skin test followed by an oral challenge
- c) Perform a graded oral challenge
- d) Continue non-beta-lactam alternative

Taking into consideration true prevalence of allergy, safety, feasibility, and clinical impact, which penicillin allergy management would be best to recommend?

- a) Perform a penicillin allergy skin test followed by full dose IV ampicillin
- b) Perform a penicillin allergy skin test followed by an oral challenge
- c) Perform a graded oral challenge
- d) Continue non-beta-lactam alternative

Patient Case 4

- After discussions with patient and patient's daughter, we proceeded with a penicillin allergy skin test
 - Keep in mind, for ~75 years she has avoided beta-lactams and was *very hesitant* for this test.
- The patient was able to transition to ampicillin and receive as a continuous infusion at home where the daughter helped manage.
 - Avoided potential vancomycin-induced nephrotoxicity
- De-labeled in chart and information provided to all her outside providers



Conclusions

Around 10% of the population has a PAL, but >90% are not truly allergic

PALs are associated with higher costs, worse outcomes, and more adverse events

Risk-based penicillin de-labeling (history, oral challenge, skin testing) is safe and effective when tailored to feasibility and patient-specific factors

Penicillin Allergy Management Across Care Settings: A Case Based Approach



Antimicrobial Stewardship Collaborative
of South Carolina

Hana R. Winders,
PharmD, BCIDP

Prisma Health-Midlands,
Columbia, SC
