Management of Patients with Reported Antibiotic Allergies

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Disclosures

- None

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Objectives

- Be able to compare drug allergy vs adverse drug reaction
- Be able to identify clinical history consistent with IgE mediated hypersensitivity
- Be able to identify clinical history consistent with severe delayed hypersensitivity reactions
- Determine when referral for antibiotic allergy skin test is warranted
- Describe the difference of the clinical outcomes of penicillin skin test compared to other antibiotic skin tests
- Identify the risk of cross reaction between different beta lactam antibiotics
- Determine when a drug challenge is a reasonable option
- Determine when desensitization is warranted

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Adverse Drug Reaction (ADR)

"A response to a medicine which is noxious and unintended, and which occurs at doses normally used in man"

World Health Organization. 1972;498:1–25

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Adverse Drug Reaction

Type A (80%)
- Predictable
- Dose Dependent
- Examples
  - Overdose
  - Side effects: sedation
  - Secondary effects
  - Drug-drug interactions

Type B (15-20%)
- Unpredictable
- Dose independent
- Drug Allergy is part of this group
- Examples
  - Intolerance
  - Idiosyncratic
  - Pseudoallergic
  - Hypersensitivity reactions = drug allergy

Blumenthal K Allergy Asthma Proc. 2014 35(3):197-203

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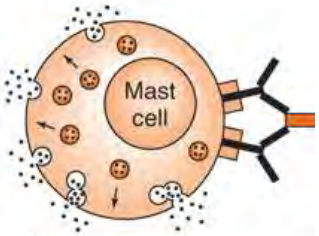
Drug Allergy

Histamine
Tryptase
Many other inflammatory mediators



Mediators (e.g., histamine) released from mast cells

"An immunologically mediated drug hypersensitivity reaction"

Johansson SG, et al. J Allergy Clin Immunol. 2004

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"Doc my pinky hurts, must be this new medicine!"

Everything is an allergy

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Nextshark.com

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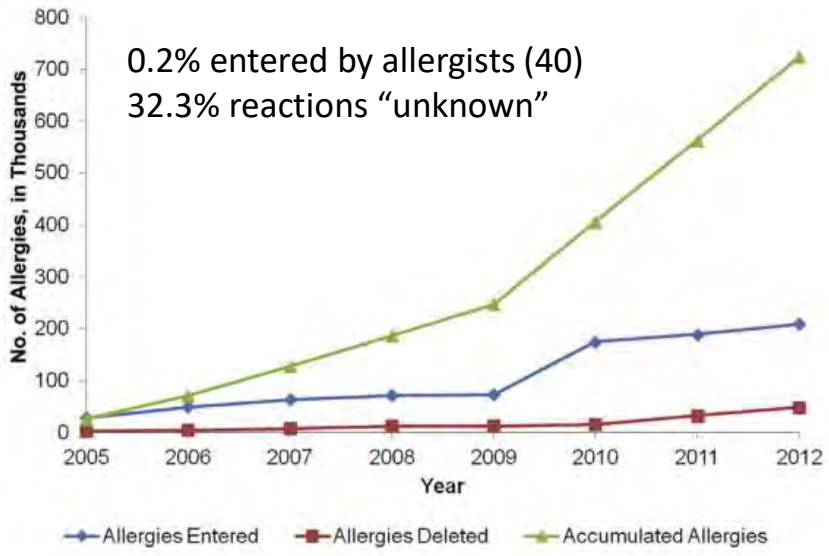
Allergies Accumulate



Blumenthal et. al 2017

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Detective Work

- Long and inaccurate drug allergy lists
- Adverse drug reaction vs drug allergy
- Poor documentation (EMR)
- Drug allergy testing
  - Typically, not validated
  - Time consuming
  - Requires care coordination and special resources (pharmacy)
- Challenges and desensitizations require emergency services

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Risk Factors for Drug Hypersensitivity

- Drug
  - Chemical properties and molecular weight (antigen)
  - Higher dose and longer duration
  - IV route more than others
  - Repetitive exposure
- Patient
  - Concurrent illness
    - HIV: TMP/SMP allergy 9-34%
    - EBV: ampicillin/amoxicillin induced rash 30-100%
  - Older age
  - Female
  - NOT atopy

Rich JD Ann Allergy Asthma Immunol. 1997;79(5):409-14.
Chovel-Sella A Pediatrics. 2013 May;131(5):e1424-7
Blumenthal K Allergy Asthma Proc. 2014 35(3):197-203

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Immunology and Drug Hypersensitivity

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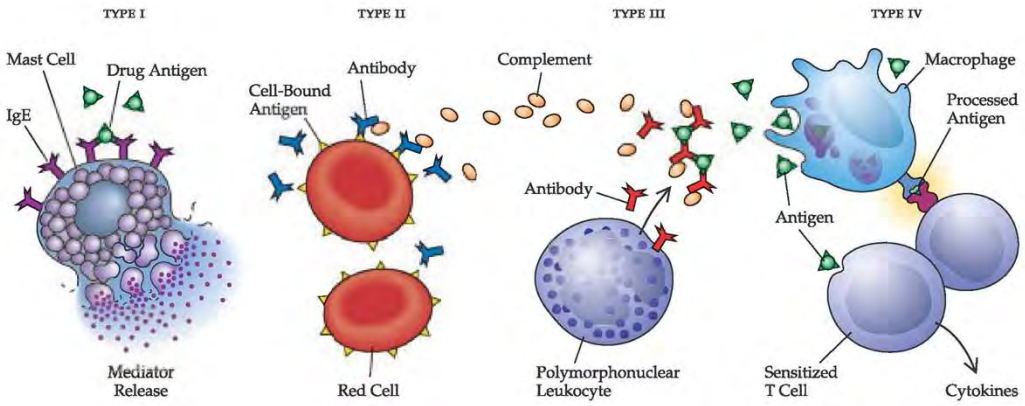
Gell and Coombs

- Most drugs cause 1 or 2 types of reactions
- Some drugs can cause all 4
  - Penicillin



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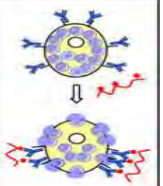
Immediate Type 1 Hypersensitivity (IgE-mediated)

	Type I
Immune reactant	IgE
Antigen	Soluble antigen
Effector	Mast-cell activation
	
Example of hypersen-sitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis

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Type 1 Hypersensitivity (IgE-mediated)

- Typically <2 hrs.. after exposure
- Reproducible (every exposure)
- Can worsen with repeat exposure
- Skin testing generally helpful
- Desensitization generally possible
- Beta lactams and Quinolones

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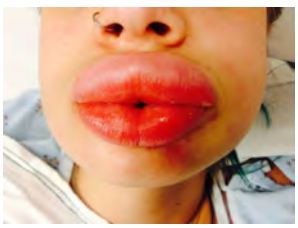
IgE-Mediated Symptoms

Palmar erythema and pruritus



Angioedema, often asymmetric

Urticaria, erythematous, raised pruritic lesions, with each lesion lasting hours (but <24 hrs.)

1. Cutaneous findings
2. GI: nausea, dysphagia, vomiting, diarrhea
3. Respiratory: throat tightness, cough, dyspnea, wheezing, stridor, hypoxia
4. CV: hypotension, tachycardia
5. Neurologic: confusion, LOC

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Urticaria

- IgE-mediated: within 30-60 minutes
- Pseudoallergic: within 90 minutes
- Delayed: days to weeks after therapy
  - Unknown T cell reactions
  - Coexisting viral infection
  - Fevers, arthralgias: serum sickness
  - End organ dysfunction: DRESS syndrome

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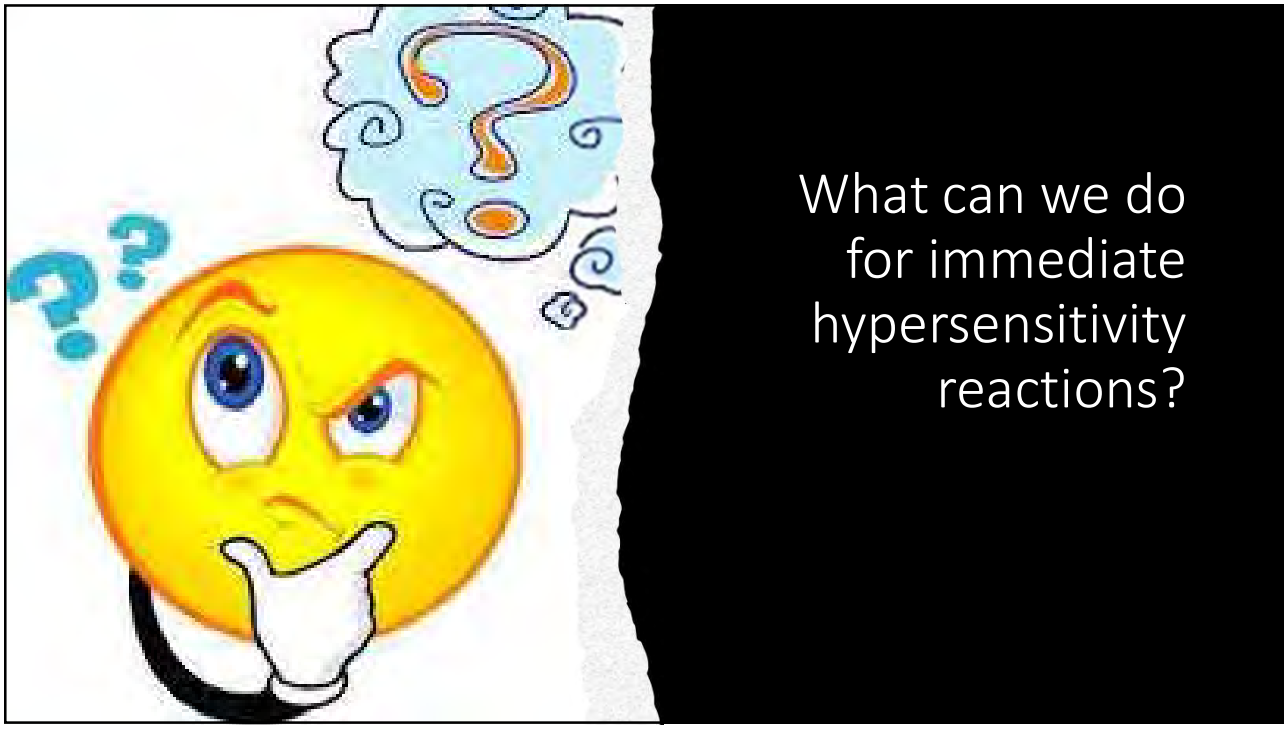

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Drug Allergy Skin Testing

Skin Prick

Intradermal test

- Type 1 reactions
- Possible Type 1 reactions
- Unknown
- Delayed reactions – delayed readings

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Drug allergy skin test procedure is not perfect!

- Only validated skin test is for penicillin
- Many non-irritating concentrations documented in the literature
- Drugs that cannot be tested
  - Sulfamethoxazole, vancomycin (other medications)
- Hypersensitivity reactions that cannot be assessed
  - Severe Cutaneous Adverse Reactions (SCARs)
  - Exfoliative dermatitis
  - Interstitial nephritis
  - Hemolytic anemia

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Management of IgE Mediated Reactions

Drug Challenge

- Negative skin test or unavailable
- Low risk
  - Beta-lactams in penicillin allergic patients
  - Low grade possible IgE mediated symptoms
  - Vague history
- Need to prove not allergic
- Does NOT modify immune response
- 2-3 steps (1/100, 1/10, full)
- Next dose in ”typica fashion”

Solensky R Ann Allergy Asthma Immunol. 2010;105(4):259-73.
Lancet. 2019 January 12;(10167): 183-198

Drug Desensitization

- IgE mediated reactions
  - Severe
  - Recent
- Performed when no alternative therapy is available
- Modifies immune system: induces temporary tolerance
- ICU/Infusion centers
- Administrating increasing doses of medication
- Many protocols

Solensky R Ann Allergy Asthma Immunol. 2010;105(4):259-73
Liu A Clin Exp Allergy. 2011 Dec;41(12):1679-89.
Castells M Curr Opin Allergy Clin Immunol. 2006

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Other Drug Hypersensitivity Reactions

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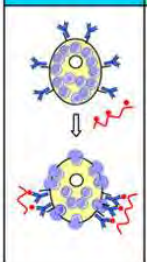
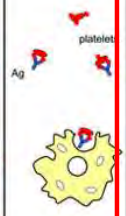
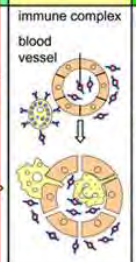
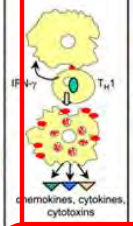
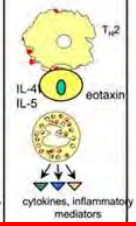
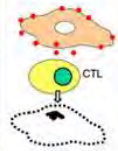
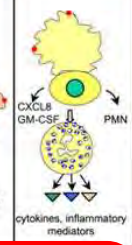
	Type I	Type II	Type III	Type IV a	Type IV b c	Type IV	Type IV d
Immune reactant	IgE	IgG	IgG	IIFN$_\gamma$, TNF$_\gamma$ (T_H1 cells)	IL-5, IL-4/IL-13 (T_H2 cells)	Perforin/ GranzymeB (CTL)	CXCL-8, IL-17 (?), GM-CSF (T-cells)
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Soluble antigen	Antigen presented by cells or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation	Cell-associated antigen or direct T cell stimulation	Soluble antigen presented by cells or direct T cell stimulation
Effector	Mast-cell activation	FcR$^+$ cells (phagocytes, NK cells)	FcR$^+$ cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
							
Example of hypersen-sitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (e.g., penicillin)	Serum sickness, Arthus reaction	Tuberculin reaction contact dermatitis (with IVc)	Chronic asthma, chronic allergic rhinitis Maculopapular exanthema with eosinophilia	Contact dermatitis Maculopapular and bullous exanthema hepatitis	AGEP Behçet disease

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Serum Sickness

- Type III hypersensitivity: Immune complex
- Fever, rash, arthralgia without mucosal involvement
- Treatment: removal of drug, avoid drug (class) may need steroids

Serum sickness of the hands and feet

Reproduced with permission from: Bielory L, Gascon P, Lawley TJ, et al. Human serum sickness: a prospective analysis of 35 patients treated with equine anti-thymocyte globulin for bone marrow failure. Medicine 1988; 67:40. Copyright © 1988 Lippincott Williams and Wilkins.

Urticarial rash as a consequence of a serum sickness reaction

Pharmacotherapy. 2006 May;26(5):705-8.

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Severe Cutaneous Adverse Reactions

- Acute Generalized Eczematous Pustulosis (AGEP)
- Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)
- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Management: avoid class

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AGEP	• Beta Lactam Antibiotics • Fever and Neutrophilia

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SJS/TEN: Triad of target lesion + mucosal involvement + epidermal necrosis

Prodromal phase: 1-3 days before skin lesions

Generalized lesions with a target-like appearance that became confluent, brightly erythematous, and bullous

Spares scalp, palms and soles

Mucosal involvement – loss of skin integrity, peeling, erythema, blistering (90% of patients)

Ocular involvement – painful crusting, conjunctivitis with purulence, bullae, corneal ulceration, uveitis, panophthalmalitis (80% of patients)

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DRESS

Fever

Rash

Systemic

- Reactivation of HHV6, HHV7 and EBV
- Management:
  - Avoid class
  - Limit antibiotic and NSAID use
  - Steroids with long taper

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Fig 1. Patient with phenytoin-induced drug reaction with eosinophilia and systemic symptoms syndrome. Well-demarcated periorbital dermatitis.

Fig 2. Patient with phenytoin-induced drug reaction with eosinophilia and systemic symptoms syndrome. Prominent lip erosions and hemorrhagic crusts.

Fig 4. Patient with phenytoin-induced drug reaction with eosinophilia and systemic symptoms syndrome. Diffuse scaling of legs.

Fig 5. Patient with vemurafenib-induced drug reaction with eosinophilia and systemic symptoms syndrome. Prominent facial edema and morbilliform eruption. (Courtesy of Michael Y. Cashman, MD, and Dominique C. Pichard, MD.)

Fig 3. Patient with phenytoin-induced drug reaction with eosinophilia and systemic symptoms syndrome. Prominent areolar erosion.

Fig 6. Patient with piperacillin-tazobactam–induced drug reaction with eosinophilia and systemic symptoms syndrome. Purpuric and petecheial lesions on the arm. (Courtesy of Naurin E. Ahmad, MD.)

J Am Acad Dermatol
Volume 68, Number 5

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Exanthems

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Management of Type IV HSR

- Testing is limited by medication
- NPV and PPV unknown

Reaction	Patch Testing	Prick/Intracutaneous Testing
Maculopapular rash	Useful 10-40% of cases	May be useful
Eczema	May be useful	May be useful
SDRIFE	Useful 50-80% of cases	Unknown
AGEP	May be useful	Unknown
Fixed drug eruption	May be useful (on affected area)	Unknown
DRESS	Useful 30-60% of cases	No
SJS/TEN	May be useful 9-23% of cases	No

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Why do we care about antibiotic allergy

- Determine Intolerance vs hypersensitivity vs contraindication
- Other drugs cost more
- Other drugs have their own ADRs and risk of hypersensitivity reactions
- Need to determine specific agent if multiple drugs given at once
- "Clean up" the allergy list
  - 2 studies in US: <1% or 11% allergic to reported drug
  - 1 Europe study: 20% allergic to reported drug
- IMPROVE PATIENT CARE

Lancet. 2019 Jan 12; 393(10167): 183-198.

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Antimicrobial Stewardship: It is a big deal!

CDC's 2019 Antibiotic Resistance Threats Report

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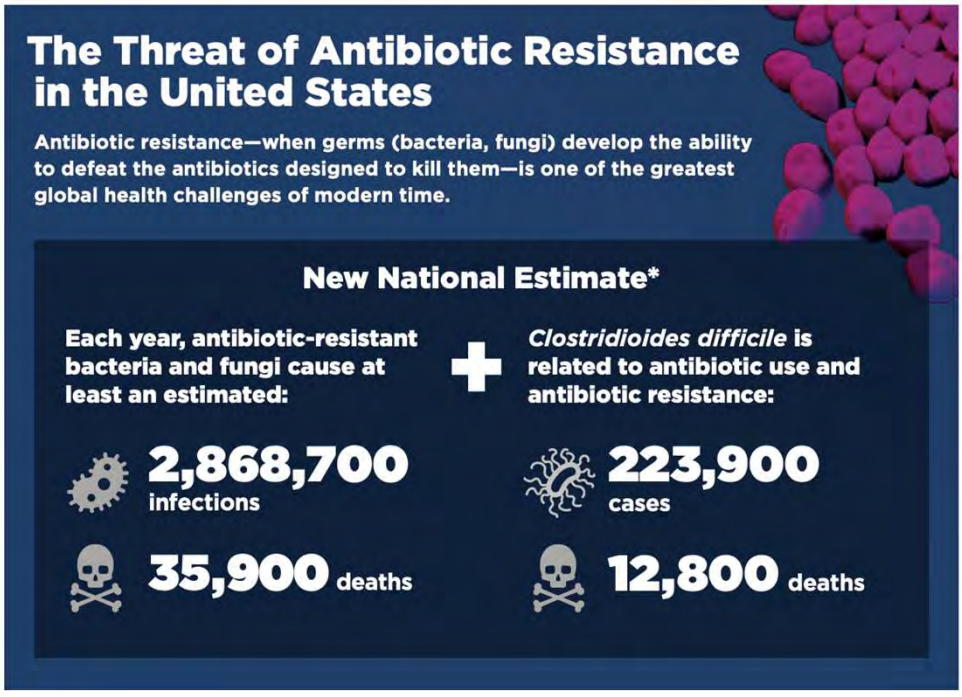

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Evidence Based Drug of Choice Often Beta-Lactam

But

10% Penicillin Allergy

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Penicillin Allergy

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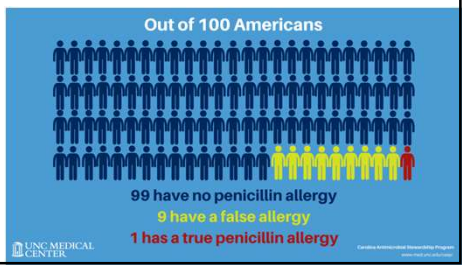
Penicillin Allergy

- 10% of patients report a penicillin allergy, >90% of these patients can tolerate penicillin
- Skin testing has an established and validated negative predictive value >95%
- Majority of penicillin reactions are due to beta-lactam ring, although it is possible to be allergic to a side chain (e.g. amoxicillin, ampicillin)
- Incidence of IgE and anaphylaxis are decreasing
  - Now oral
  - New formulations
  - Cephalosporin use



Solensky R Ann Allergy Asthma Immunol. 2010;105(4):259-73.
Macy E J Allergy Clin Immunol Pract. 2013;1(3):258-63.

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Hospital Outcomes Worse in PCN Allergic Subjects

- Retrospective, Matched Cohort Study
- 52,000 patients with PCN allergy

VARIABLE	PCN ALLERGY
Hospital stay	0.59+ days
C. Difficile Infection	↑ 23.4%
MRSA Infection	↑14.1%
VRE Infection	↑30.1%

J Allergy Clin Immunol. 2014 Mar;133(3):790-6. doi: 10.1016/j.jaci.2013.09.021. Epub 2013 Nov 1.

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Antibiotic Use

P<.0001

TABLE IV. The top 10 antibiotics used by cases and control subjects during hospitalizations

	Cases (51,582)	Control subjects (103,164)
1	Vancomycin: N = 16,685 n = 10,872 (21.2%)	Cefazolin: N = 38,117 n = 32,614 (31.6%)
2	Ciprofloxacin*: N = 15,154 n = 10,888 (21.1%)	Ceftriaxone*: N = 30,220 n = 21,726 (21.1%)
3	Clindamycin*: N = 14,447 n = 12,579 (24.4%)	Vancomycin: N = 20,099 n = 12,77[illegible] (12.4%)

N, Courses of antibiotic; *n* (%), unique subjects exposed.

J Allergy Clin Immunol. 2014 Mar;133(3):790-6. doi: 10.1016/j.jaci.2013.09.021. Epub 2013 Nov 1.

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Antibiotic Cost Higher in PCN Allergic Subjects

Study	Cost: + PCN Allergy	Cost: No PCN Allergy
Kraemer MJ (1987)	$4.6	$1.75
MacLauglin EJ (2000)	$28.6	$16.3
Sade K (2003)	$81.7	$52.5
Sade K (2003)	$43.0	$31.0

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Who Should Be Tested?

- Anyone
- Anyone penicillin allergy > 10 years ago*
- Especially
  - Underlying illness
  - Frequent infections
  - Planned surgery
  - Immunosuppressed

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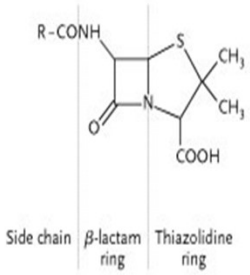
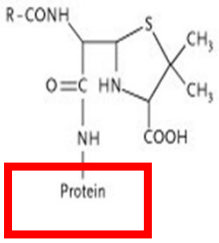
AR [2]1

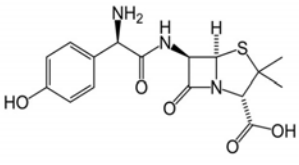
Penicillin Skin Test Panel



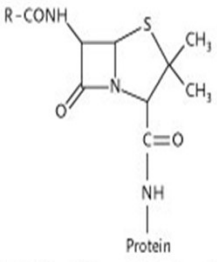
Penicillin



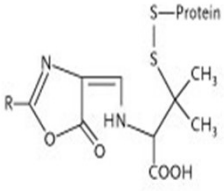
Major Determinant
Pre-Pen



Amoxicillin



Penicillin G



Minor Determinant Mixture

N Engl J Med 2019; 381:2338-2351

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Slide 42

AR [2]1 Andrew Rorie, 5/25/2017

2 Phases to Penicillin Testing

Skin prick test

Intradermal test

Approximate 1 hour clinic visit

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Penicillin Skin Test Outcomes

If **negative** skin testing to the major WITHOUT all minor determinants
- NPV > 95%
- 2 step amoxicillin challenge

If **negative** testing with ALL major and minor determinants
- NPV = 100%

Negative workup for both
- Risk of **immediate** allergic reaction same as general population
- 3% adult and 10% pediatric patients develop T-cell mediated drug eruption
- EMR updated

If **positive** skin test:
- Penicillin drug allergy remains and avoidance recommended.
- Desensitization

Lancet. 2019 Jan 12; 393(10167): 183-198.

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86-100%
Test Negative

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Inpatient Direct Amoxicillin Challenge

- Screened patients (372 patients)
- EXCLUDED: itchy rash <1 year, SCAR, moderate-severe IgE symptoms, rash NOS less than 20 years ago
- INCLUDED: rash NOS, hives, or unknown reaction >20 years ago without ED treatment needed; GI symptoms only and Family History
- 3 step oral amoxicillin challenge performed: 97.9% tolerated (47 patients), 1 patient had redness and swelling under the eye
- Negative PCN SPT -> 1 dose challenge, 100% tolerated

JACI Prac. 2020 Jul-Aug. 8(7): 2296-2301.

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Outpatient Direct Amoxicillin Challenge

- Direct challenge: 1/10 then full dose
- Less than 5 y/o: Direct challenge 13 patients (100%) tolerated
- 5+ years older
- Cutaneous only or unknown reaction
  - 5-17 y/o: >1 year ago
  - 18+ y/o: >10 years ago
- 1:1 randomized to PST or 2 step DC
  - PST: 80 patients, negative testing in 70 (87.5%) and all tolerated challenge
  - DC: 79 patients, tolerated in 76 (96.2%), all reactions were minor
- Any extracutaneous reactions -> PST: 13 patients, 2 had positive PST
- Brings up question: PST overcall penicillin allergy (more reactions than direct challenge)

JACI Prac. 2019 Sep-Oct. 7(7): 2163-2170.

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First immunology, now chemistry

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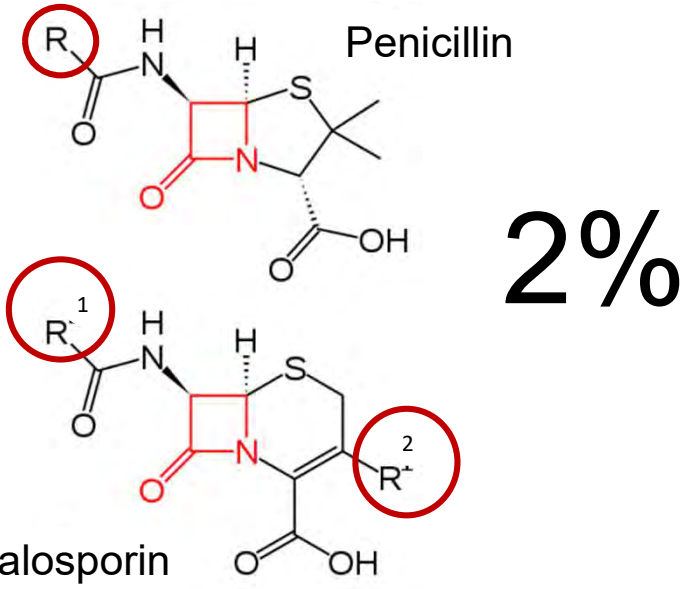
Beta Lactam vs Side Chain

- Unlike other beta lactams PCNs
  - have a thiazolidine ring
  - Do not have R2 or additional side chain structures
- Selective aminopenicillin allergy:
  - rare in USA
  - 1/3 cause of reactions in southern Europe
  - 25-35% of these patients cross-reaction with aminocephalosporins



2%

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Beta Lactam Cross Reactivity

- Possible through core ring = rare
- Adjacent thiazolidine (penicillin) or dihydrothiazine (cephalosporin) ring
- Side chain R1 or R2
- True cross-reactivity is primarily due to R1 side chains
  - Similar still an issue
  - R2 still a possibility
- 99% of patients tolerate carbapenems
- Amoxicillin = Ampicillin
  - Avoid cephalosporins with similar side chains

Lancet. 2019 January 12; 393(10167): 183-198

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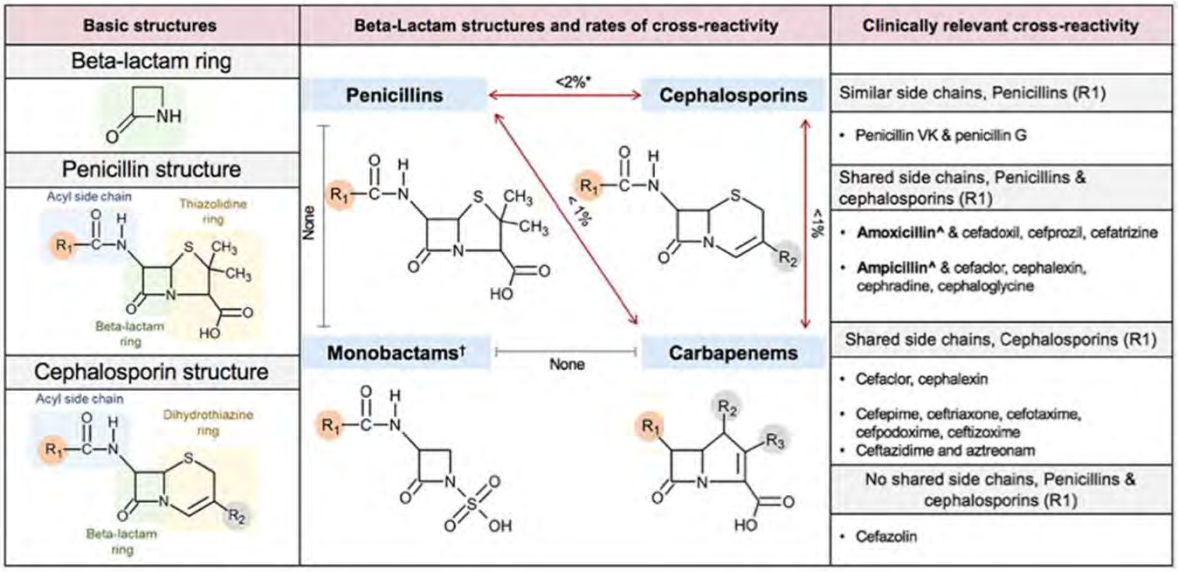

Lancet. 2019 January 12; 393(10167): 183-198

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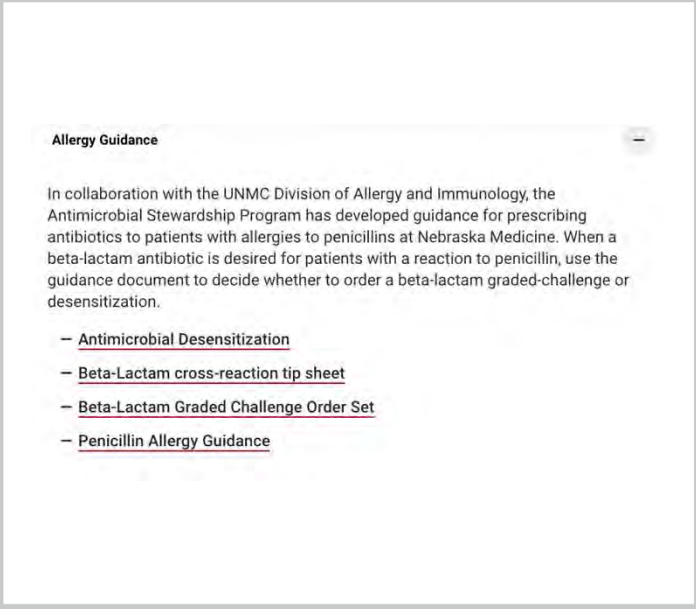
Beta-Lactam Challenge UNMC AMS

- https://www.unmc.edu/intmed/divisions/id/asp/clinicalpath.html



Allergy Guidance

In collaboration with the UNMC Division of Allergy and Immunology, the Antimicrobial Stewardship Program has developed guidance for prescribing antibiotics to patients with allergies to penicillins at Nebraska Medicine. When a beta-lactam antibiotic is desired for patients with a reaction to penicillin, use the guidance document to decide whether to order a beta-lactam graded-challenge or desensitization.

- Antimicrobial Desensitization
- Beta-Lactam cross-reaction tip sheet
- Beta-Lactam Graded Challenge Order Set
- Penicillin Allergy Guidance

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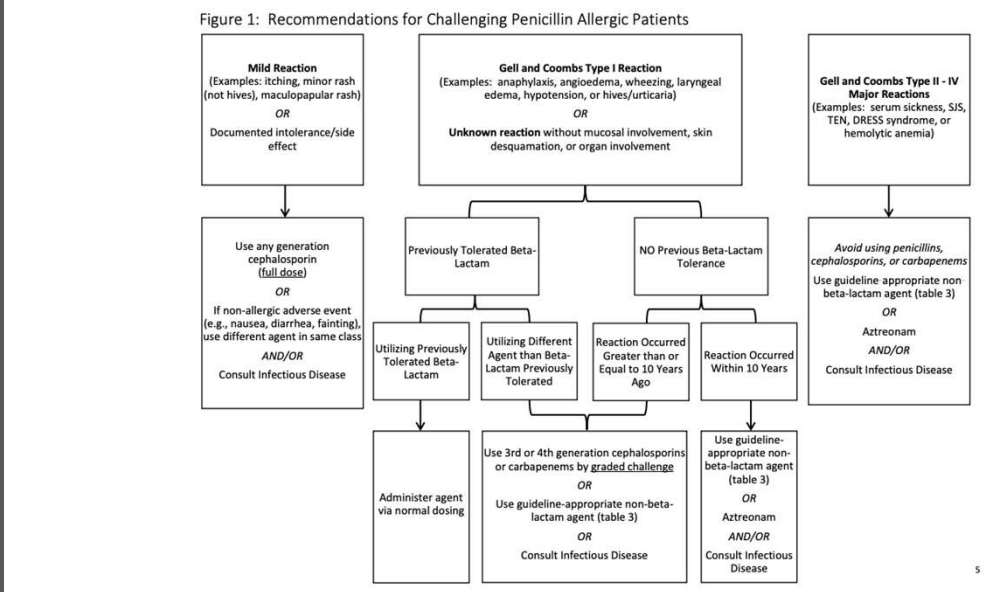

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Cephalosporin Allergy

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Cephalosporin Allergy

- Hypersensitivity from 0.0001-3% of administrations
  - IgE
  - Cefaclor and cefprozil: serum sickness-like reactions
  - SCARs
- Sensitivity resolves with time
  - 60% no longer positive skin test at 5 years
- Allergy commonly directed at side chain/R- group
  - Cephalosporins with identical side chains appear to be cross-reactive
- No validated skin testing available, but skin testing can be performed

Romano A J Allergy Clin Immunol. 2015 Apr 27. [Epub ahead of print]
Macy E J Allergy Clin Immunol. 2014;133(3):790-6
Macy E J. Allergy Clin. Immunol. 135, 745–52 (2015).
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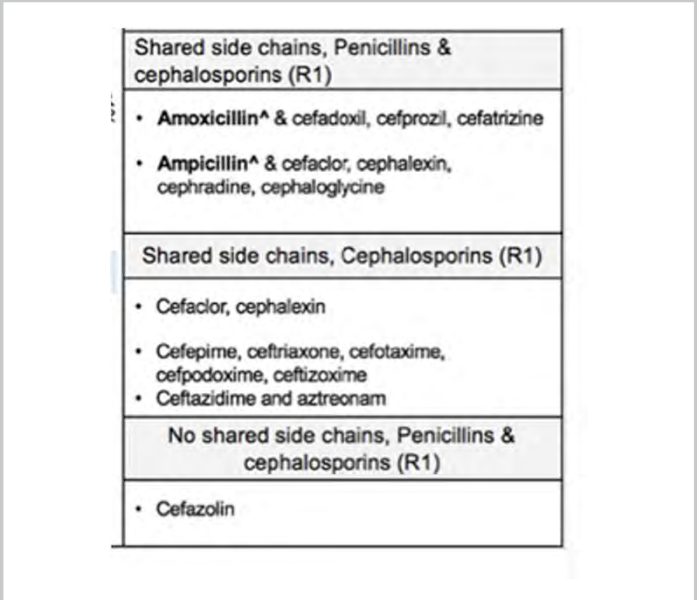
Romano: IgE-mediated hypersensitivity to cephalosporins: cross-reactivity and tolerability to alternative cephalosporins

- 102 patients, 89 reactions were anaphylaxis by definition
- 100% had positive skin test to culprit agent
- Highest offenders: ceftriaxone, cefaclor, and ceftazidime
- 4 Groups
  - Group A, B and C
  - Group D: no pattern
- Skin testing performed and challenges based on these findings



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Other Antibiotics

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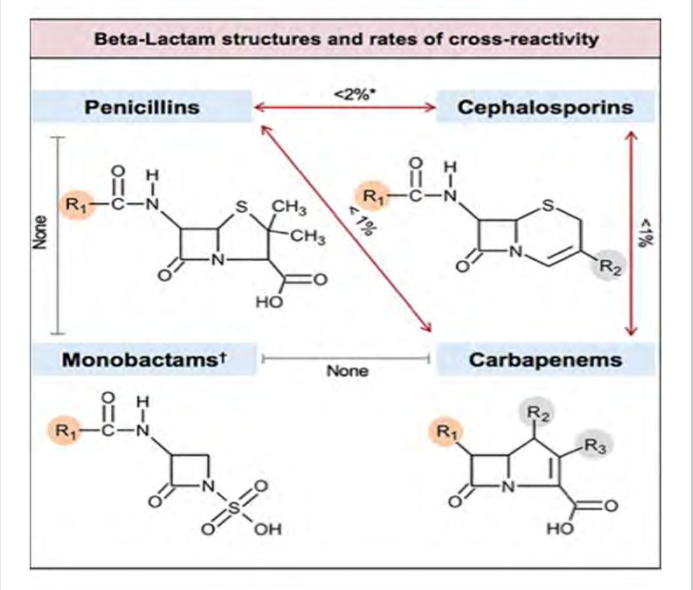
Carbapenem Allergy

- Lower rates than penicillin and cephalosporin reactions
- Limited Cross-reactivity Data (99% tolerable outcomes)
- Even positive penicillin skin test ->challenge
- Non validated skin test is available



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Clavulanic Acid

- Beta-lactam with beta-lactamase inhibitor
- Associated with selective IgE mediated reaction
- Unable to obtain agent on it's own in US

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Sulfa antibiotics

- Sulfamethoxazole-Trimethoprim only available ABX
- Rarely cause IgE-mediated reactions
- Delayed hypersensitivity reactions with maculopapular rash
  - Second to amoxicillin for cutaneous ADR in the hospital
- Cannot perform skin testing
- HIV: 34-50% sensitivity
- Can challenge (73% high-risk patients tolerate repeat challenge)
- Can perform oral desensitization (PCP prophylaxis)
- Does not cross-react with other sulfonamide drugs
- Should tolerate Dapsone, avoid with severe reactions

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Vancomycin

- IgE-mediated reactions very rare
- 50% (10-80%) will experience Red Man Syndrome
  - Slow infusion and premedicate
  - Can desensitize if severe
- Morbilliform rash common
- DRESS: HLA:A*31:01
- Linear IgA bullous disease
- Cannot skin test

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Fluoroquinolones

- IgE mediated reactions are increasing
  - Highest: moxifloxacin
- Cross reactivity within class
  - In vitro studies, not clinical studies
  - Need evaluation, otherwise avoid entire class
  - Delayed reactions seem to be drug specific
- 2% delayed hypersensitivity with exanthems
  - Highest: Ciprofloxacin
- Beta-lactam hypersensitivity – increased risk factor
- Can skin test: high false positive rate

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To Summarize

- Drug allergy sections are inaccurate
- Most common drug hypersensitivity reactions are immediate or delayed Type 4 maculopapular rash
- Certain reactions need to be identified for patient safety (SCARs)
- Penicillin skin test is only validated skin test
- Skin testing for many antibiotics is available at certain centers
- Cross reactivity between penicillin and other beta lactam antibiotics is rare
- Drug challenges can be utilized in many clinical scenarios
- Desensitization is also available when needed

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Questions?

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