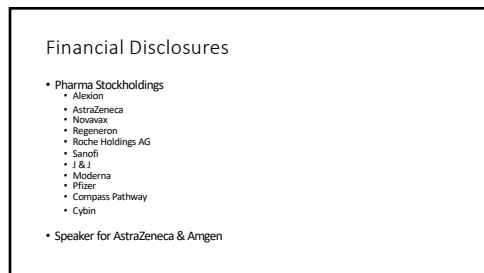




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2



3

Topics in Allergy/Immunology

- Allergic Rhinitis (25%)
- Asthma (8%)
- Drug Allergy (35-50%)
- Urticaria (20%)
- Atopic Dermatitis (10-20%)
- Food Allergy (8%)
- Non-Allergic Rhinitis
- Stinging Insect Allergy
- Angioedema
- Eosinophilic Esophagitis
- Immune Deficiency
- Pruritus
- Anaphylaxis
- Hereditary Angioedema
- Contact Dermatitis
- Urticarial Vasculitis
- Mastocytosis
- Exercise-Induced Bronchospasm
- Innate Immunity
- Adaptive Immunity
- Neutropenia
- Allergic Bronchopulmonary Aspergillosis
- Allergy Diagnostics
- Latex Allergy
- Metal Allergy
- Chronic Cough
- Eosinophilic Esophagitis
- Food protein-induced enterocolitis syndrome (FPIES)
- Hypersensitivity pneumonitis
- Human Microbiome
- Nasal Polyps
- Aspirin-exacerbated respiratory disease
- Environmental and occupational pollutants
- Hypereosinophilic syndrome

4



Ankeny West Des Moines



Taking residents for rotations!
Pediatrics, Family Practice, Internal Medicine

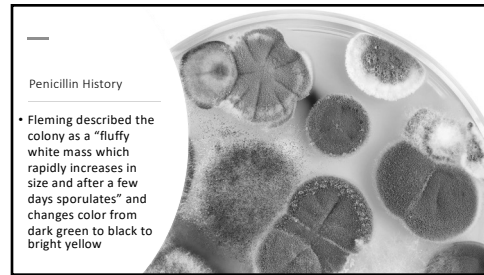
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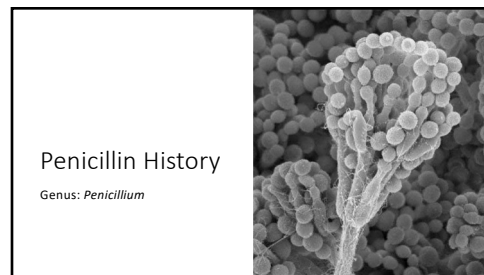
Penicillin History

- Alexander Fleming (Scottish) discovered penicillin in 1928
- Described as a careless lab technician, Fleming returned from a two-week vacation to find that a mold had developed accidentally on staphylococcus culture plate
- Noticed the mold prevented the growth of staphylococci

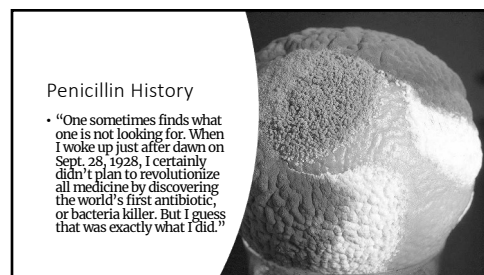
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9

Penicillin History


- First patient: In 1941, Albert Alexander (Oxford) had scratched his face on a rose bush, the wound had become infected.
- Injected with penicillin regularly over four days, greatly improved. Even with extracting penicillin from his urine and re-injecting it, supplies ran out before his cure was complete. Relapsed and died a month later.



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Penicillin History


- 1942
- First American patient: Anne Miller. Septic after a miscarriage with fever (103°F) for multiple weeks. Surgery and blood transfusions had not helped.
- By chance, another patient at the same hospital happened to know a British scientist who was working on developing penicillin



11

Penicillin History

- Miller's doctor used that connection to get the government to release roughly a tablespoon of penicillin for her. It was half of the entire store of antibiotic in the US at the time.
- Within about a day, her temperature was back to normal. Miller was cured.
- Miller died at age 90 in 1999.



12

Penicillin History

- There were only 400 million units of penicillin available during the first five months of 1943
- When WWII ended, U.S. companies were making 650 billion units a month

13

Why Think About the Importance of Penicillin History?

- Reminder that many drugs (especially antibiotics) we have created are close to being miracles, so don't take them for granted
- Diagnosing or Misdiagnosing a drug allergy can be life-altering for a patient
- **IGNORING** a drug allergy can also adversely affect patients

14

Skin Testing

- First described in 1867 by Dr. Charles Blackley, skin tests (prick/puncture and intradermal/intracutaneous) have evolved as reliable, cost effective techniques for the diagnosis of **IgE-mediated diseases**. (B)
- Prick/puncture tests are used to confirm clinical sensitivity induced by aeroallergens, foods, **DRUGS**, venom, and a few chemicals

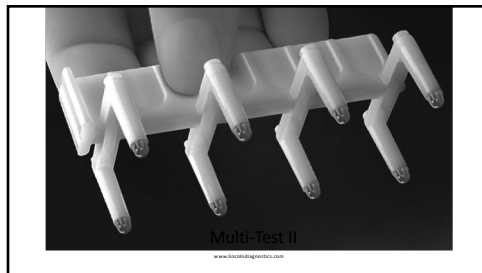


Reaction Preparation

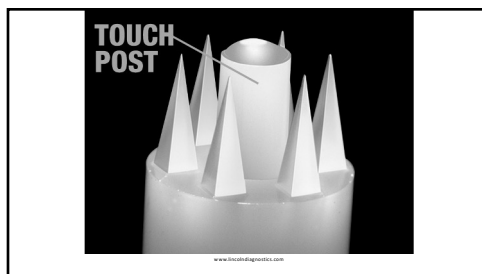
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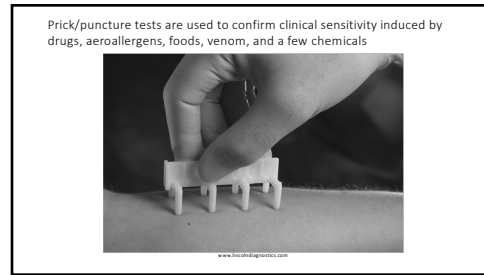
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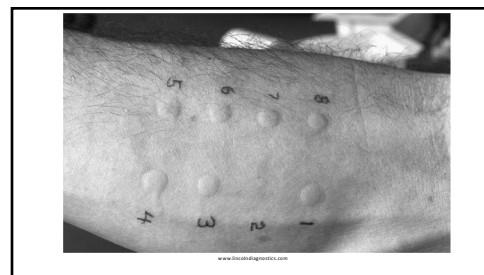
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21

What does "Allergy" mean?

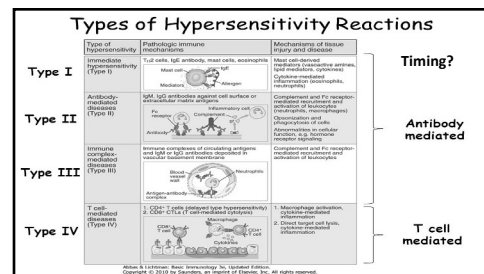
- Everyone thinks they're allergic to something
- Careful about use of the word

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My own definition

- A clinically relevant, predictable reaction to an antigen involving the immune system.

23

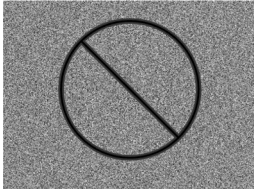


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Types of Hypersensitivity Reactions			
Type of hypersensitivity	Pathologic immune mechanism	Mechanisms of tissue injury and disease	
Type I Immediate (Type I)	T cell, IgE, antibody, mast cells, eosinophils Hypersensitivity to allergens	Mast cell degranulation, eosinophil degranulation, complement-mediated damage to cells	Minutes to Hours
Type II Antibody-mediated (Type II)	IgG, IgM antibodies against cell surface or extracellular matrix antigens Complement, macrophages, neutrophils, eosinophils	Complement and Fc receptors mediate cell damage and inflammation, neutrophil degranulation, macrophage degranulation	Minutes to Hours Antibody mediated
Type III Immune complex-mediated (Type III)	Immune complexes of circulating antigens and IgG or IgM antibodies deposited in tissues Macrophages, neutrophils, eosinophils	Complement and Fc receptors mediate inflammation and activation of macrophages	Hours to Weeks
Type IV T cell-mediated (Type IV)	CD4+ T cells (Th1, Th2, Th17, Treg) CD8+ T cells (CTLs) Macrophages, dendritic cells, T cells	Macrophage activation, dendritic cell activation, CD8+ T cell cytotoxicity	T cell mediated Days to Weeks

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The Immune System is **NOT** Static



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Drug Allergies

- Initially one of my favorite topics
- Easy? Sometimes
- Different drug classes follow different rules
- Is it a true "allergy" or adverse reaction/intolerance? Or reaction is from something else?
- Validated testing available?
- Risk/benefit of challenging/desensitization?
- Probability of cross-reactivity for a given drug class?
- Risk/benefit of alternatives?
- Treating through severe reactions?

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TABLE 79.1 Classification of Adverse Drug Reactions		
	Drug Reaction	Examples
Generally Predictable Most drug reactions	TYPE A: REACTIONS OCCURRING IN MOST NORMAL PATIENTS GIVEN SUFFICIENT DOSE AND DURATION OF THERAPY	
	Overdose	Hepatic failure (acetaminophen)
	Side effects	Nausea, headache (with methylxanthines)
	Secondary or indirect effects	GI bacterial alteration after antibiotics
	Drug interactions	Erythromycin increasing theophylline/digoxin blood levels
Generally UNPREDICTABLE Only 10% to 15% of all ADRs	TYPE B: DRUG HYPERSENSITIVITY REACTIONS RESTRICTED TO A SMALL SUBSET OF THE GENERAL POPULATION	
	Intolerance*	Tinnitus after a single aspirin tablet
	Idiosyncrasy† (pharmacogenetics)	G6PD deficiency: anemia after antioxidant drugs
	Immunologic drug reactions (allergy)	Anaphylaxis from β-lactam antibiotics
	GI, Gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase. *Side effects at subtherapeutic doses. †Drug effect not attributable to known pharmacologic properties of drug and not immune mediated.	

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	GI, Gastrointestinal; G6PD, glucose-6-phosphate dehydrogenase. *Side effects at subtherapeutic doses. †Drug effect not attributable to known pharmacologic properties of drug and not immune mediated.	

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Adverse Drug Reactions (ADRs)

- ADRs have been reported to affect 10% to 20% of hospitalized patients and up to 25% of outpatients
- In the US, about 1 of every 300 hospitalized patients dies from an ADR, and 6% to 10% of these reactions may be allergic in origin
- What type of reaction (I-IV) is penicillin allergy?

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Drug Allergy?

- Anyone learned this in medical school for H&P?
- How many lectures have you sat through for drug allergy?

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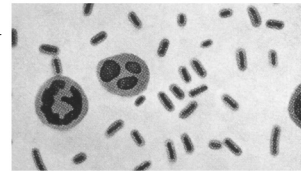
Why so Important? Antibiotic Stewardship

- Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing *Klebsiella pneumoniae*
- Essentially all US antibiotics

A Superbug That Resisted 26 Antibiotics

JANUARY 11, 2007 / JEFFREY L. LEVINE

STANFORD MEDICAL CENTER



The *Klebsiella pneumoniae* strain shown here is resistant to 26 different types of antibiotics, including penicillins, tetracyclines, cephalosporins, and carbapenems.

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Superbug Resistant to Last-Resort Antibiotic Arises in China

1% percent of *E. coli* & *Klebsiella* carry the *mcr-1* gene (transferable between bacterium)

Resistance to colistin



China has been using the antibiotic colistin in pig farming, a practice that may have led to the development of the *mcr-1* gene. Credit: Dan Boonstra/Flickr (CC BY 2.0)

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STAT
PUBLIC HEALTH

Superbug Resistant to Last-Resort Antibiotic Arises in China

Not unique; 80% of antibiotics in the USA are used for livestock to speed growth

Overprescribing of antibiotics or using more broad spectrum antibiotics than necessary due to drug "allergies" contribute to the problem



China has been using the antibiotic colistin to speed growth of farm animals

China has been using the antibiotic colistin in agriculture, a practice that may have led to the development of the mcr-1 gene. Credit: Dan Boonstra/Flickr (CC BY 2.0)

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STAT
PUBLIC HEALTH

Superbug Resistant to Last-Resort Antibiotic Arises in China

Some countries (Mexico, Viet Nam, China, India, etc.) don't require rx for antibiotics

Patients in these countries treat themselves to whichever antibiotic at whatever dose and duration they want

When we give in to patients for antibiotics or don't attempt to clear their antibiotic allergy a similar phenomenon happens

Breaking News: bacteria and their resistance travels globally



China has been using the antibiotic colistin in agriculture, a practice that may have led to the development of the mcr-1 gene. Credit: Dan Boonstra/Flickr (CC BY 2.0)

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Why So Important? Side Effects

- FDA 2016: **serious side effects** associated with fluoroquinolone antibacterial drugs **generally outweigh** the benefits for patients with **acute sinusitis, acute bronchitis, and uncomplicated UTIs** who have other treatment options
- Fluoroquinolones should be reserved for those who do not have alternative treatment options

www.fda.gov

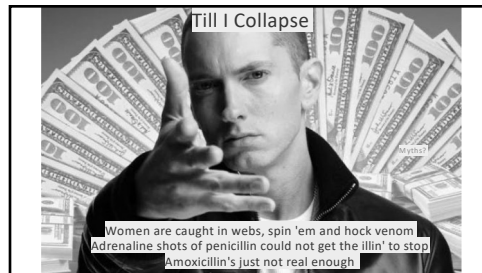
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Why So Important? Side Effects

- Associated with disabling and **potentially permanent** serious side effects that can occur together include:
 - tendon rupture
 - blood sugar fluctuations
 - muscle/joint pain
 - peripheral neuropathy
 - depression/psychosis
 - memory impairment/disorientation
 - cardiac arrhythmias
 - phototoxicity
- Side effects had continued for an **average of 14 months** to as long as **9 years** after stopping the medication

www.fda.gov

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Why So Important? Just works **better**

Penicillin first line:

- Strep (pharyngitis, endocarditis, CAP, etc.)
- MSSA
- Syphilis
- Otitis Media
- Meningitis
- H pylori
- Intra-abdominal infections
- List goes on

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Is it Really a Penicillin Allergy?

Evaluation and Diagnosis of Penicillin Allergy for Healthcare Professionals

Did You Know? 5 Facts About Penicillin Allergy (Type 1, Immunoglobulin E (IgE)-mediated)

1. Approximately 10% of all U.S. patients report having an allergic reaction to a penicillin class antibiotic in their past.

2. However, many patients who report penicillin allergies do not have true IgE-mediated reactions. When evaluated, fewer than 1% of the population are truly allergic to penicillins.¹

3. Approximately 80% of patients with IgE-mediated penicillin allergy lose their sensitivity after 10 years.²


4. Broad-spectrum antibiotics are often used as an alternative to penicillin. The use of broad-spectrum antibiotics in patients labeled "penicillin-allergic" is associated with higher healthcare costs, increased risk for antibiotic resistance, and suboptimal antibiotic therapy.³

5. Correctly identifying those who are not actually penicillin-allergic can decrease unnecessary use of broad-spectrum antibiotics.⁴

10% of the population reports a penicillin allergy but <1% of the whole population is truly allergic.

www.cdc.gov

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Before prescribing broad-spectrum antibiotics to a patient thought to be penicillin-allergic, evaluate the patient for true penicillin allergy (IgE-mediated) by conducting a history and physical, and, when appropriate, a skin test and challenge dose.

History and Physical Examination

The history and physical examination are important components when evaluating a patient's drug reactions.¹

Questions to ask during the examination:

- What medication were you taking when the reaction occurred?
- What kind of reaction occurred?
- How long ago did the reaction occur?
- How was the reaction managed?
- What was the outcome?

Characteristics of an IgE-mediated (Type 1) reaction:

- Reactions that occur immediately or usually within one hour¹
- Hives: Multiple pink/red raised areas of skin that are intensely itchy²
- Angioedema: Localized edema without hives affecting the abdomen, face, extremities, genitalia, oropharynx, or larynx²
- Wheezing and shortness of breath²
- Anaphylaxis: severe signs or symptoms in at least two of the following systems:
 - Skin, hives, flushing, itching, and/or angioedema (continued on next page)

Additional facts:

- Broad-spectrum antibiotics are often used as an alternative to narrow-spectrum penicillins.
- Using broad-spectrum antibiotics can increase healthcare costs and antibiotic resistance, and may mean your patient receives less than the best care.
- Correctly identifying if your patient is actually penicillin-allergic can decrease these risks by reducing unnecessary use of broad-spectrum antibiotics.

National Center for Emerging and Zoonotic Infectious Diseases
Division of Healthcare Quality Promotion
www.cdc.gov

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(continued from previous page)

- Respiratory: Cough, nasal congestion, shortness of breath, chest tightness, wheeze, sensation of throat closure or choking, and/or change in voice quality (laryngeal edema)
- Cardiovascular: Hypotension, faintness, tachycardia or less commonly bradycardia, tunnel vision, chest pain, sense of impending doom, and/or loss of consciousness
- Gastrointestinal: Nausea, vomiting, abdominal cramping, and diarrhea¹

Penicillin Skin Tests and Challenge Doses

Based on the patient history and physical exam, additional tests may be needed to confirm a penicillin allergy. Penicillin skin testing is a reliable and useful method for evaluating IgE-mediated penicillin allergy.²

A positive result means the patient is likely to have a penicillin allergy. If negative, the skin test is usually followed by an oral penicillin class challenge (e.g., with amoxicillin) to safely rule out an IgE-mediated penicillin allergy.²

- Skin tests currently include penicilloyl/polylysine, the major antigenic determinant that indicates hypersensitivity to penicillin.
- However, it is important to note that the patient can also be allergic to other reactive breakdown products, called minor determinants, which include penicillin G (benzylpenicillin), penicilloate, and penicillate—many of which are not commercially available. Of these, only penicillin G is available from pharmacies.
- To rule out penicillin allergy, an oral challenge dose can be done after skin testing. The negative predictive value of skin testing with the major and minor determinants is more than 95%, but approaches 100% when followed by a challenge dose.²

www.cdc.gov

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Special Considerations

Patients with severe hypersensitivity syndromes—like Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness, acute interstitial nephritis, hemolytic anemia, and drug rash with eosinophilia and systemic symptoms (DRESS)—should not use the offending drug in the future. The skin test and challenge described here are not appropriate for patients with these severe hypersensitivity syndromes.^{1,2}

Cephalosporins can be penicillin-allergic patients.

Many cephalosporins, especially in the later generations, can be safely tolerated despite a penicillin allergy.^{3,4} Patients with anaphylaxis or other severe reactions to penicillin may require further evaluation prior to the use of cephalosporins.

Penicillin patients

Children who are receiving amoxicillin or ampicillin and have Epstein Barr virus infection can develop a non-allergic, non-pruritic rash that can appear similar to an IgE-mediated reaction.^{5,6}

For more information about appropriate antibiotic use, visit www.cdc.gov/getsmart.

References

1. Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2010;105:100-132.
2. Gottrup-Carrasco A, Rodriguez L. Penicillin allergy: a practical guide for clinicians. *Clinic Clin J Med*. 2015;83(2):295-300.
3. Horan TM, Rogers SD, Jones RM, Upton H. Future outcomes in penicillin allergy. *New York, McGraw-Hill*. 2012 (and 2015 Aug 14). Available from: <http://accessmedicineonline.com/content/9780323080428-02244288>
4. Hernandez JA. Update on cephalosporins: indications, response, and treatment. *Allergy Asthma Proc*. 2011;32(6):400-412.
5. Sampson HA, Muñoz-Fernández A, Campbell EL, Adkinson NF Jr, Brook SA, Burrows B, et al. Second component of the definition and management of anaphylactic summary report: second National Institute of Allergy and Infectious Diseases Food Allergy and Anaphylaxis Network symposium. *Ann Trans Med*. 2006;40:155-160.
6. Burrows B, Sampson HA, Muñoz-Fernández A, Campbell EL, Adkinson NF Jr, Brook SA, Burrows B, et al. Effect of a drug allergy educational program and antibiotic prescribing guideline on repeat clinical practice antibiotic prescribing. *J Allergy Clin Immunol*. 2014;134(4):e7-12.
7. Macy E, Napp R. Recommendations for the management of beta-lactam hypersensitivity. *Clinical Ther Allergy Immunol*. 2014;47:44-54.
8. Pothoche JF. A review of evidence supporting the American Academy of Pediatrics recommendation for penicillin and cephalosporins for penicillin-allergic patients. *Pediatrics*. 2004;114(4):1048-1052.
9. Centers for Disease Control and Prevention (CDC). *Antibiotic Resistance (ARM)*. Accessed 2014 Aug 14. Available from: <http://www.cdc.gov/antibiotic-resistance>

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Penicillin Allergy

- Study at American College of Allergy, Asthma & Immunology 2016
- Surveyed inpatient providers from different specialties regarding penicillin allergy. Total of 276 surveys
- Clinical vignettes presented regarding penicillin allergy

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Penicillin Allergy

- 42.4% of respondents believed that penicillin allergy does not resolve over time
- In the vignettes provided, only 20.0% identified appropriate patients for penicillin skin testing
- How many here didn't know that you can outgrow penicillin allergy?

48

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Words from other Physicians

- "Once an allergy always an allergy"
- "You're allergic to penicillium (mold), you can't take penicillin (drug) and need an epipen"
- "You have a penicillin allergy but it's up to you if you want to get tested and get it cleared"
- "You'll probably never need penicillin again"

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Name the two criteria for referral for penicillin testing

- 1. History of penicillin allergy
- 2. Possess skin
- An "allergy" is often a permanent thing on a patient's chart unless someone actively addresses it
- What if you don't have skin?
- Usually someone will raise their hand at this time during lecture. To ask?

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Penicillin Allergy Decision Rule (PEN-FAST)

Identify low risk penicillin allergies

INSTRUCTIONS
Apply this calculator to patients who have reported a penicillin allergy

Refer to Use in

Ever penicillin or beta-lactam reaction ☐ No ☒ Yes ☐

Angioedema or anaphylaxis OR severe cutaneous adverse reaction ☐ No ☒ Yes ☐

Examiners required for reaction ☐ No ☒ Yes ☐

0 points
PEN-FAST Score

<1 %
Very low risk of penicillin penicillin allergy test

[Copy Results](#) [Next Steps](#)

Wishah.com

PEN-FAST score of less than 3 is associated with a high negative predictive value, can identify low-risk penicillin allergies that can potentially skip skin testing and go directly to oral challenge in a **primary care setting**.

What is a challenge?

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[illegible][illegible][illegible]

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DRESS Syndrome- Drug Rash with Eosinophilia and Systemic Symptoms

- Type IV reaction
- Major cause of hospitalization for dermatological complications in patients treated with **anticonvulsants (also NSAIDs, antibiotics, allopurinol, etc.)**
- Incidence of 1 in 1000-10,000 per exposure to offending drugs
- Typically occur within **2 to 6 weeks** after initiating drug therapy
- **Fatal in 5-10% of cases**

Comparison of the Causes and Clinical Features of Drug Rash With Eosinophilia and Systemic Symptoms and Stevens-Johnson Syndrome. Youniss et al. J Allergy Asthma Immunol 2000; 102: 491-497

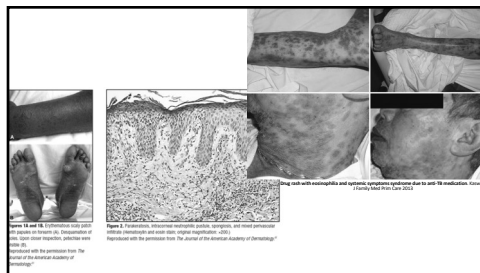
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DRESS Syndrome- Drug Rash with Eosinophilia and Systemic Symptoms

- Common presentation: fever, rash and lymphadenopathy
- Common labs: eosinophilia, leukocytosis and lymphocytosis
- Liver involvement range from a transitory increase in LFTs to fulminant hepatic failure
- Other potentially fatal complications are hypersensitivity myocarditis, pericarditis, pneumonitis, nephritis

Comparison of the Causes and Clinical Features of Drug Rash With Eosinophilia and Systemic Symptoms and Stevens-Johnson Syndrome. Youniss et al. J Allergy Asthma Immunol 2000; 102: 491-497

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Most Common Cause of **Fatal** Anaphylaxis?

• A) Medications

• B) Venom (bees, wasps, hornets, fire ant)

• C) Food

• D) Environmental/chemical (pollen, mold, latex)

• E) Other/Idiopathic

• Surprising? Why?

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Table 1
Causes of fatal anaphylaxis

Study	Food	Insects	Medication	Other (RCM)	Unclear
Liew WK et al ²⁷	6%	18%	58%	5%	13%
Greenberger et al ¹²	16%	24%	28%	24%	0

Abbreviation: RCM, radiocontrast media.

Emergency department diagnosis and treatment of anaphylaxis: a review for primary care. Campbell et al. JAMA Allergy Asthma Immunol 2023;10(1):1-10

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Table 1
Population based data for rate of fatal anaphylaxis triggered by drugs

Region	Data Source	Time period	Total deaths	Rate of fatal drug anaphylaxis (per million/year)	Age	Gender predominance	Leading causal drug	Risk factors identified	Authors
Australia	Australian Bureau of Statistics and National Causes Mortality System	1987-1997 cases in total 2017-2019 triggered by drugs RCD code 198A	147 cases in total 84 cases triggered by drugs RCD code 198A	1987-1997 0.007 2017-2019 0.013	Median 60 (IQR 35-75) range 20-90	Male > female	Anesthetics 47%, Insulin 24%, Anticoagulant 16%, Antibiotic 14%, Radiocontrast 20%	Age Cardiovascular disease 75%, Known penicillin allergy 17% (19% of those with condition)	Medlin et al., 2023 ²⁸
Canada (Ontario)	Ontario Cancer's database	1996-2011 19-12-79 drugs Cause specific matched RCD codes 494 total	81 19-12-79 drugs Cause specific matched RCD codes 494 total	81 19-12-79 drugs Cause specific matched RCD codes 494 total	Mean 69 (range 56-86) 86	Male 59 (range 56-86) 86	Anesthetics 44%, Radiocontrast 29%	Age Known allergy to the drug is 1 of 15 cases with data available (20%)	Yu et al., 2023 ²⁹
France	French National Pharmaco-Vigilance Database ³	2008-2015 All deaths of fatal anaphylaxis cases	16 cases Pharmaco-Vigilance Database	Not calculated	Mean age 59	Male > female	Not stated	Male gender, Fluoroquinolone and sulfonamide combination therapy	Reuter et al., 2023 ³⁰
United Kingdom	National fatal anaphylaxis register	1992-2012 2012 drugs 157% of total RCD code 198A	479 total 2012 drugs 157% of total RCD code 198A	1992-2012 0.126 2012-2019 0.136	Median 59 (range 30-81) 59-81	Not stated	Not stated	None stated	Turner et al., 2023 ³¹
United States	National Center for Health Statistics	1999-2019 1408 deaths 17% of total RCD code 178A & 180A	2439 total 1408 deaths 17% of total RCD code 178A & 180A	1999-2017 0.27 2018-2019 0.15	Median 60 (IQR 45-75) 75	Male	Anesthetics Insulin Anticoagulant Antibiotic Radiocontrast	African American ethnicity None age	Reichen et al., 2023 ³²

Fatal Anaphylaxis: Mortality Rates and Risk Factors. Turner et al. J Allergy Clin Immunol Pract. 2023

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5-Year-Old Admits It Pretty Messed Up Spider-Man Visiting His Birthday Party When He Could Be Out Saving Lives

8/29/18 11:40am

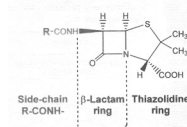


WESTCHESTER, NY—Acknowledging that there were definitely far more pressing issues for the young superhero to address, 5-year-old Sam Byer admitted Wednesday that it was pretty messed up that Spider-Man had chosen to entertain guests at his birthday party when he could be out saving lives. "Look, I'm glad he showed up..."

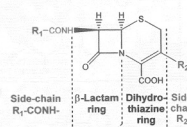
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Cephalosporin Administration to Patients With a History of Penicillin Allergy? (IgE)

PENICILLINS



CEPHALOSPORINS



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Cross-reactivity

- Cross-reactivity between penicillins and 1st and early (before 1980) 2nd gen cephalosporins has been reported to occur in up to **10%** of penicillin allergic patients
- 3rd gen; 2–3 % of penicillin-allergic patients
- However, **contamination** of these early cephalosporins with trace amounts of benzylpenicillin resulted in overestimation of cross-reactivity
- Anecdotal false

Cross-Reactivity among Beta-Lactams: A Review of the Literature
J. Allergy Clin. Immunol. 1994;93:1000-1006

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












Cross-reactivity

- Meta-analysis of studies performed between 1966 and 2005, comparing hypersensitivity reactions to cephalosporins in penicillin-allergic and non-penicillin-allergic patients
- Significant increase (OR = 4.8) in allergic reactions to all 1st gen cephalosporins (e.g. cephalothin, cephaloridine, cephalexin) plus cefamandole, but **NO** increase with 2nd or 3rd gen cephalosporins
- There are many other studies with slightly different cross-reactivity rates
- **Who do you listen to??**

Cross Reactivity among Beta-Lactams, A. Rasmussen et al.
J Am Allergy Asthma Soc 2004;10

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Table 16. Group of 14 beta-lactams that share identical R-group side chains

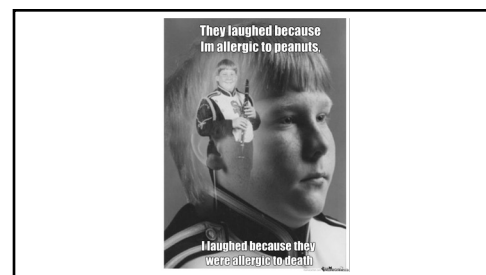
Amoxicillin	Ampicillin	Cefadroxil	Cefaclor	Cefprozil	Cefuroxime	Cefixime	Ceftriaxone	Cefepime	Cefotaxime	Cefotetan	Cefoperazone	Cefepime
												

Each column represents a group with identical R-group side chains.

Cross-reactivity rates as high as 30% when identical/similar side chains

Cross Reactivity among Beta-Lactams, A. Rasmussen et al.
J Am Allergy Asthma Soc 2004;10

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Drug Allergy: An Updated Practice Parameter 2010

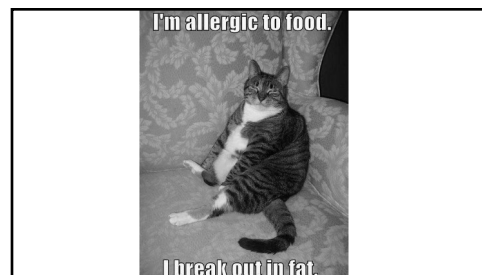
- There is no evidence to suggest allergic cross-reactivity between sulfonamide antibiotics and nonantibiotic sulfonamides. (C)
- Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. Strom et al, NEJM 2003:
 - Retrospective cohort study from pool of 8 million patients in the UK
 - Of 969 patients with an allergic reaction after a sulfonamide antibiotic, 96 (9.9%) had an allergic reaction after subsequently receiving a sulfonamide nonantibiotic
 - Of 19,257 who had no allergic reaction after a sulfonamide antibiotic, 315 (1.6%) had an allergic reaction after receiving a sulfonamide nonantibiotic
- CROSS-REACTIVITY??

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Conclusion

- Allergy to a sulfonamide antibiotic increases rate of allergic reaction to sulfonamide nonantibiotic, but this association appears to be due to a predisposition to allergic reactions in general rather than to cross-reactivity with sulfonamide-based drugs
- This confounds many studies on drug allergy; patients predisposed to drug allergies (multiple drug allergy syndrome)


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Radiocontrast Media Anaphylactoid Reactions

- RCM reactions occur in approximately 1% to 3% of patients who receive ionic radiocontrast media and less than 0.5% of patients who receive nonionic agents
- Severe life-threatening reactions occur in 0.22% of patients receiving ionic RCM and 0.04% of patients receiving nonionic RCM




Reaction Parameters

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Radiocontrast Media Anaphylactoid Reactions

- Risk factors for anaphylactoid reactions to RCM
 - Female sex, asthma, history of previous anaphylactoid reaction to RCM
 - Beta-blocker exposure and/or the presence of cardiovascular conditions is associated with greater risk for more serious anaphylactoid reaction

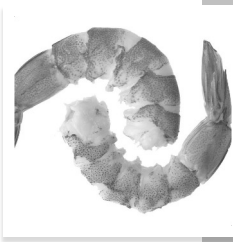


Reaction Parameters

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Radiocontrast Media Anaphylactoid Reactions

- No convincing evidence that individuals with seafood allergy are at elevated risk for anaphylactoid reaction to RCM compared with the general population
- The pathogenesis of anaphylactoid reactions is unrelated to iodine. Rates of anaphylactoid reactions to low-osmolar contrast agents are significantly lower than rates observed with conventional contrast, yet their content of iodine is similar



Reaction Parameters

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Radiocontrast Media Anaphylactoid Reactions

- Management of a patient who requires RCM and has had a prior anaphylactoid reaction to RCM includes the following:
 - (1) determine whether the study is essential
 - (2) determine that the patient understands the risks
 - (3) ensure proper hydration
 - (4) use a nonionic, iso-osmolar RCM, especially in high-risk patients (asthmatic patients, patients taking beta-blockers and those with cardiovascular disease)
 - (5) use a pretreatment regimen that has been documented to be successful in preventing most reactions
 - One reported regimen consists of prednisone, 50 mg, at 13, 7, and 1 hour before the procedure; diphenhydramine, 50 mg, at 1 hour before the procedure; and either ephedrine, 25 mg, or albuterol, 4 mg, at 1 hour before the procedure

Reactions: Preventions

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Malpractice Award in Iowa

- 2015: 40-year-old Carrie DeJongh, who died on June 9, 2015 while receiving a CT scan awarded a \$29.5 million verdict by Sioux County jury
- DeJongh was at the center to receive a CT scan. She had an allergic reaction to the contrast dye given to her for the scan and went into anaphylactic shock and lost consciousness
- Doctor administering the scan gave DeJongh Benadryl but failed to immediately take her vital signs and did not administer epinephrine, which could have reversed her anaphylactic shock, attorney stated

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Radiocontrast Media Anaphylactoid Reactions

- Delayed reactions to RCM, occurring between 1 hour and 1 week after administration, occur in approximately 2% of patients. Usually mild, self-limited cutaneous eruptions and do not require any treatment. Although SJS, DRESS, TEN can occur

Reactions: Preventions

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Aspirin/NSAIDs – anaphylaxis or anaphylactoid

- Aspirin/NSAIDs can cause a spectrum of drug allergic reactions;
 - Exacerbation of underlying respiratory disease (aberrant arachidonic acid metabolism)
 - Urticaria/angioedema (may or may not cross-react depending on mechanism)
 - Anaphylaxis (generally no cross-reactivity between NSAIDs)
 - Rarely pneumonitis and meningitis
- Selective COX-2 inhibitors are generally well tolerated in patients with chronic idiopathic urticaria, although there may be rare exceptions

Reactive Airways

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Dermatologists Recommend Regularly Checking Body For Screaming Demon Face Bulging Out Of Skin

4/15/18 8:00am



NEW YORK—Saying it can be as easy as doing a quick once-over in the shower, the American Dermatological Association released a statement Friday recommending thorough, regular checks of the entire body for screaming demonic faces bulging out of your skin. "It's important to catch these things early, so we suggest..."

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Steroid allergy- possible?

- Yes!
- First documented allergy to CS in the 1950s to topical and injected hydrocortisone
- CS allergy following topical application ranges from 0.2% to 5% (contact dermatitis)
- Reactions (anaphylaxis) following systemic use of CS about 0.1%
- ABCD classification system of CS based on structural and clinical characteristics determine cross-reactivity rates


Allergic hypersensitivity to topical and systemic corticosteroids: a review. Allergy 2008; 63: 1111-1121

81

[illegible]

83

[illegible][illegible]



Local Anesthetic Allergy

- Most adverse reactions to local anesthetics are not due to IgE-mediated mechanisms but are due to nonallergic factors:
 - vasovagal responses
 - anxiety
 - toxic reactions including dysrhythmias
 - idiosyncratic reactions due to inadvertent IV epinephrine
- Documentation of IgE-mediated reactions is extremely rare

Practice Procedures

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Local Anesthetic Allergy

- Summary Statement 145: To exclude the rare possibility of an IgE-mediated reaction to local anesthetics, skin testing and graded challenge can be performed in patients who present with a reaction history suggestive of possible IgE-mediated allergy to these drugs. (B)



Practice Procedures

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Local Anesthetic Allergy

- Local anesthetics are either group 1 benzoic acid esters or group 2 amides
- On the basis of patch testing, the esters cross-react with each other, but they do not cross-react with amide drugs. Unknown relevance this has on immediate-type reactions to local anesthetics
- Testing reagent should not contain epinephrine or other additives, such as parabens or sulfites

Practice Procedures

TABLE 2. Local anesthetics

AMIDE GROUP	ESTER GROUP
Lidocaine	Cocaine
Mepivacaine	Procaine
Bupivacaine	Chloroprocaine
Etidocaine	Tetracaine
Prilocaine	

Practice Procedures

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Gadolinium-based Contrast Allergy

- 112 immediate hypersensitivity reactions (0.079%) of 141,623 total doses
- Among the 6 evaluated MR contrast media, gadodiamide had the lowest rate (0.013%) of immediate hypersensitivity reactions, while gadobenate dimeglumine had the highest rate (0.22%)
- Risk factors
 - Female patients
 - Allergies
 - Asthma
 - Higher frequency of exposure to MR contrast
- Patients with a previous history of immediate hypersensitivity reactions had a 30% recurrence after re-exposure to MR contrast

Immediate Hypersensitivity Reaction to Gadolinium-based MR Contrast Media
J Am Coll Radiol 2013;10:1003-1012

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Gadolinium-based Contrast Allergy

- The most common symptom was urticaria (91.1%), and anaphylaxis occurred in 11 cases (9.8%). The mortality rate was 0.0007% because of one fatality.
 - 76yo F w/hypotension, dyspnea, nausea, and decreased consciousness after gadobutrol injection. Died despite prompt cardiopulmonary resuscitation
- Breakdown of reactions
 - Mild reactions – 83%
 - Moderate reactions – 7.1%
 - Severe reactions – 9.8%
- The over incidence of mild, moderate, and severe reactions – are 0.066%, 0.006%, and 0.008%, respectively

Immediate Hypersensitivity Reaction to Gadolinium-based MR Contrast Media
J Am Coll Radiol 2013;10:1003-1012

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Gadolinium-based Adverse Reactions

- Severe reactions endangering patient's life
 - rate between 0.001%–0.01%
 - Severe respiratory distress, responsiveness, arrhythmia, convulsion, cardiopulmonary arrest, progressive angioedema, marked hypotension

Immediate Adverse Reactions to Gadolinium-Based MR Contrast Media: A Retrospective Analysis on 10,608 Examinations. *Granata et al. Visceral Research*

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Fluoroquinolone Allergy?

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