The Hidden Cost of Penicillin Allergy

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Disclosures

- I have no actual or potential conflict of interest in relation to this program/presentation

Objectives

- Examine the epidemiology and cost of penicillin allergy
- Briefly review the immune system
- Appreciate the pathophysiology of beta lactam allergy
- Understand the testing procedure
- Discuss predictive value
- Evaluate efficacy and safety of testing in sub-populations
- Review cephalosporin cross reactivity

Penicillin Allergy

Penicillin Allergy

- Most commonly reported drug allergy
- Penicillin allergy is self-reported in 10% of American population
  - 20-25 million Americans
  - Type I immediate hypersensitivity
- Systematic review/meta-analysis of 2010 – 2015 databases; Prevalence of β-lactam hypersensitivity:
  - 1.98% pediatric group
  - 7.78% adult group
  - 2.84% combined group

Reasons for Discordance

- Decreasing rate of positive skin test results over last 20 years
  - Rates of positive penicillin testing declined from >10% to <5% from 1995-2007 (Macy et al. The Permanente Journal 2009)
- Waning reactivity
- Index reaction was not attributable to penicillin
  - Alternative antibiotic
  - Underlying illness
  - Interaction between infection and antibiotic

Natural History

- Penicillin specific IgE antibodies decrease over time
  - 50% of patients lose sensitivity 5 years after last reaction
  - 80% of patients lose sensitivity 10 years after last reaction
- Prevalence of positive skin test was related to time elapsed from index reaction (Sullivan et al. JACI 1981)
  - 93% positive 7-12 months after reaction
  - 22% positive 10 years after reaction

Morbidity of β-Lactam Allergy

- Increased use of broad spectrum antibiotics
  - Vancomycin: 20-40% versus 12-17%
  - Fluoroquinolones: 25% versus 14%
  - Clindamycin: 24% versus 6%
  - 3rd generation cephalosporins

Macy et al. JACI 2014 & Picard et al. JACI In Practice, 2013

Morbidity of β-Lactam Allergy

- Antibiotic resistance
  - Vancomycin resistant enterococci
    - 30% more VRE
    - Risk factors: Vancomycin, cephalosporins & quinolones
  - MRSA: 14% more often
  - Clostridium difficile
    - 23% more often
    - Quinolones and cephalosporin

Macy et al. JACI 2014 & Picard et al. JACI In Practice, 2013

Surgical Morbidity

- 2016 study examining preoperative prophylactic antibiotic choice and surgical site infection rates after hysterectomy
- Patients received β-lactam or alternative to β-lactam antibiotics
- 21,000 + hysterectomies
- Overall rate of surgical site infection: 2.06%
  - β-lactam: 1.8%
  - Non-β-lactam: 3.1%; adjusted OR 1.7

Uppal, Obstet Gynecol Feb 2016

Health care use and serious infection prevalence associated with penicillin "allergy" in hospitalized patients: A cohort study

Eric Macy, MD, MS,[a] and Richard Contreras, MS[b] *San Diego and Pasadena, Calif*

- Retrospective, matched cohort study of 52,000 patients with charted allergy to penicillin on admission
  - Kaiser Foundation hospitals 2010-2012
  - 11.2% of hospitalized patients
- Primary and secondary goals
- Cases with penicillin allergy
  - Averaged **0.59** more hospital days
  - Significantly more fluoroquinilones, clindamycin and vancomycin ($p<.0001$)
  - Increased prevalence of C. difficile, MRSA and VRE infections

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 = 12,772 (12.4%)
4	*	Ceftriaxone*: N = 11,683 n = 8,570 (16.6%)		Metronidazole: N = 18,392 n = 14,341 (13.9%)
5		Metronidazole: N = 11,427 n = 8,542 (16.6%)	*	Ciprofloxacin*: N = 17,461 n = 13,416 (13.0%)
6		Cefazolin: N = 8,489 n = 7,490 (14.5%)		Piperacillin: N = 14,561 n = 11,157 (10.8%)
7		Gentamicin: N = 6,025 n = 5,329 (10.3%)		Azithromycin: N = 12,837 n = 10,045 (9.7%)
8		Azithromycin: N = 5,812 n = 4,610 (8.9%)		Ampicillin: N = 7,153 n = 6,536 (6.3%)
9	*	Moxifloxacin*: N = 3,908 n = 3,194 (6.2%)		Gentamicin: N = 6,480 n = 5,809 (5.6%)
10	*	Ceftazidime*: N = 3,641 n = 2,741 (5.3%)	*	Ceftazidime*: N = 5,916 n = 4,641 (4.5%)

* Antibiotics associated with increased risk of C. difficile

N: Courses of antibiotics
n: Unique subjects exposed

Macy JACI March 2014

Economic Cost of β-lactam Allergy

- Outpatient antibiotic cost
  - $26.81 versus $16.28
- Inpatient antibiotic cost
  - $137 versus $75
  - Equivalent of $241.61/hospital stay
- Duration of hospital stay
  - 0.59 days longer than control subjects
- Potential cost savings for penicillin skin testing compared to extended hospital stay
  - Calculated as $60 million during 3 year study period
- Multiply cost savings over patient's lifetime

Clinical Outcomes of Allergy Label

- 12,000 inpatients who received 1 antimicrobial
- 11% (1324) with antimicrobial allergy label
- Adjusted Outcomes:
  - Length of stay was 1.16 days longer
  - ICU admission 1.4 times greater (aOR)
  - Receipt of >1 course of antibiotics 1.6 (aOR)
  - Increased risk of death 1.56 (aOR)
  - NOT associated: readmission within 4 weeks of discharge

Charneski et al. Pharmacotherapy, 2012

Persistence of EMR Labeling

- Persistence of penicillin allergy label (PAL) in an EMR despite documented penicillin tolerance
- Ambulatory Patients >18 years or older with >3 visits
  - 67% were labeled upon entry into the EMR
  - 96% remained persistently labeled
- **39% (4321/11,216) had EMR documentation of having received and tolerated a penicillin**
- Increased prevalence of C. difficile infection
- Greater broad spectrum antibiotic utilization

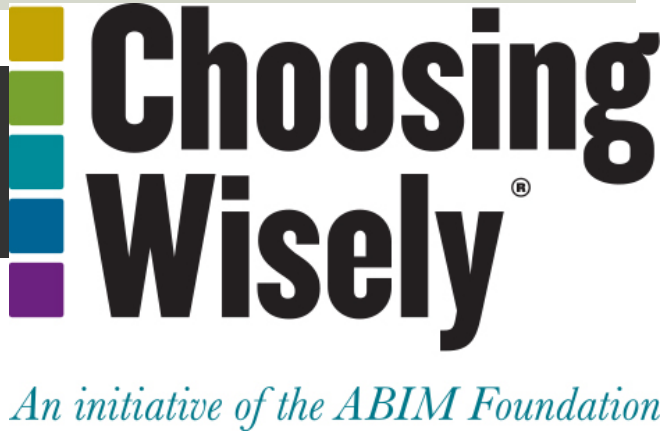
Gerace et al. JACI 2015

Survey on Prescriber Understanding

- 276 prescribers surveyed early 2016
  - Advanced practice providers & attending physicians
- Only 30% correctly identified that 90% of patients with PAL would tolerate penicillin
- 80% of prescribers consult allergy 0-1 time a year
- 42% believed penicillin allergy does not resolve with time

ACAAI 2016 Meeting: Abstract O054. November, 2016

Antibiotic Stewardship



- Less than 0.1% of subjects with history of penicillin allergy undergo allergy testing in the US annually (Macy et al, JACI 2014)
- Skin test is rarely used to undiagnose allergy
- Choosing Wisely: Don't overuse non-beta lactam antibiotics in patients with a history of penicillin allergy, without an appropriate evaluation
- Antibiotic Stewardship Programs: should promote [antibiotic] allergy assessments and penicillin skin testing when appropriate

Proof of Concept

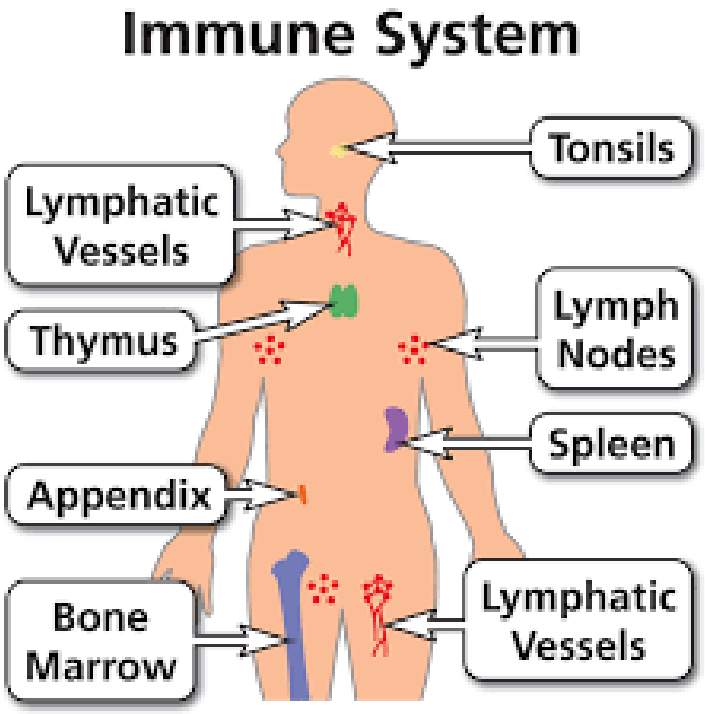
- Prospective case controlled study 2010-2012
- Penicillin allergy testing, primarily done in the outpatient setting, resulted in (per coverage year):
  - 0.09 fewer out patient visits
  - 0.13 fewer ED visits
  - 0.55 fewer hospital days ($P < .001$)
  - Cost savings:
    - $1915 per patient per year
    - $2 million in 3.6 year study span

Macy et al. JACI In Practice 2017

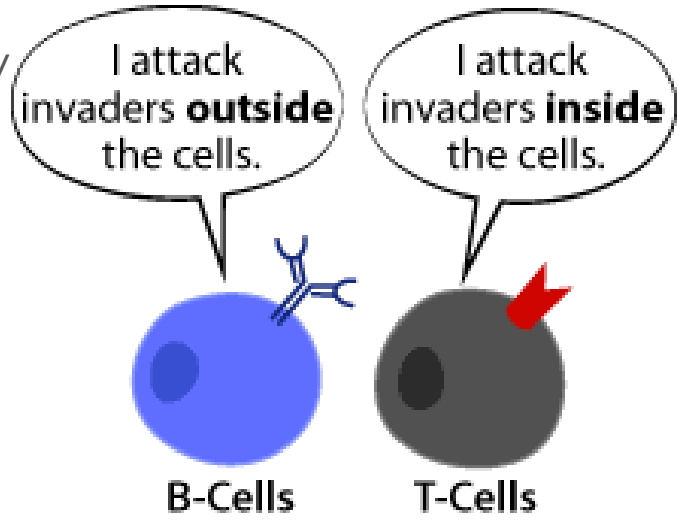
Immune System Overview

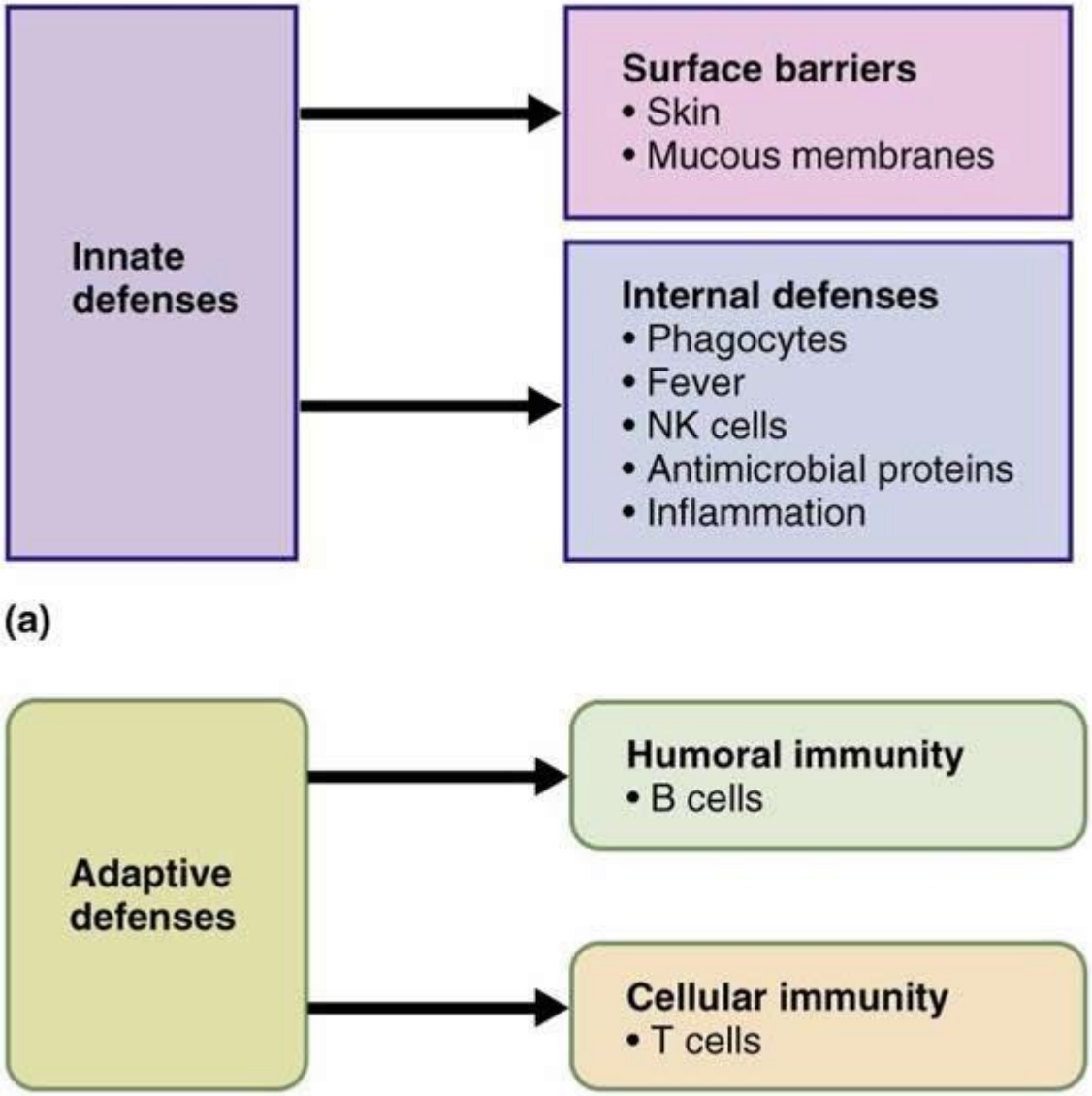
Immune System Overview

- Network of cells, tissues and organs that work together to defend the body against attack by foreign invaders
  - Bacteria, viruses, parasites

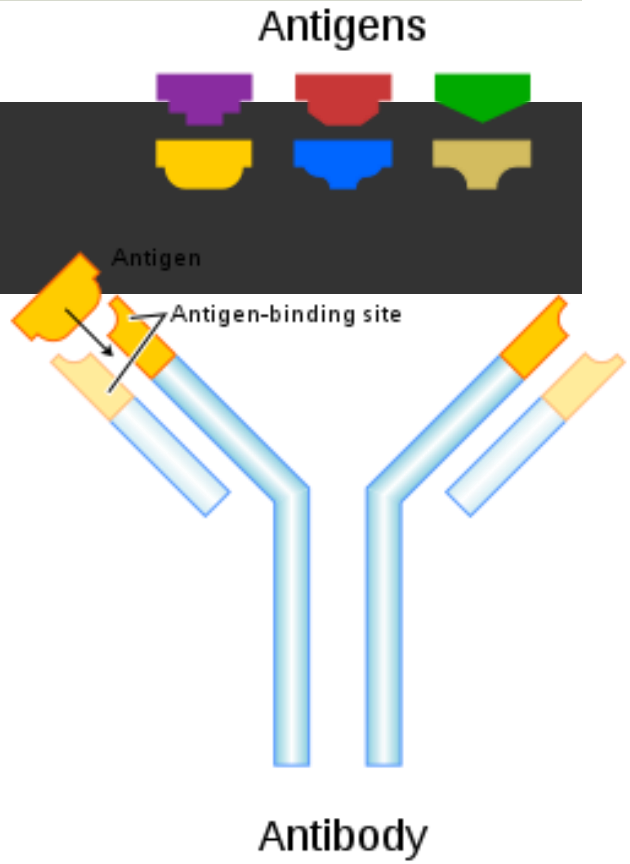


- Innate Immunity
  - Provides early, rapid response
  - Responds the same way each time
  - Alerts and recruits adaptive immunity
- Adaptive Immunity
  - Recognizes and reacts, with specificity and memory
  - Microbial and nonmicrobial antigens
  - Components
    - B cells
    - T cells



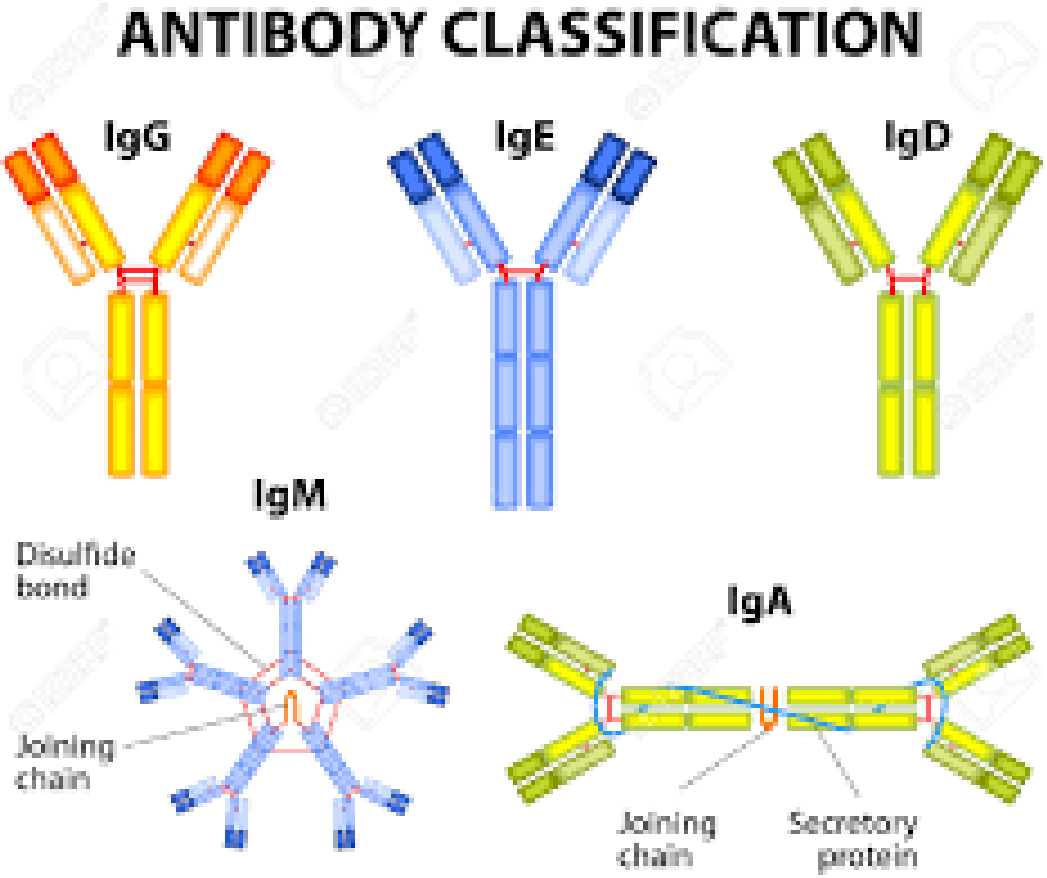

Innate defenses
Surface barriers
• Skin
• Mucous membranes
Internal defenses
• Phagocytes
• Fever
• NK cells
• Antimicrobial proteins
• Inflammation
(a)
Adaptive defenses
Humoral immunity
• B cells
Cellular immunity
• T cells
(b)

Antibodies



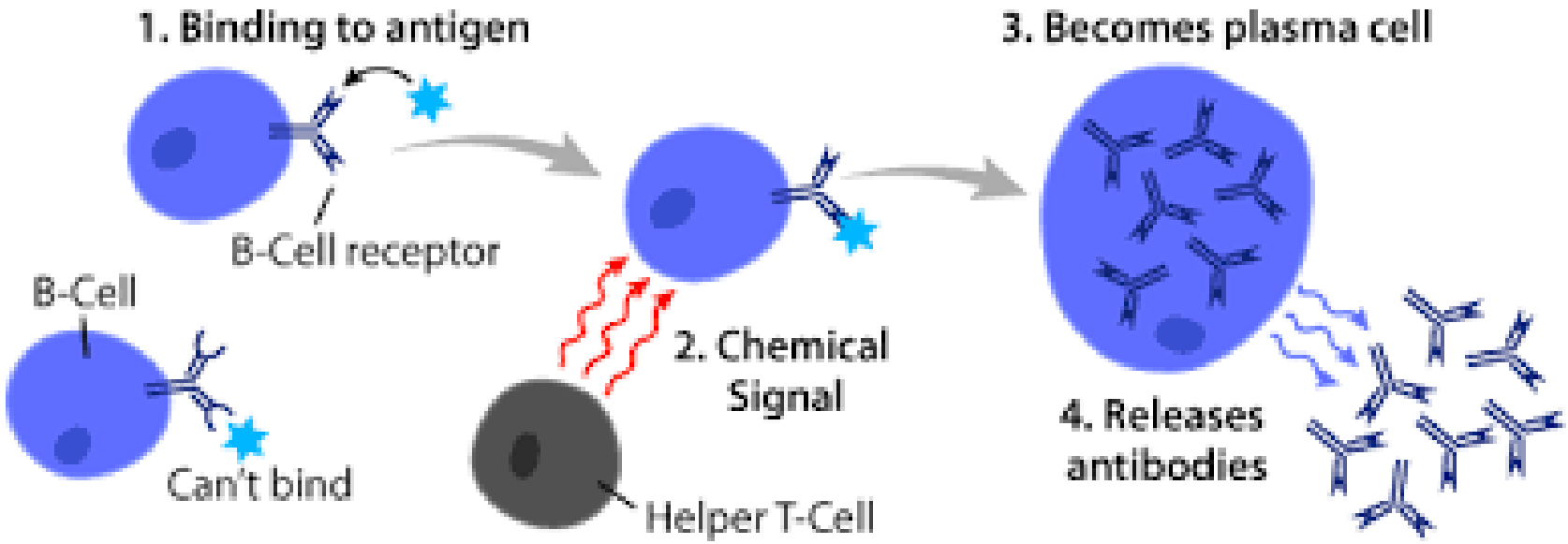
- Immunoglobulins (Ig) or antibodies (Ab) are Y shaped proteins produced by B cells
- They are used by the immune system to neutralize pathogenic bacteria and viruses
- The antibody binding site recognizes a specific epitope on an antigen

Types of Antibodies



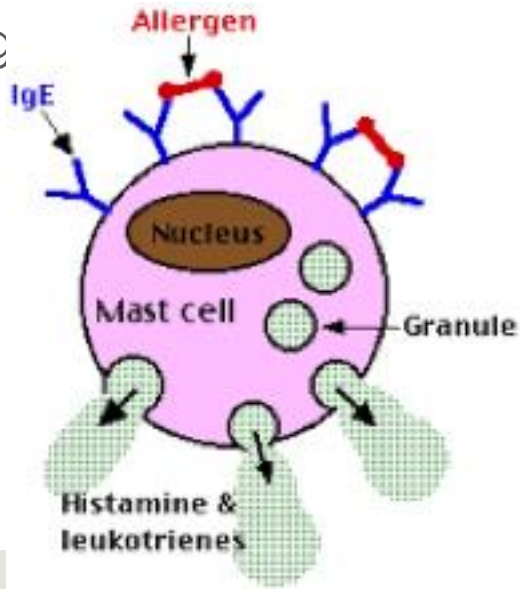
Antigen

- Unique molecular pattern on a pathogen or protein that stimulates an immune response



Mast Cells and Anaphylaxis

- Mast cells are granulocytes that contain
  - Histamine, heparin, tryptase, cytokines
- IgE, produced in response to an initial exposure to an allergen, is bound to mast cells
- Upon the 2nd exposure, allergen cross links IgE primed mast cells, causing degranulation
- Anaphylaxis: body wide degranulation, leading to vasodilation
  - Urticaria and angioedema
  - Bronchospasm
  - Rhinitis, conjunctivitis
  - Hypotension



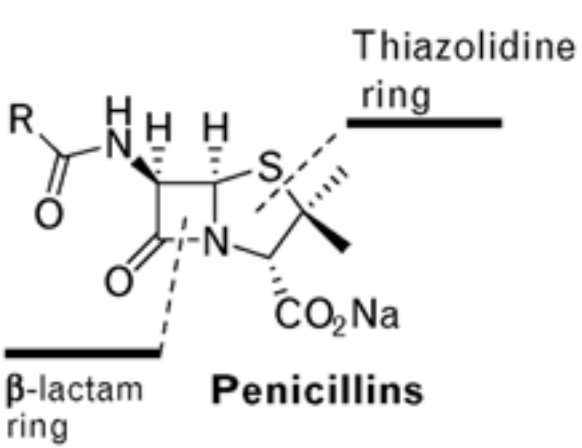
Pathophysiology of β-Lactam Allergy

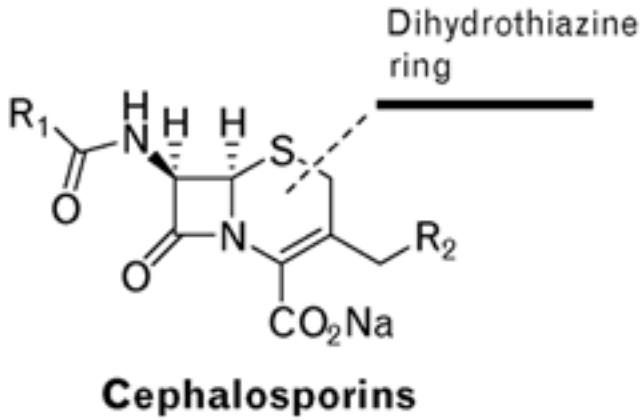
β-Lactam Antibiotics

Dorothy Hodgkin

- 2 major classes:
  - Penicillins
  - Cephalosporins

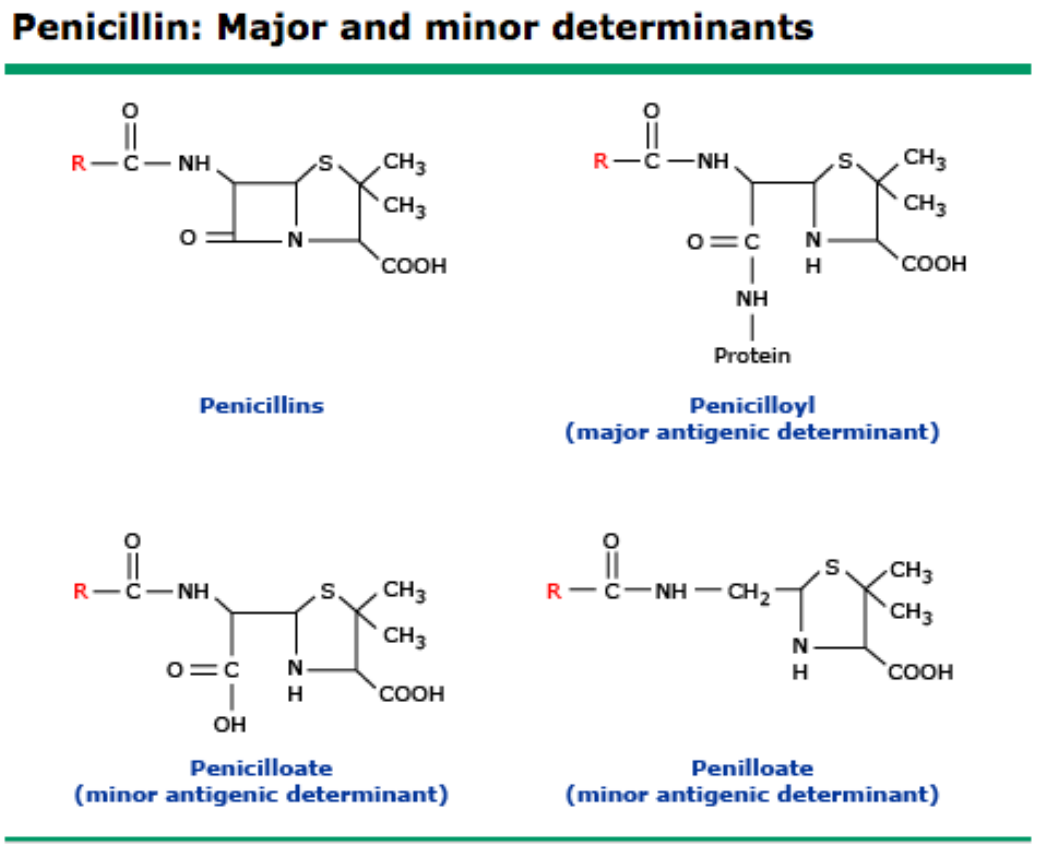
- 4 minor classes:
  - Monobactams, carbpenems, oxacephems, beta-lactamase inhibitors





Allergenicity of Penicillin

- Chemically inert in natural state
- Reactive intermediate
- Hapten-carrier effect
  - Hapten: penicillin degradation product
  - Carrier: protein
- IgE forms to penicillin-self protein complex



Cephalosporin allergy

- Cephalosporins are β-lactams that also bind to proteins
  - Haptenization is slower and less efficient
  - R2 is lost after the opening of the BL ring
- IgE antibodies recognize
  - R1 side chain and part of the BL ring structure
- Cross-reactivity between cephalosporins is explained through similarity of R1 side chain

Penicillin Skin Testing

Penicillin Skin Testing

- Skin testing detects specific IgE on a patient's mast cells
  - Allergen introduced into the skin, comes into contact with cutaneous mast cells
  - Allergen cross links specific IgE bound to mast cells, and the cells are activated
  - Mast cell activation results in a transient wheal and flare reaction
- Sensitization: detectable penicillin specific IgE
  - High risk for immediate hypersensitivity reaction
- Most rapid, sensitive and cost effective testing modality

Indications for Skin Testing

- History of immediate hypersensitivity reaction
- Unclear histories of past penicillin reactions
  - Isolated urticaria, isolated angioedema, or unspecified rash
- Ideally performed when the patient is well and not in urgent or immediate need of antibiotic therapy
- Trend for testing even if they have alternatives to penicillin or beta-lactam therapy
- Special populations
  - Subjects in ICU, children and pregnant women

Contraindications for Skin Testing

- History of severe blistering skin reactions, such as Stevens Johnson syndrome or toxic epidermal necrolysis (TEN)
- History of non-IgE mediated reaction
  - Hemolytic anemia, interstitial nephritis
- Over-reactive skin conditions
  - CIU, dermatographia

- Inability to temporarily hold medications which interfere with skin testing or interfere with treatment of anaphylaxis
- Delay testing for 4 weeks following acute reaction

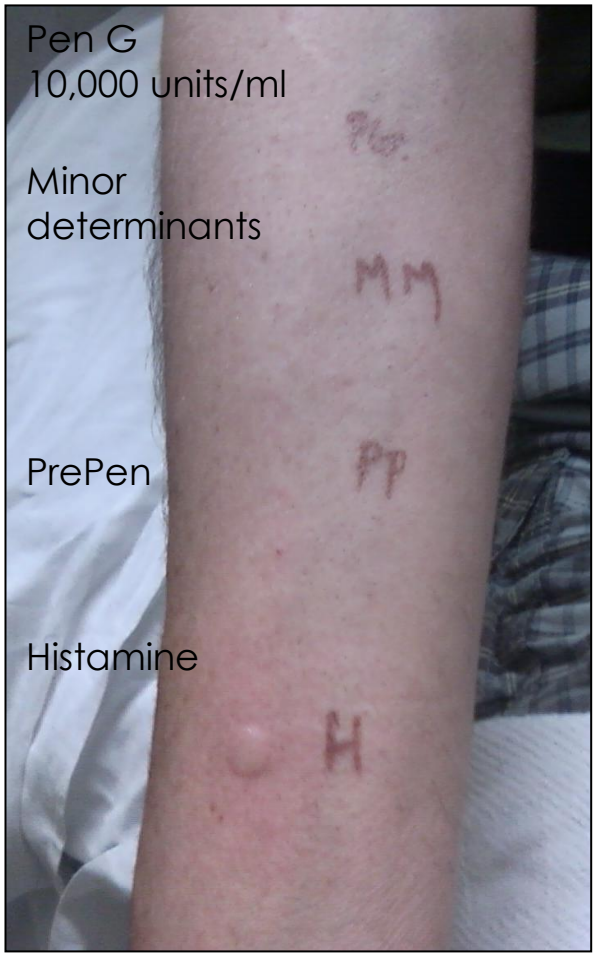
Skin Testing Reagants

- Major determinant
  - Penicilloyl-polylysine (PPL)
- Minor determinants
  - Benzylpenicillin/Penicillin G (10,000 units/mL)
  - Penicilloate (0.01 M)
  - Penilloate (0.01M)

MDM: minor determinate mixture

- Ampicillin or amoxicillin
- Positive and Negative controls
- Full strength skin prick, followed by intradermal injections, in duplicate
  - Dilute 1:10, 1:100 for history of severe allergic reaction

Skin Prick



Photographs courtesy of Laurianne Wild, MD

Intradermal Testing

Predictive Values

- Positive Predictive Value
  - Studies limited due to ethical concerns
  - Avoid natural, amino(ampicillin, amoxicillin) and semisynthetic penicillin
- Negative Predictive Value with minor determinant: 97-99%
  - 1-3% of penicillin skin test negative patients develop reactions upon drug challenge
  - Absence of MDM: potentially misses 1-10%
  - Current NPV without MDM: 90-93%
- Confirmatory oral challenge after negative skin test
- In vitro testing: unknown predictive value

Future Risk of Adverse Drug Reaction

- Patient with negative penicillin skin testing and oral challenge will have new penicillin associated ADR rates similar to the general population
  - 0.5 – 5.0%
  - Dependent on gender and other drug "allergy" history
  - Higher rates
    - Parenteral administration
    - Female subjects
    - Multiple-drug intolerance syndrome (MDIS)
      - Increased overall health care use
      - No increase in mortality rate
  - No need for repeat skin testing

Inpatient Experience

- 43 year old male, PMH of asthma, active IVDU and adverse reaction to penicillin, found to have MSSA bacteremia
  - Treated with vancomycin, unable to achieve therapeutic trough level, transitioned to daptomycin
  - Serial blood cultures MSSA positive
- Penicillin Allergy
  - Gum and facial swelling and respiratory compromise, age 3-4
- ID: nafcillin is the therapeutic agent of choice

Penicillin Skin Test

	Skin Prick	ID #1	ID #2
Pre-Pen	0/0 mm NEG	0/0 mm NEG	0/0 mm NEG
Pen G (10,000 U)	0/0 mm NEG	0/0 mm NEG	0/0 mm NEG
Histamine	4/23 mm POS	NA	NA
Saline	0/0 mm NEG	3/0 mm NEG	NA

Skin Test Results: No evidence of penicillin specific IgE on prick and intradermal skin testing with major determinant and Pen G. Patients with negative skin testing will tolerate penicillin, at the time of testing, without the risk of an IgE mediated reaction with 90-93% certainty.

Proceeded with oral ingestion challenge.

Oral Ingestion Challenge

- Amoxicillin 250 mg/5 mL oral suspension
- Small amount was applied to patient's lower lip mucosa
- After 15 minutes, patient reported some throat discomfort. Patient was examined, and physical exam was negative for lip, tongue or gum edema, posterior oropharynx erythema, inspiratory or expiratory wheezing
- Patient proceeded with full dose oral challenge, and was observed for 60 minutes. Patient tolerated procedure well, and remained at baseline

Results

- Penicillin allergy was removed from the patient's listed allergies
- Patient has risk of future acute reaction and delayed reaction to penicillin equivalent to the standard population
- Nafcillin therapy was initiated

Post-Penicillin Rash

- Over the next 3 days, the patient developed progressively worsening morbilliform eruption
  - Present on back prior to nafcillin
  - Spread to abdomen, upper & lower extremities
- Pruritus improved with 2nd generation antihistamine, bid
- Possible etiologies
  - Delayed hypersensitivity reaction to current or prior Abx
  - Viral induced
  - Heat induced dermatitis
- Counseled and continued therapy
  - Resolved

Skin Testing in Sub-Populations

Skin Testing in Pregnant Women

- Study examined safety and utility of PST in pregnant women with a history of penicillin allergy & GBS colonization
- 56 pregnant women were skin tested, and if negative, penicillin class antibiotics were recommended for intrapartum GBS prophylaxis
- 2 reactions associated with PST
  - generalized pruritus (hives, +); fainting (fainting,-)
- 3 positive PSTs
- 47/53 PST negative patients received intrapartum PCN
  - 2 delayed onset rashes
  - 1 immediate onset rash with vancomycin

Macy, Anals of AAI 2006

Skin Testing in Hospitalized Patients

- NIAID collaborative clinical trial to evaluate the predictive value of penicillin skin testing, with major and minor determinants, in hospitalized adults
- 1539 patients: 11.4% positive skin tests
  - 825 history positive: 18% positive PST
  - 104 unsure: 4% positive PST
  - 616 history negative: 4% positive PST
- 1.2% immediate reactions to penicillin: all history +/PST-
- NPV with PPL and MDM: 99%
  - 16% reacted to solely MDM

Sogn, Arch Internal Medicine 1992

Pediatric Population

- Penicillin skin testing is a safe and effective tool for evaluating penicillin allergy in the pediatric population
- 778 children <18 yo underwent skin testing with PPL, Pen G, amoxicillin and penicilloate (institution produced)
  - 90.4% negative
  - 8.5% positive
  - No adverse reaction to SPT
- 50% of patients with negative SPT had oral challenge
  - 3.8% mild adverse reaction

Fox JACI Jul 2014

Cephalosporin Allergy

Cephalosporin Use

- Most common antibiotic class in both penicillin allergic and control subjects
- CDC: 2.5% cross reactivity, primarily in cephalosporins which share identical R-group side chains to penicillins
  - "Negligible" for most 2nd and all 3rd generation cephalosporins
- Cross reactivity amongst cephalosporins related to R-1 side chain determinants
- In penicillin-allergic subjects, >30% cross-reactivity when cephalosporins has identical side chains to penicillin
  - <1% cross-reactivity between penicillins and carbapenems or aztreonam

Romano, Curr Allergy Asthma Rep 2016

Groupings By R Side Chain

Amino Amino Methoxyimino

Table 16. Groups of β-Lactam Antibiotics That Share Identical R_1-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			

Tolerated cefaclor, and cefazolin, cefibuten

[a] Each column represents a group with identical R_1 side chains.

Aminocephalosporins tolerated cefuroxime, ceftriaxone, cefazolin, cefibuten

Table 17. Groups of β-Lactam Antibiotics That Share Identical R_2-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 R_2 side chains.

Drug Allergy Practice Parameters

Conclusions

- Penicillin testing is safe, reproducible and effective in delabeling up to 90% of individuals with beta-lactam allergy
- Less health care utilization
- Fewer broad spectrum antibiotics
- High yield patients
  - Remote history of any adverse reaction to penicillin
  - Multiple listed antibiotic allergies
  - Penicillin allergy label + higher risk of infection:
    - Diabetes, HIV, malignancy, immunosuppression
  - Inpatients with PAL when the therapeutic agent of choice is a beta lactam


Penicillin
Allergy

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