

Beta-lactam Allergies in Persons with HIV

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Disclosures

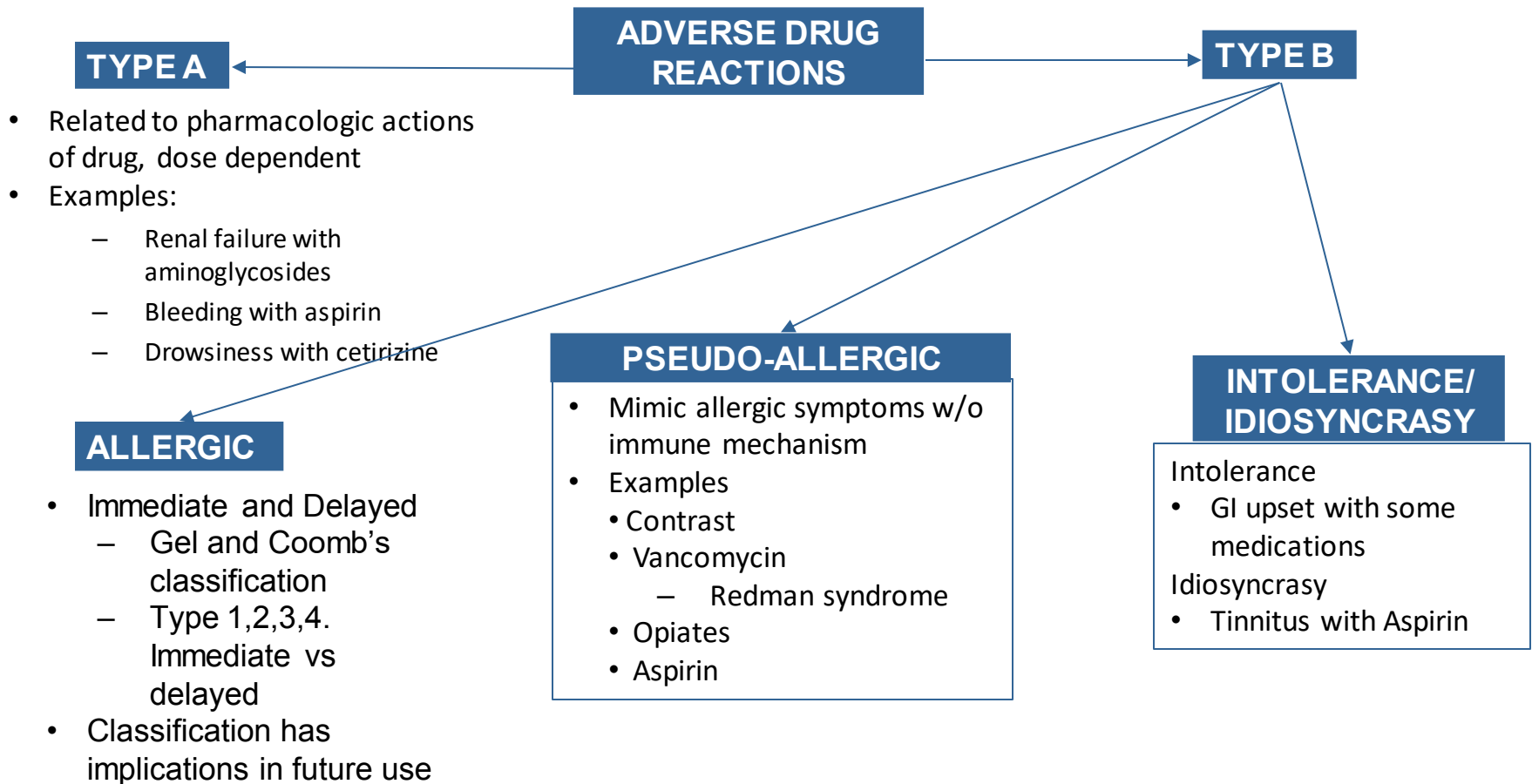
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Objectives



- **Types of drug allergies**
- **Recognizing the symptoms of drug allergy**
- **Beta-lactam allergies in HIV**
- **Diagnostic modalities**
- **Importance of delabeling**
- **Graded challenge/test dose**
- **Desensitization**

Classification of Adverse Drug Reactions



Characterizing the Reaction

26-year-old male with h/o HIV presents with sore throat, fever 102.4, rapid strep test is positive, but he tells you that he had rash after taking penicillin few years ago.

What would you ask him?

- Remote or recent
- Immediate vs delayed
- Type of rash
- Skin peeling
- Mucous membrane involved
- Systemic symptoms
- Has he received any other penicillin like ampicillin, amoxicillin, or cephalosporins

Immediate Reactions(IgE mediated/Type1)

- Within 1-6hrs
- Likely IgE mediated
- Urticaria/hives, angioedema, respiratory symptoms (bronchospasm, cough, dyspnea), GI symptoms (nausea, vomiting, diarrhea, abdominal pain)(>90% will have cutaneous signs)
- Hives can occur after few days-delayed but still can be IgE mediated
- Skin test helpful in IgE mediated reactions



“I was covered in hives within few minutes”

“I had facial redness and lips got swollen within a few hours”

“My rash resolved after Benadryl”- hives

“Had redness all over, my throat was closing and I had trouble breathing”

“I started itching all over - my face was red”

“Rash resolved soon after stopping the medication, rash was gone in a day”



Delayed/Maculopapular Reactions(Type 4)

- 6hrs - 7days (variable onset)
- Mostly non IgE mediated , T cell mediated
- Erythema, fine papules, itchy/non itchy, burning
- Usually begins on trunk, spreads to extremities, typically symmetric
- Often resolves with scaling/peeling

“Rash appeared all over after 4 days of starting the medication”

“The rash lasted for 7-10 days, they gave me prednisone to clear the rash”

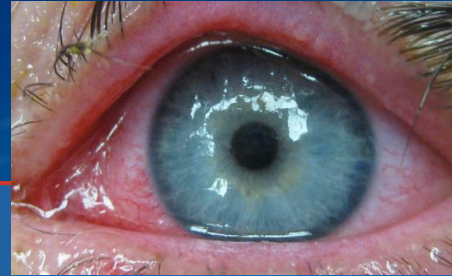
“My skin started peeling after few days”



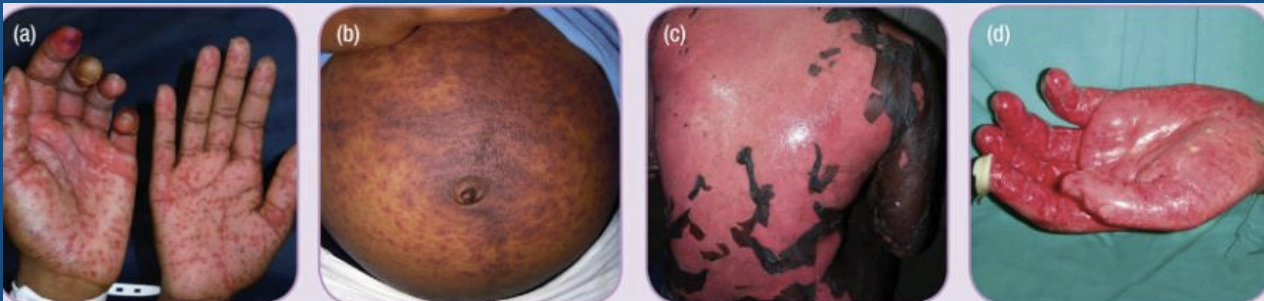
Severe Cutaneous Adverse Drug Reactions

- SJS/TEN - **Stevens-Johnson syndrome** / Toxic epidermal necrolysis
- DRESS syndrome - Drug rash with eosinophilia and systemic symptoms

SJS/TEN Symptoms:

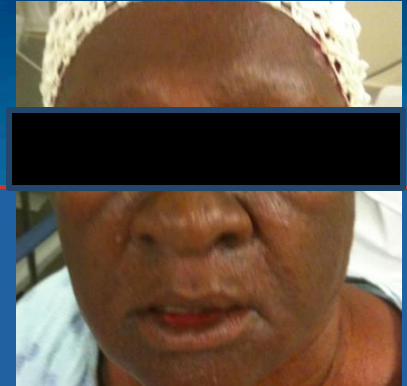


- Latent period- 4-28 days
- Preceded by a prodrome of fever, general malaise, nonproductive cough, stinging eyes, and a sore mouth
- Often confused with an URI
- Rapidly progress to an exanthem of macules and targetoid lesions, epidermal detachment, bullae and erosive mucositis of at least 2 surfaces, usually within 3 days
- Early painful erythema of the palms and soles is a major feature of SJS/ TEN
- The hallmark feature of SJS/TEN -mucosal involvement (present in 80% of cases)- oral > ocular and genital



Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (a) focal tender erythematous macules on the palms in SJS (b) focal areas of early epidermal necrosis in a background of erythema in a pregnant woman with SJS (c and d) stripping of the epidermis on the back and palms in TEN.

DRESS Syndrome



Clinical features:

- Latent period is 2-8 weeks
- Urticaria-like plaques or an exanthem
 - Other types-vesicles, pustules, cheilitis, purpura, targetoid lesions, and erythroderma have been reported
- Fever, edema (particularly facial and acral puffiness)
- Lymphadenopathy
- Leukocytosis, eosinophilia, and/or atypical lymphocytosis
- Long-standing severe lesions are characterized by extensive scaling referred to as exfoliative dermatitis
- When could this be DRESS and not just a benign drug exanthem
 - 50% of the body surface area, severe edema, infiltrated skin lesions, scaly erythema, and purpura
- Organ involvement

Intolerance Prevalence and Immunogenicity of Common Antibiotics

Antibiotic or antibiotic family	Intolerance prevalence	IgE-mediated allergy	T-cell-mediated delayed hypersensitivity	Intrafamily immunologic cross-reactivity
Penicillins	7.9%	Possible	Possible	Common
Sulfonamides	4.3%	Unlikely	Possible	Unlikely
Macrolides	1.2%	Unlikely	Unlikely	Unknown
Cephalosporins	1.1%	Possible	Possible	Unlikely
Tetracyclines	0.70%	Unlikely	Unlikely	Unknown
Quinolones	0.46%	Possible	Unknown	Common
Nitrofurantoin	0.24%	Unlikely	Unlikely	NA
Clindamycin	0.20%	Unlikely	Possible	NA
Metronidazole	0.15%	Unlikely	Possible	NA

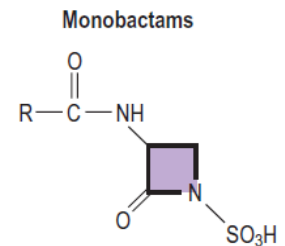
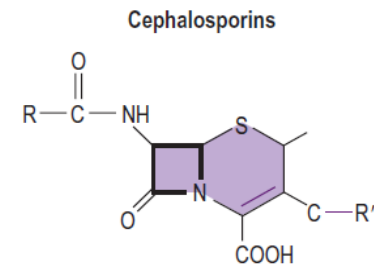
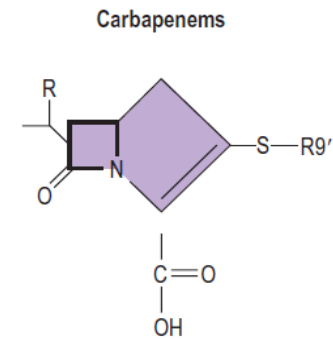
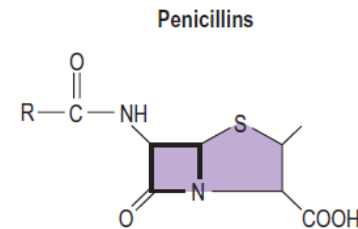
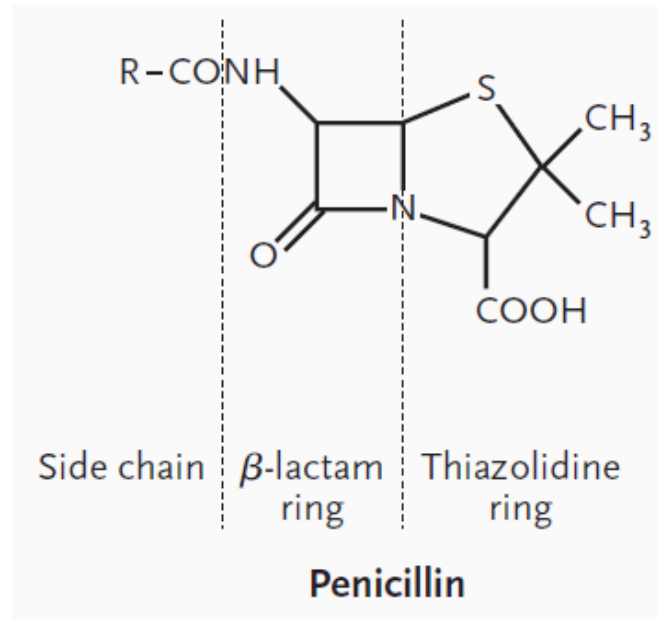
Beta-lactams

2 major classes

- Penicillins
- Cephalosporins

4 minor classes

- Carbapenems
- Monobactams
- Oxacephems
- Clavams



Penicillin Allergy

- **Most common** reported allergy- **10%** of the population
- Among these - >90% able to tolerate
 - Based on large scale skin test studies, oral challenge studies
- Anaphylaxis - 1 in 1000
- Severe cutaneous reactions - 1 in 10,000
- Fatal reactions after oral penicillin exposures – 1 in 100,000,000 amoxicillin courses administered over 35 years

Penicillin Skin Testing and Serum IgE

- **Penicillin Skin Test:**
 - **Negative predictive value around 97%**
 - Positive predictive value between 40% and 100%
 - **Confirm with oral challenge when negative**

- **Specific Serum IgE to Penicillin:**
 - Specificity (97%-100%) but lower sensitivity (29%-68%)
 - Rarely used in clinical practice
 - Can be helpful in patients with recent anaphylaxis

Drawbacks of Penicillin Skin Testing

- Variability in testing and interpretation
- False positive reactions
- Oral challenges studies on low positives vs negative skin test
 - No difference in prevalence of adverse reaction

Delabeling Penicillin Allergy

- Delabeling by history alone
 - Non allergic mild subjective symptoms
- Delabeling by skin testing followed by oral challenge
 - Commonly done based on guidelines
- Delabeling by oral challenge without skin testing
 - Multiple recent studies have shown the safety of direct challenges in low risk patients

Case

50-year-old male with the past medical history of HIV and diabetes presents with a penile lesion, diagnosed with early syphilis has history of allergies to penicillin, doxycycline, ciprofloxacin, ibuprofen, cetirizine.

Allergy history

- Penicillin: “My mother told me that I am allergic to penicillin” when I was a child (“I don’t know what happened”)
- Doxycycline: “I became pretty sick with fever and rash after few days, I had to be hospitalized”
- Ciprofloxacin: “I had diarrhea”

What would you do?

1. Refer him for penicillin skin test while you treat him with an alternative antibiotic
2. Can consider test dose of amoxicillin and observe
3. Can give Doxycycline since his history of fever is less likely to be hypersensitivity

Proposed Screening Questionnaire to Grade Penicillin Allergy History Risk

Penicillin allergy questionnaire	Y e s	N o
1. Did your reaction occur within the past year?		
2. Did your reaction involve any systemic symptoms other than a rash or other skin symptoms? If unknown, mark NO.		
3. Was your reaction life-threatening (i.e., severe anaphylaxis requiring epinephrine, Emergency Room visit, hospitalization, intubation)?		
4. Did your reaction involve blistering, ulceration, sloughing of your skin or lining of your mouth, eyes, genitals—OR—diagnosed with Stevens–Johnson syndrome or toxic epidermal necrolysis?		
5. Did your reaction involve any organ dysfunction/failure—OR—were you diagnosed with serum sickness, drug reaction with eosinophilia, acute interstitial nephritis?		

- If the patient has tolerated any penicillins following their initial reaction, they are delabeled and no additional testing is indicated
- If all questions 1–5 are NO, patient is deemed low risk, proceed to oral challenge with 250 mg amoxicillin. Monitor for 1 h
- If any answers 1–3 are YES, patient is higher risk, skin testing recommended and if negative with adequate controls, proceed to 250 mg amoxicillin challenge
- If any answers 4–5 are YES, continued avoidance recommended

Delabeling by Direct Oral Challenge

- Limitations of skin testing in low-risk patients
- Only minority of patients with penicillin allergy are truly allergic
- Risk of anaphylaxis is low with oral amoxicillin
- Skin testing not available everywhere
- History has shown to be effective in identifying low risk patients
- Multiple studies in the recently shown the safety of direct oral challenge (1-3% immediate rash, 3-6% delayed non severe rash, no systemic reaction)

Guidelines for Direct Oral Challenges

Direct oral amoxicillin challenge can be performed in any patients with a history of the following symptoms associated with penicillin occurring more than 12 months ago:

- Any benign rash
- GI symptoms
- Headaches
- Other benign somatic symptoms
- Unknown history

Request allergy to penicillin skin test first if

- The reaction to penicillin has occurred within the past 12 months
- The patient has any history of shortness of breath or anaphylaxis associated with penicillin and proceed to amoxicillin challenge only if skin test negative

Do not perform any penicillin allergy testing if there is a history of penicillin-associated

- Blistering rash involving $\geq 10\%$ of body surface area with skin loss
- Hemolytic anemia
- Nephritis
- Hepatitis

Cephalosporin Antibiotics

- Rate of anaphylaxis - 5 in 901,908 courses of oral cephalosporins and 8 in 487,630 courses for parenteral exposures in one large US-based health plan
 - Cephalexin most common - 1.1% and Cefazolin-most common perioperative
- Previously thought crossreactivity rate with penicillins- 10%
 - Contamination of early generation cephalosporins by penicillin
- Recent studies - low levels of immunologic cross-reactivity with penicillins - around 2%
- Beta-lactam ring is not the major antigenic determinant
- Cross-reactivity higher with penicillins with similar R chain than a beta-lactam ring
 - Ex: Amoxicillin with cefadroxil and Ampicillin with cephalexin (R1 chain)

R Chain/Cross-Reactivity

Table 16. Groups of β -Lactam Antibiotics That Share Identical R₁-Group Side Chains^a

Amoxicillin	Ampicillin	Ceftriaxone	Cefoxitin	Cefamandole	Ceftazidime
Cefadroxil	Cefaclor	Cefotaxime	Cephaloridine	Cefonicid	Aztreonam
Cefprozil	Cephalexin	Cefpodoxime	Cephalothin		
Cefatrizine	Cephradine	Cefditoren			
	Cephaloglycin	Ceftizoxime			
	Loracarbef	Cefmenoxime			

^a Each column represents a group with identical R₁ side chains.

Table 17. Groups of β -Lactam Antibiotics That Share Identical R₂-Group Side Chains^a

Cephalexin	Cefotaxime	Cefuroxime	Cefotetan	Cefaclor	Ceftibuten
Cefadroxil	Cephalothin	Cefoxitin	Cefamandole	Loracarbef	Ceftizoxime
Cephradine	Cephaloglycin		Cefmetazole		
	Cephapirin		Cefpiramide		

^a Each column represents a group with identical R₂ side chains.

- With a reported cephalosporin allergy, testing and oral challenge should be with a cephalosporin that does not share the same R-chain

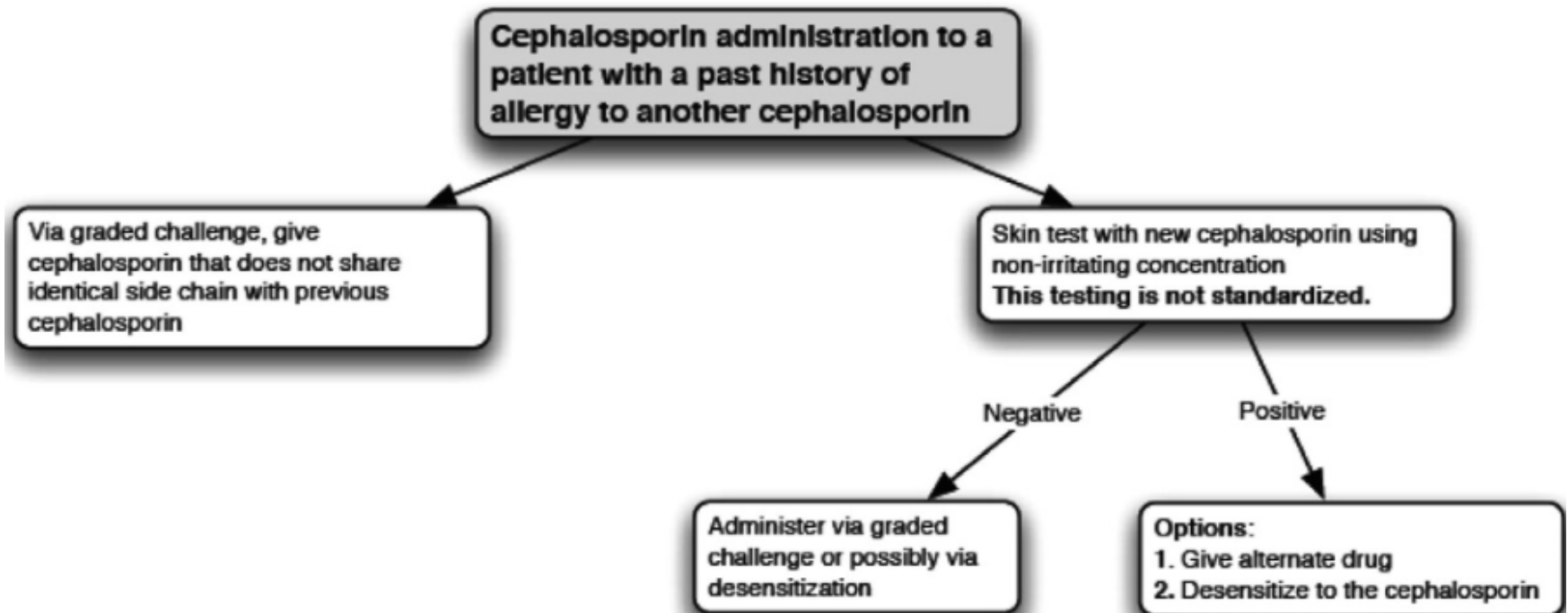
Cephalosporin Allergy

45-year-old male with HIV with gonorrhea needs ceftriaxone + azithro, but has history of generalized hives after a procedure 3 years ago which was presumed secondary to cefazolin.

What would be your choice?

1. Desensitize for ceftriaxone
2. Avoid all cephalosporins
3. Can consider skin testing with ceftriaxone, if negative can do graded challenge or graded challenge with ceftriaxone

Giving Cephalosporin in Cephalosporin Allergy



Case

36-year-old MSM with gonorrhea. He reports history of hives within 30 min of taking penicillin about 5 years ago. Denies any systemic symptoms. **What is the best choice?**

1. Can use 3rd generation cephalosporin (ceftriaxone) as part of treatment
2. Recommend avoiding penicillin and cephalosporins
3. Treat him with azithromycin only
4. Treat with amoxicillin since penicillins do not cross-react with amino-penicillins

Using Cephalosporin in Penicillin Allergy

- Cross reactivity may be higher in 1st generation
- Crossreactivity negligible with 2nd and 3rd generation cephalosporin
- C.diff more common than allergic reaction in patients with h/o penicillin allergy than reacting to cephalosporins
- Penicillin allergy testing is not useful in evaluating the risk of cephalosporin-associated reactions
- Skin testing and *in vitro* testing are not well enough validated
- Typically we choose alternative cephalosporin, which ideally does not share a side chain is a safe and commonly used approach in low risk allergic reactions

Pichichero ME et al. Safe use of selected cephalosporins in penicillinallergic patients: a meta-analysis. *Otolaryngol Head Neck Surg* 2007;136:340-7.

Pichichero ME et al. Penicillin and cephalosporin allergy. *Ann Allergy Asthma Immunol* 2014;112:404-12.

Lee QU. Use of cephalosporins in patients with immediate penicillin hypersensitivity: cross-reactivity revisited. *Hong Kong Med J* 2014;20:428-36.



Penicillin in Cephalosporin Allergic

- If anaphylaxis to 1st and 2nd generation cephalosporins, recommend skin testing with penicillin before challenge
- If anaphylaxis to 3rd or 4th generation cephalosporins- oral challenge with penicillin can be considered
- If benign rash with cephalosporins- can consider direct challenge with penicillin(keep in mind some cephalosporins cross react with Amoxicillin and Ampicillin R chains)

Key Points

- Documentation of symptoms and temporality
- Skin testing if appropriate. Challenge if skin test negative
- Consider direct challenge/test dose in low risk patients
- Desensitize if likely to be allergic

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