Augmentin' your allergy program: Antibiotic allergy evaluation and testing

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Let’s talk about

- Penicillin allergies and how to evaluate them
- Describe the decision points for evaluating a specific patient allergy and determining how to proceed
- Illustrate how R1 side chains are instrumental in determining cross reactivity for cephalosporins
- Overview of available services

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Epidemiology

- Penicillin allergy is the most commonly reported medication allergy
- Upon formal evaluation, less than 10% of patients who report an allergy are truly allergic
- Approximately 50% of penicillin allergies fade after 5 years and greater than 80% after 10 years
- Discrepancies are multifactorial and may include mislabeling of adverse events and misreported patient history in addition to waning sensitivities

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Shenoy E, et al. JAMA. doi:10.1001/jama.2018.19283

Clinical effects of a penicillin allergy label

- Increased length of stay
- Increased risk of ICU admission
- Increased risk of clinical failure
- Increased rates of *Clostridioides difficile*, MRSA, VRE
- Increased use of second line antibiotics
- Increased rates of surgical site infections
- Increased inpatient mortality

Macy E, Contreras R. *J Allergy Clin Immunol*, 2014. Jeffres MD, et al. *J Allergy Clin Immunol,* 2016. Picard M, et al. *J Allergy Clin Immunol Pract,* 2013.
Blumenthal KG, et al. *Clin Infectious Dis*, 2018. Charneski L, et al. SW. *Pharmacotherapy*. 2011.

Types of allergic reactions

	Type I Immediate	Type II	Type III	Type IV Delayed
Immune mediator	IgE	IgG	IgG	T lymphocytes
Mechanism	Antigen binds and crosslinks IgE, leading to degranulation	Drug antigen-specific IgG binds antigen on the cell and activated phagocytic cells	Immune complexes that activate complement and phagocytic cells	Activation of T lymphocytes
Timing of onset	Minutes to hours	Days to weeks	Days to weeks	Days to weeks
HSR	Anaphylaxis Angioedema Urticaria	Hemolytic anemia Thrombocytopenia	Serum sickness Drug fever	Maculopapular rash SJS/TEN

SJS- Stevens-Johnson Syndrome
TEN – Toxic epidermal necrolysis

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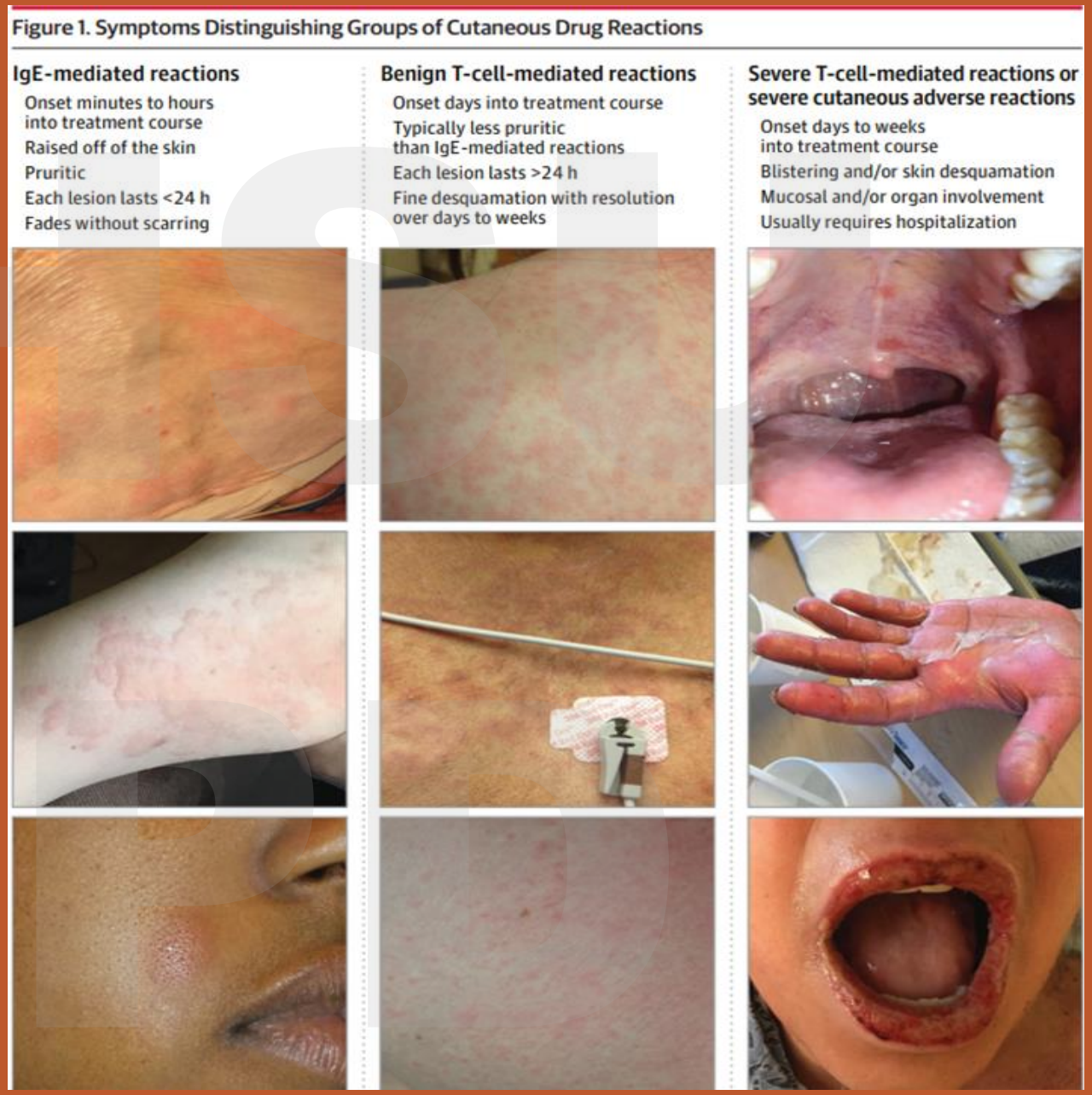
A refresher on allergies

	Type I Immediate	Type IV Delayed	Who knows?
Immune mediator	IgE	T lymphocytes	N/A
Mechanism	Antigen binds and crosslinks IgE, leading to degranulation	Activation of T lymphocytes	Unclear
Timing of onset	Minutes to hours	Days to weeks	I was a baby
HSR	Anaphylaxis Angioedema Urticaria	Maculopapular rash SJS/TEN	My mom told me

SJS- Stevens-Johnson Syndrome
TEN – Toxic epidermal necrolysis

Types of allergic reactions



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Elements of a penicillin allergy evaluation and testing program

- Detailed interview (Supported by the medical record)
- Penicillin skin testing (PST)
  - Prick Test
  - Intradermal Test
  - Oral challenge
- Graded oral challenge

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Most important questions

What was the reaction?

- IgE mediated?
  - How quickly did you react?
  - If rash, how quickly did rash come on and how long before it went away?

How long ago was it?

- Was it more than 10 years ago?

Have you had a penicillin more recently?

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Chart review

- Receipt of penicillins since index reaction
- Identify any medications that may interfere with testing
- Assess clinical need for specific antibiotics in the future

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Penicillin Skin Testing vs Graded Oral Challenge

Penicillin Skin Testing

- Oral challenge needed for confirmation
- Requires specialized training, equipment, materials and resources
- More expensive

Graded Oral Challenge

- Theoretically increased risk of reaction
- Less expensive

Graded challenges vs Desensitization

Graded challenge – Do you have an allergy?

- Method to determine if allergy exists or still exists
- Allergy can be removed after successful challenge

Desensitization – you have an allergy; how can we keep it from hurting you?

- Method to introduce a temporary state of tolerance to antibiotic
- Allergy cannot be removed after successful desensitization

Letters

Updates to penicillin allergy delabeling: Reducing the need for direct testing

Jordana F. Brown BS, Joyce Kim MD, YoungYoon Ham PharmD, Shyam R. Joshi MD

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Delabeling without challenge

- Documented administration of a penicillin, if not administration, at least dispense
- Not even slightly an allergy in the first place
- No reaction recalled to the administered or dispensed medication
  - In case of dispense, also that they took it
- Understanding and consent of deleting allergy label

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In summary

1. Penicillin allergies are extremely common in the medical record
2. Most patients with penicillin allergies can tolerate a penicillin
3. The penicillin allergy label has considerable clinical and financial consequences

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Allergy evaluation at OHSU – Walking through the algorithm

Case 1

JB is a 78 yo male with a penicillin allergy without any details or description. When asked about his reaction, he says that he was a baby and doesn't remember his reaction, but his mother had always told him to avoid penicillins. When pressed, he mentions that he thought maybe he developed a rash or something. What would be the most reasonable way to proceed?

A. Avoid penicillins, treat with non-beta lactam antibiotics
B. Penicillin Skin Testing, followed by oral challenge
C. Directly to oral challenge
D. Just give therapeutic dose penicillins without challenge

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Case 2

UI is a 45 yo woman who reports an allergic reaction to a penicillin given to her in a hospital when she was 10 years old. She was being treated for an infection with IV antibiotics when she developed an anaphylactic reaction and had to be given two doses of epinephrine. She has had no penicillin since then. What would be the most reasonable way to proceed?

A. Avoid penicillins, treat with non-beta lactam antibiotics

B. Penicillin Skin Testing, followed by oral challenge

C. Directly to oral challenge

D. Just give therapeutic dose penicillins without challenge

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Case 3

LB is a 36 yo male with a history of hives to penicillin 6 years ago. He describes distinct itchy, raised splotches of skin that immediately erupted within an hour of his taking some amoxicillin for a dental appointment. He took some diphenhydramine and the hives went away after a few hours. What would be the most reasonable way to proceed?

A. Avoid penicillins, treat with non-beta lactam antibiotics

B. Penicillin Skin Testing, followed by oral challenge

C. Directly to oral challenge

D. Just give therapeutic dose penicillins without challenge

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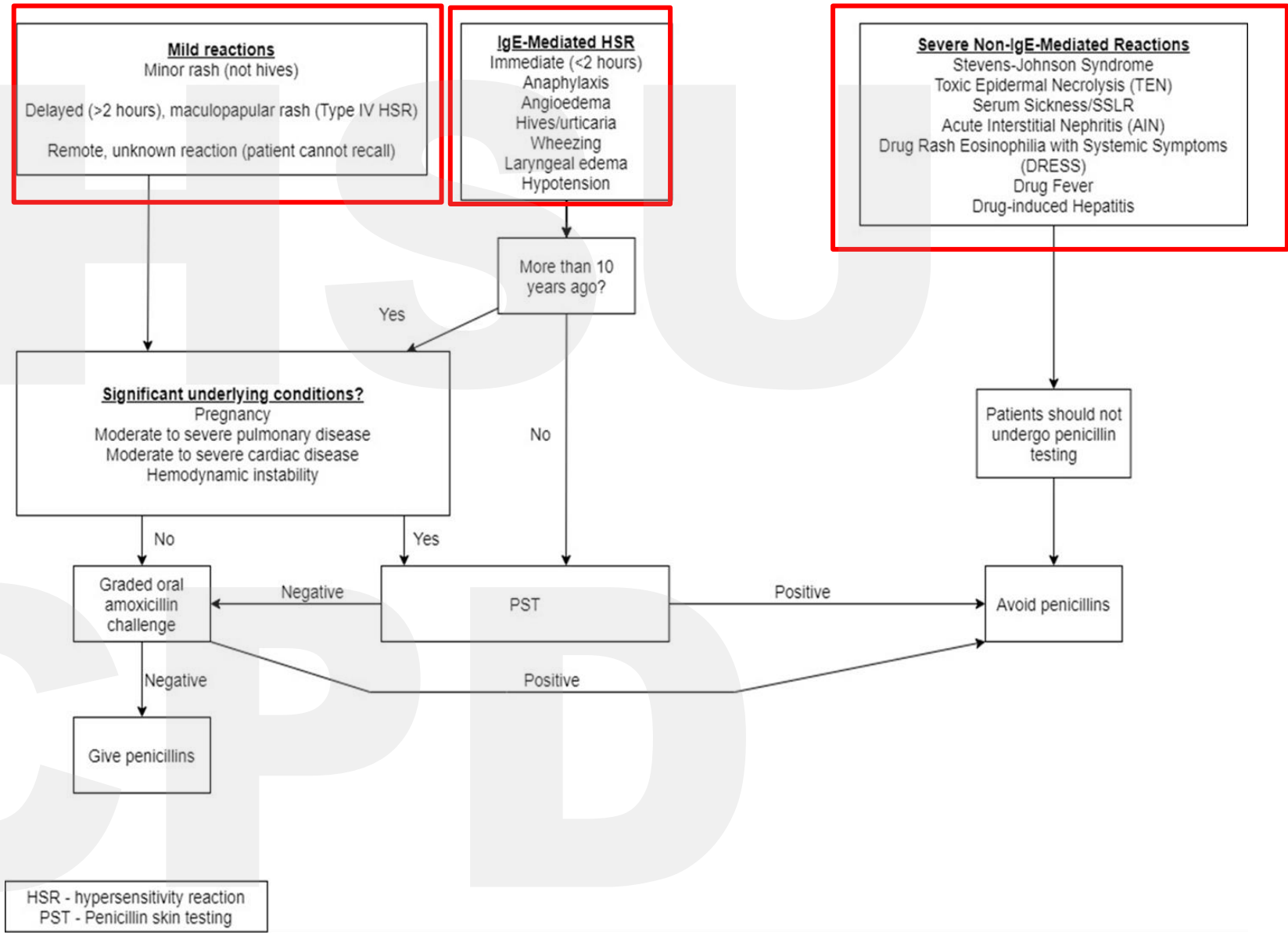
Evaluation algorithm



Cephalosporin allergies and cross reactivity

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Cross-reactivity

Loosely grouped into two categories

- Penicillin allergies → cephalosporins
- Cephalosporin allergies → other cephalosporins

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Case 4

WH is a 50 yo woman who had an allergic reaction to penicillin 4 years ago. She reports that she developed angioedema and her throat started to close up after a dose of ampicillin-sulbactam. She now requires surgery and the first line surgical prophylaxis antibiotic is cefazolin. What would be the most reasonable way to proceed?

A. Prophylaxis with second line, non-beta lactam antibiotic

B. Penicillin Skin Testing, followed by oral challenge

C. Directly to graded oral challenge

D. Give therapeutic dose cefazolin without challenge

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Case 5

BN is a 55 yo male who has an allergy of hives to cephalosporins in his chart. You talk to the patient after a detailed chart review and you find that the index reaction was to cephalexin, which he received for cellulitis 10 years ago. He is due for surgery where the first line antibioticfor prophylaxis would be cefazolin. What would be the most reasonable way to proceed?

A. Avoid cephalosporins, give carbapenem
B. Avoid beta lactams, give fluoroquinolone
C. Intravenous challenge with cefazolin
D. Give therapeutic dose cefazolin without challenge

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Cephalosporin allergies

- Cephalosporin allergies are not a class effect
- Detailed interview can be helpful in narrowing down cephalosporin allergies

Fig. 1 **General structure of cephalosporins**

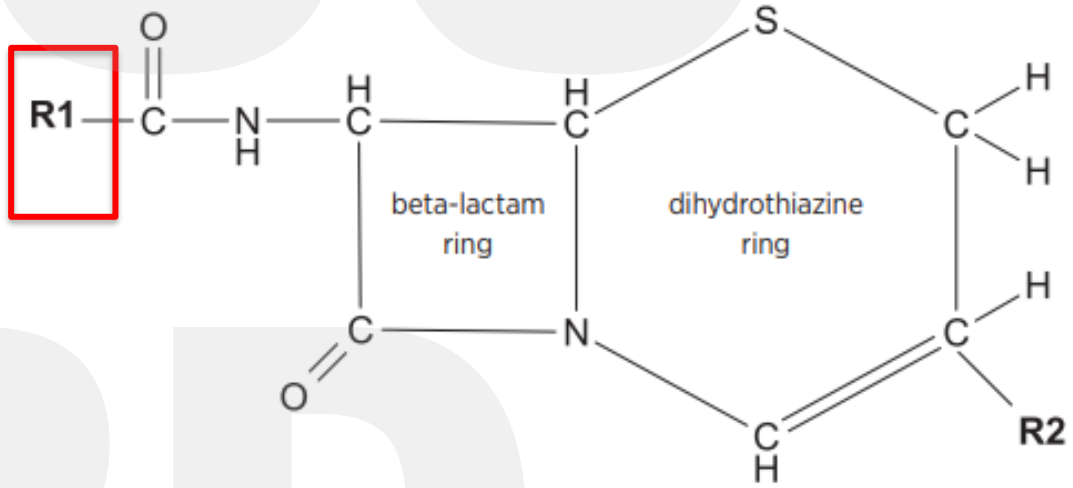

Image source: Yuson et al. Australian Prescriber Vol 41, N 2. April 2018

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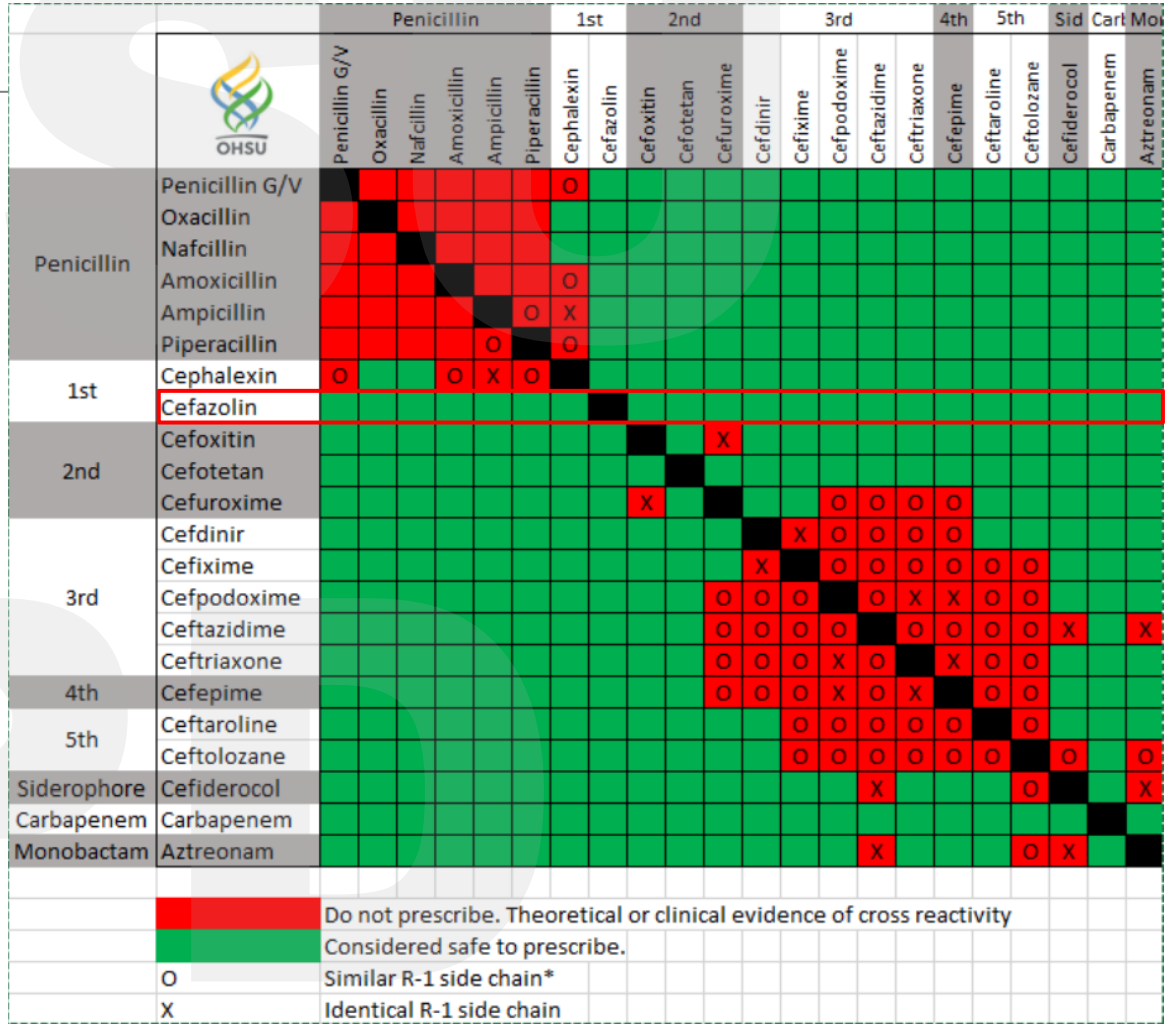
Cross reactivity

- Early studies were confounded by contamination
- Dependent on the R1 side chain



		Penicillin						1st		2nd			3rd					4th	5th		Sid	Carb	Mon
	OHSU	Penicillin G/V	Oxacillin	Nafcillin	Amoxicillin	Ampicillin	Piperacillin	Cephalexin	Cefazolin	Cefoxitin	Cefotetan	Cefuroxime	Cefdinir	Cefixime	Cefpodoxime	Ceftazidime	Ceftriaxone	Cefepime	Ceftaroline	Ceftolozane	Cefiderocol	Carbapenem	Aztreonam
Penicillin	Penicillin G/V							O															
	Oxacillin																						
	Nafcillin																						
	Amoxicillin							O															
	Ampicillin						O	X															
	Piperacillin					O		O															
1st	Cephalexin	O			O	X	O																
	Cefazolin																						
2nd	Cefoxitin											X											
	Cefotetan																						
	Cefuroxime									X					O	O	O	O					
3rd	Cefdinir													X	O	O	O	O					
	Cefixime												X		O	O	O	O	O	O			
	Cefpodoxime											O	O	O		O	X	X	O	O			
	Ceftazidime											O	O	O	O		O	O	O	O	X		X
	Ceftriaxone											O	O	O	X	O		X	O	O			
4th	Cefepime											O	O	O	X	O	X		O	O			
5th	Ceftaroline													O	O	O	O	O		O			
	Ceftolozane													O	O	O	O	O	O		O		O
Siderophore	Cefiderocol															X				O			X
Carbapenem	Carbapenem																						
Monobactam	Aztreonam															X				O	X		

	Do not prescribe. Theoretical or clinical evidence of cross reactivity
	Considered safe to prescribe.
O	Similar R-1 side chain*
X	Identical R-1 side chain

Steps in a cephalosporin allergy evaluation

- Most important: Which cephalosporin did the patient react to?
- Let R1 side chains guide evaluation
- If dissimilar side chain, can give without issue
- If similar but not identical side chain, can consider a challenge to be sure

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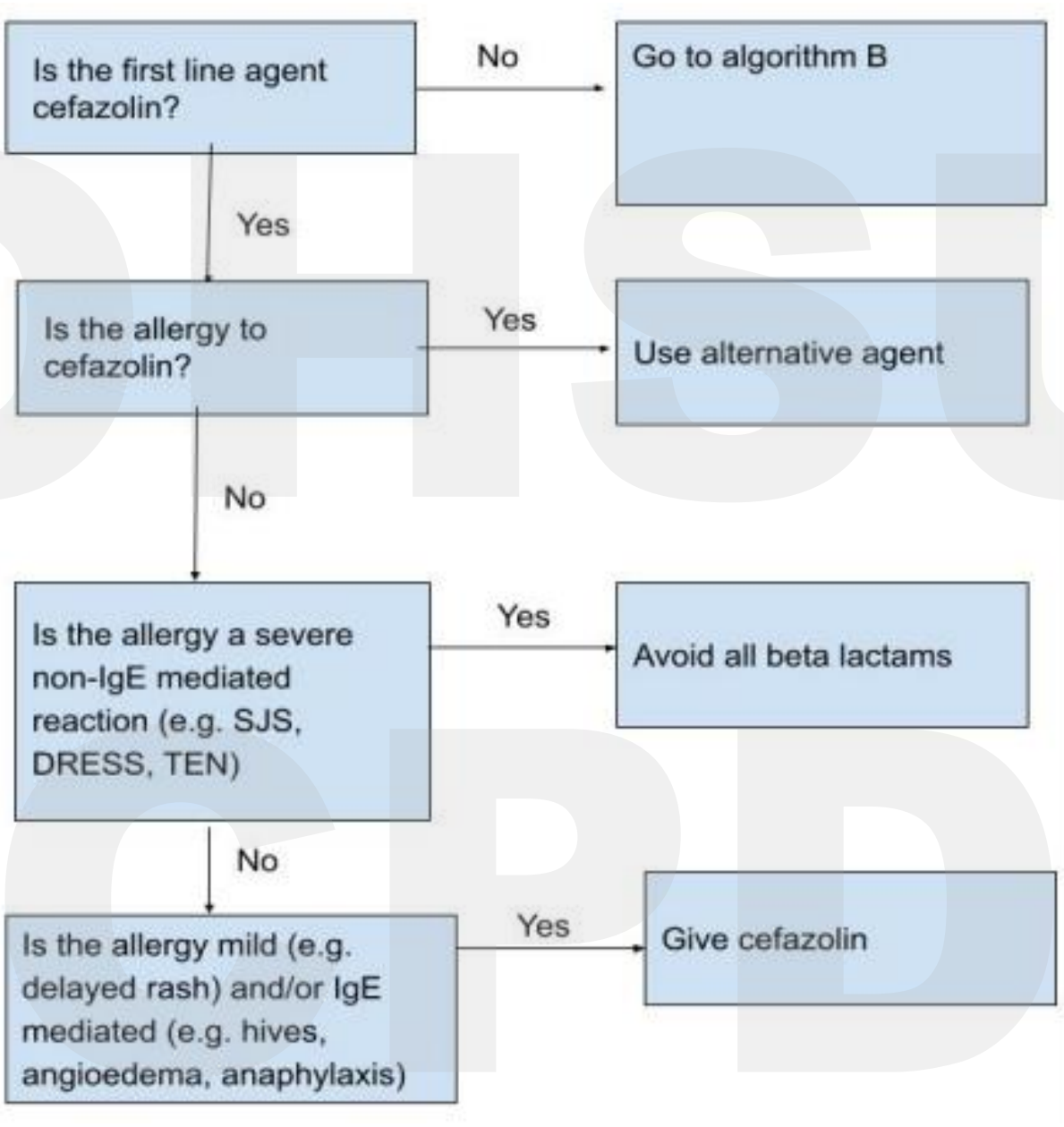
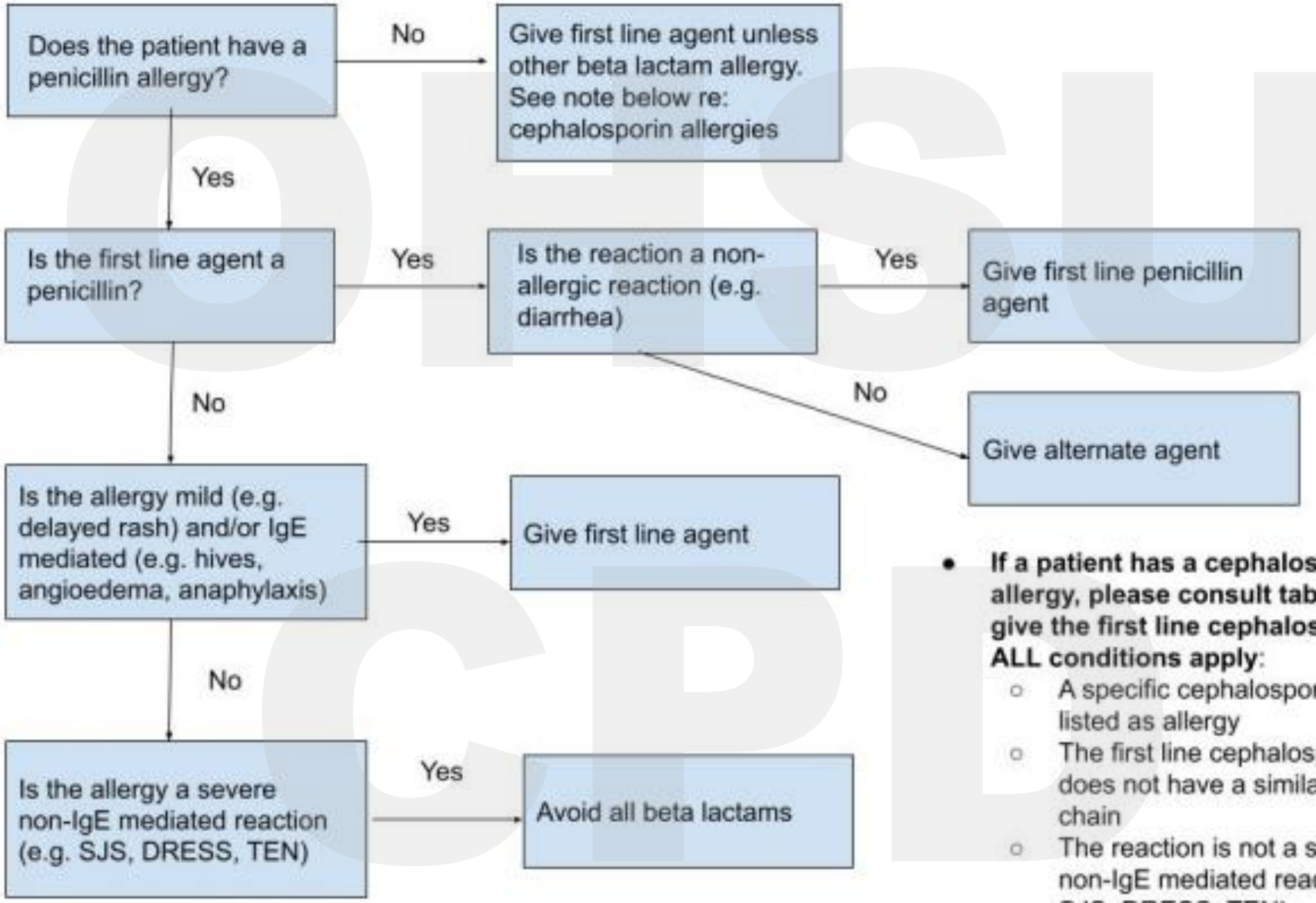

Is the first line agent cefazolin?
No
Go to algorithm B
Yes
Is the allergy to cefazolin?
Yes
Use alternative agent
No
Is the allergy a severe non-IgE mediated reaction (e.g. SJS, DRESS, TEN)
Yes
Avoid all beta lactams
No
Is the allergy mild (e.g. delayed rash) and/or IgE mediated (e.g. hives, angioedema, anaphylaxis)
Yes
Give cefazolin



- **If a patient has a cephalosporin allergy, please consult table 2 and give the first line cephalosporin if ALL conditions apply**:
  - A specific cephalosporin is listed as allergy
  - The first line cephalosporin does not have a similar side chain
  - The reaction is not a severe non-IgE mediated reaction (e.g. SJS, DRESS, TEN)

Table 2: β-Lactam agents with common cross reactivity

If mild reaction to:	AVOID these agents:
Penicillin G	Other penicillins, Cefoxitin
Amoxicillin	Other penicillins, Cephalexin
Ampicillin	Other penicillins, Cephalexin
Zosyn (pip-tazo)	Other penicillins
Cefazolin	None (no cross reactivity with any other β-lactam)
Cephalexin	Amoxicillin, Ampicillin
Cefoxitin	Penicillin G, Cefuroxime
Cefuroxime	Cefoxitin, Cefotaxime, Cefepime, Ceftriaxone, Ceftazidime
Ceftriaxone	Cefotaxime, Ceftazidime, Cefepime, Cefuroxime
Cefotaxime	Ceftriaxone, Cefuroxime, Ceftazidime, Cefuroxime
Ceftazidime	Ceftriaxone, Cefotaxime
Cefepime	Cefuroxime, Ceftriaxone, Cefotaxime

Note: Only commonly used agents are listed. For complete list, see Table 2 (p. 339) in Hermanides et al. *Presumed ß lactam allergy and cross-reactivity in the operating theater.* Anesthesiology, Aug 2018, 129(2): 335-42.

Procedure	1st Line Agent (no β-Lactam allergies)	2nd Line agent (for pts with severe β-Lactam allergies)
CARDIAC		
Sternotomy/CABG/valve/TAVR/PPM Implant		Vancomycin pre-op and post-CPB
Heart transplant		Vancomycin pre-op and post-CPB
Heart transplant with hx of VAD		Ciprofloxacin PLUS vancomycin pre-op and post-CPB
VAD placement		Ciprofloxacin PLUS vancomycin pre-op and post-CPB
THORACIC		Ciprofloxacin PLUS Vancomycin
GASTRODUODENAL		Ciprofloxacin PLUS Vancomycin
Pancreaticoduodenectomy (Whipple)	Piperacillin-tazobactam	Vancomycin PLUS Ciprofloxacin PLUS Metronidazole
Other (e.g., bariatric, vagotomy, anti-reflux)		Vancomycin PLUS Ciprofloxacin
BILIARY TRACT		Vancomycin PLUS Ciprofloxacin OR gentamicin
SMALL INTESTINE		
Appendectomy		Ciprofloxacin PLUS MetroNIDAZOLE
Non-obstructed		Vancomycin PLUS Ciprofloxacin OR gentamicin
Obstructed		Ciprofloxacin PLUS MetroNIDAZOLE
Hernia repair		Vancomycin
COLORECTAL		Ciprofloxacin PLUS MetroNIDAZOLE
GENITOURINARY		
Penile implant or other prosthesis		Vancomycin PLUS Gentamicin
Lower tract instrumentation with risk factors for infection		Ciprofloxacin OR Gentamicin
Clean, without entry into the urinary tract		Vancomycin
Clean, with entry into the urinary tract		Ciprofloxacin
Clean-contaminated		Ciprofloxacin PLUS Vancomycin
HEAD AND NECK		
Clean		None
Clean with placement of prosthesis		Vancomycin
Clean-contaminated surgery with exception of tonsillectomy and functional endoscopic sinus procedures	Ampicillin/Sulbactam	Vancomycin
NEUROSURGERY		Vancomycin
OB/GYN		
C-Section		Clindamycin
Hysterectomy (abdominal or vaginal)		Ciprofloxacin PLUS Metronidazole
ORTHOPEDIC		
Clean operations involving hand, knee, foot, and notinvolving implantation of foreign materials		None
All other orthopedic procedures		Vancomycin
VASCULAR		Vancomycin
TRANSPLANT		
Liver	Ampicillin PLUS Ceftriaxone	Ciprofloxacin* PLUS Vancomycin *For patients on fluoroquinolone prophylaxis for SBP within the previous year: Aztreonam PLUS Vancomycin
Kidney		Ciprofloxacin PLUS Vancomycin
Simultaneous kidney-pancreas	Ampicillin-sulbactam PLUS Ceftriaxone	Ciprofloxacin PLUS Vancomycin PLUS MetroNIDAZOLE

Summary

- The vast majority of patients with a penicillin allergy label are not truly allergic
- The presence of penicillin allergy can have significant clinical and financial consequences
- Cephalosporin cross reactivity and allergies should be evaluated based on the similarity of the R1 side chain
- You can give cefazolin pretty much all of the time

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