ALBANY COLLEGE OF PHARMACY
AND HEALTH SCIENCES

Antibiotic Safety: From Allergy to QTc

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Disclosures

- I have no actual or potential conflicts of interest related to this presentation.

Objectives

- Compare cardiac risks between macrolides and fluoroquinolones
- Summarize the literature on vancomycin- and vancomycin/piperacillin-tazobactam- induced nephrotoxicity
- Describe an evidence-based approach to assess beta-lactam cross reactivity

When assessing risk of beta-lactam cross-reactivity:

- Class to class risk assessments appear to be sufficient (Eg, penicillin and cephalosporins)
- Robust data are limited to within-class assessments (eg, penicillin to penicillin)
- Agent-specific assessments appear to be best (eg, amoxicillin and ceftriaxone)
- Data are insufficient to easily assess cross reactivity

http://www.quickmeme.com/fingers-crossed

QT prolongation & Torsades de Pointes (TdP)

- Mechanism: Potassium current (I_{kr}) inhibition → delays cardiac repolarization
- TdP risk factors
  - QTc >500 msec or >60 msec change from baseline
  - Bradycardia
  - Electrolyte imbalances
  - Heart disease (also HFrEF, MI)
  - Female gender
  - Age >65 years
- "Swiss cheese" effect

Li and Ramos. PT 2017 Jul; 42(7): 473–477

Azithromycin and levofloxacin

- QTc prolongation themselves (& versus other class agents)

- Cardiac risks: Lu et al., 2015: 15 case reports/series, 5 observational studies, 5 clinical trials

Agent	Study	Outcome; population	Estimate
Azithromycin	Ray et al. 2012	CV death; Medicaid	Amox (D1-5): HR 2.49 (1.38, 4.50) Levo (D1-5): HR 1.27 (0.66, 2.47)
	Svanstrom et al. 2013	CV death; general	Pen V (D1-5): RR 0.93 (0.56, 1.55)
	Rao et al. 2014	Arrhythmia; Veterans	Amox (D1-5): 1.77 (1.20, 2.62) Levo (D1-5): 0.73 (0.47-1.13)
	Mortensen et al. 2014	CV events; Veterans	Other abx: OR 1.01 (0.98-1.05)
Levofloxacin	Ray et al. 2012	CV death; Medicaid	Amox (D1-5): HR 1.99 (0.93, 4.23)
	Rao et al. 2014	Arrhythmia; Veterans	Amox (D1-5): HR 2.43 (1.56, 3.79)

Amox, amoxillin; levo, levofloxacin; abx, antibiotics; pen V, penicillin; D1-5, days 1-5

Lu et al. Expert Opin Drug Saf 2015;14(2):295-303

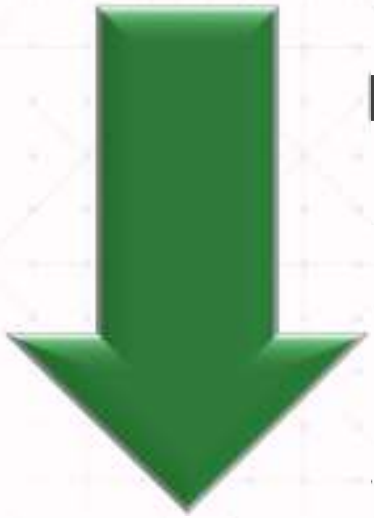
Considerations

- Populations (co-morbidities, severity of illness)
- Correlation vs causation
- Non-randomized design

Fluoroquinolone arrhythmia risk factors

Cardiovascular Disease

45-85 events/100,000 patients



No Cardiovascular Disease

5-44 events/100,000 patients

AMDAC and DSaRM Advisory Committee. FDA Briefing Information, 2015.

Management

- Correct modifiable risk factors (e.g., replete K, Mg)
- Monitoring
  - Modifiable risk factors
  - EKG at baseline, periodically during treatment depending on risk assessment
  - Patients: signs/sxs of dizziness, palpitations, syncope

Patient #1

- 60 yo F presents w/ chills, lightheadedness, hemoptysis
- PMH: afib (on sotalol), HFpEF, CAD, COPD
- All: cefdinir (nausea)
- Afebrile, BP 87/52→101/62, HR 78, 5L NC, respiratory alkalosis on ABG, WBC 13.3
- Urine legionella Ag+, Scr 0.69
- QTc 500 (SR, LBBB)
- Ceftriaxone 1g IV q24h, doxycycline 100mg IV q12h

Vancomycin nephrotoxicity

- Acute tubular necrosis?
- Risk factors
  - Daily doses >4 grams
  - Trough levels >20 mcg/ml
  - Therapy >6 days
  - Concurrent nephrotoxins
  - Pre-existing renal disease
  - Obesity
  - Severe illness
- Negative consequences

Mergenhagen and Borton. J Pharm Practice 2014;27(6):545-53

Vancomycin-piperacillin/tazobactam (VPT) nephrotoxicity

- Hammond et al: 2017 Meta-analysis (14 studies)

Population	Unadjusted analysis	Adjusted analysis
All studies	OR 3.12 (2.04, 4.78) p<0.001	OR 3.11 (1.77, 5.47) p<0.001
Vanco + other BL	OR 3.60 (2.28, 5.68) p<0.001	OR 3.31 (2.13, 5.12) p<0.001
Vanco + cefepime	OR 2.63 (1.62, 4.28) p<0.001	OR 3.78 (2.48, 5.78) p<0.001
Vanco alone*	OR 3.16 (0.67, 14.91) p=0.146	OR 2.50 (0.41, 15.44) p=0.323
Critically ill	OR 3.83 (1.67, 8.78) p=0.002	OR 2.83 (0.74, 10.85) p=0.128
Non-critically ill	OR 2.44 (1.40, 4.27) p=0.002	OR 3.04 (1.49, 6.22) p=0.002

*Meta-analysis by Luther et al. (2018) found increased risk of VPT-AKI vs vancomycin alone (OR 3.40, 95% CI 2.57-4.50)

Hammond et al. Clin Infect Dis 2017;64(5):666-74;
Luther et al. Crit Care Med 2018;46:12-20

VPT nephrotoxicity (Hammond et al. cont'd)

- Considerations:
  - Retrospective observational studies
  - Heterogeneity: I^2 78% in adjusted analysis (E.g. definitions of AKI)
  - Vancomycin duration
  - Concurrent nephrotoxin data
- Per Luther et al., NNH=11

Hammond et al. Clin Infect Dis 2017;64(5):666-74;
Luther et al. Crit Care Med 2018;46:12-20

Navalkele et al. 2017

- VPT vs vanco-cefepime (VC) nephrotoxicity
- Retrospective, matched cohort study (n=558)
  - Illness severity, ICU, duration of combo therapy, vancomycin dose, number of concomitant nephrotoxins
- Combo therapy for ≥48 hours; excluded Scr >1.2
- Primary outcome: incidence of acute kidney injury (AKI)
  - RIFLE, AKIN, vancomycin consensus guidelines

Navalkele et al. Clin Infect Dis 2017;64(2):116-23

Navalkele et al. 2017 (cont'd)

- 279 VPT-VC pairs
- Mean age: 55.9 +/- 16.6 years
- Comparable:
  - Age, length of ICU stay, Charlson comorbidity index, baseline Scr, nephrotoxins, vancomycin (load, dose, pre-AKI troughs)
- More in VPT: septic shock, skin & soft tissue
- More in VC: hypertension, enterobacteriaceae

Navalkele et al. Clin Infect Dis 2017;64(2):116-23

Navalkele et al. 2017 (cont'd)

- Outcomes

Definition	Findings	Hazard ratio
RIFLE	VPT 29% (81/279) vs VC 11% (31/279)	HR 4.0, 95% CI 2.6-6.2, p<0.0001
AKIN	VPT 32% vs VC 14%	HR 3.5, 95% CI 2.3-5.2, p<0.0001
Vancomycin guidelines	VPT 24% vs VC 8.2%	HR 4.4, 95% CI 2.7-7.3, p<0.0001

- MV analysis: VPT independently associated with RIFLE-defined AKI (HR 4.3, 95% CI 2.7-6.7, p<0.0001)

Navalkele et al. Clin Infect Dis 2017;64(2):116-23

Navalkele et al. 2017 (cont'd)

- Outcomes
  - Median onset of AKI: VPT 3 days (IQR 2-5 days) vs VC 5 days (IQR 3-7 days)
  - Median length of stay: VPT 8 days vs VC 6 days (p=0.01)
  - Vancomycin trough (<15 mcg/ml vs ≥15 mcg/ml)
    - VPT: no association
    - VC: AKI 1% (1/76) for <15 mcg/ml vs 13% (20/160) for ≥15 mcg/ml (p=0.003)
- Considerations: pre-AKI troughs; 20% ICU; excluded baseline renal insufficiency

Navalkele et al. Clin Infect Dis 2017;64(2):116-23

Management

- Antimicrobial stewardship
  - Assess need for combo therapy daily/antibiotic time outs
  - Treatment guidelines
  - Antibiotic restrictions
- Monitor Scr
- Assess other risk factors

Patient #2

- 62 yo M presents with coughing and SOB
- PMH: HFrEF (EF 40%), afib, T2DM; recent hospitalization
- Afebrile, BP 102/74, HR 90; WBC 10; Scr 1.0
- Meds of note: bumetanide, lisinopril
- Vancomycin 1250mg (16.5 mg/kg) IV q12h, pip/tazo 3.375g q6h started in ED
- Scr on hospital day 1: 1.7

Types of reactions

- Immediate* (generally <60 min) vs. non-immediate (>60 min)
- Type I* vs. Types II-V
- Type A vs. Type B*
  (immunologic, idiosyncratic)

*IgE-mediated

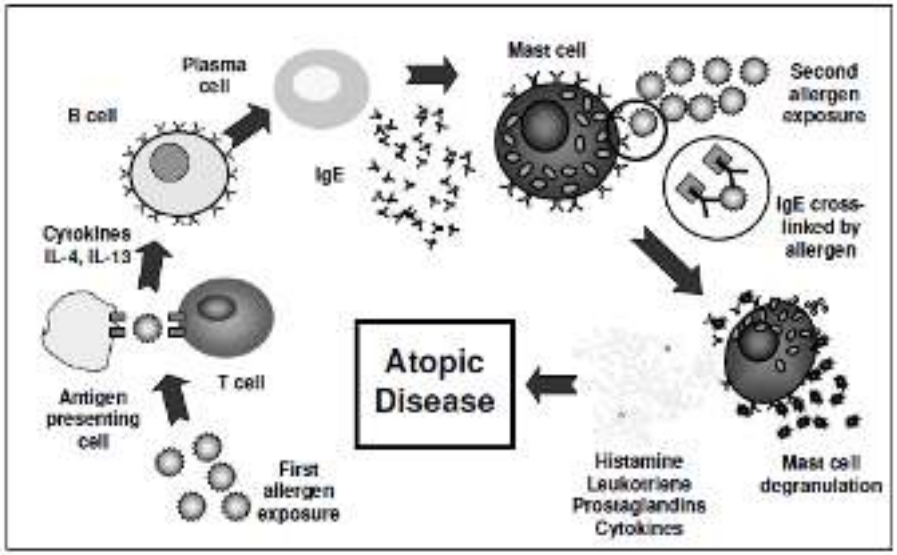


Figure 2. Overview of the IgE-mediated inflammatory cascade

DePestel et al. J Am Pharm Assoc 2008;48:530-40
Figure: Brownell, Casale. Immunol Allergy Clin North Am 2004;24:551-68

What percent of the population reports a PCN allergy versus is truly allergic?

- 20-30%; ≤5%
- 20-30%; ≤1%
- 10-20%; ≤5%
- 10-20%; ≤1%

Penicillin skin testing (inpatient)

Benefits:

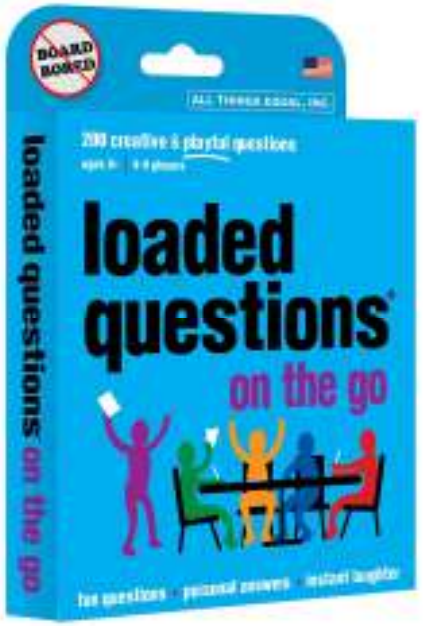
- 60-90 minutes
- Negative predictive value >95%
- Increases beta-lactam usage
- Cost savings
- Safe in children, pregnant women

Limitations:

- Clinical utility
- IgE reactions only
- Interference with antihistamines
- Contraindicated with SJS, TEN, others

Sacco et al. Allergy 2017;72(9):1288-96

Cross-reactivity



- PCN-PCN
- PCN-cephalosporin
- PCN-carbapenem
- Cephalosporin-carbapenem

- Cross-reactivity study limitations: geography, ADRs vs allergies, product purity

PCN-PCN cross-reactivity in (+)skin test patients (Solley et al.)

Antibiotic	Reaction	Treatment	Reaction	Onset
Penicillin G	Urticaria	Carbenicillin	Mild urticarial	12-24 hr
Penicillin G	Urticaria	Methicillin	Morbilliform rash, AIN	2 weeks
Penicillin G	Urticaria	Nafcillin	Urticaria	24-48 hr
Penicillin G	Angioedema	Penicillin G	Urticaria	6 days
Penicillin G	Unknown	Carbenicillin	None	-
Penicillin G	Rash	Carbenicillin	None	-
Penicillin G	Morbilliform rash	Penicillin G	None	-
Methicillin	Hypotension	Methicillin, oxacillin	None	-

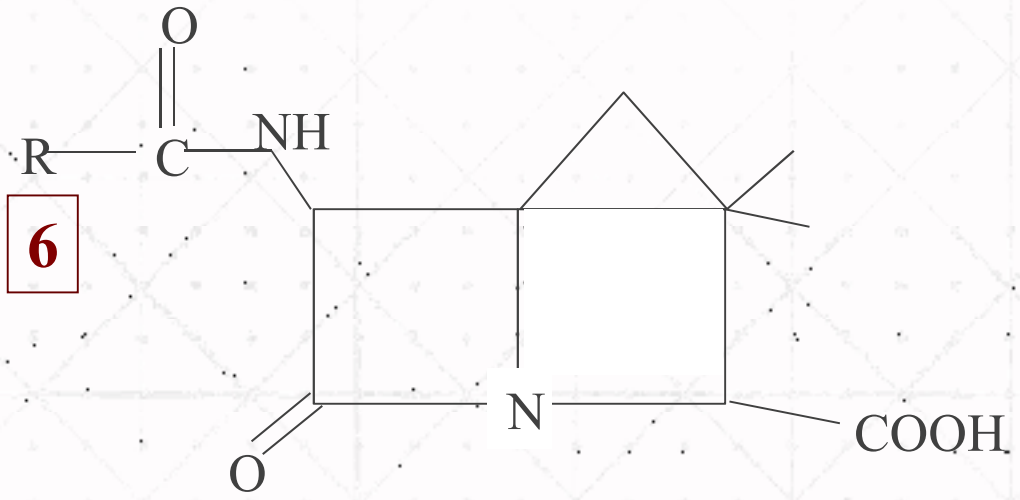
Solley et al. J Allergy Clin Immunol 1982;69(2):238-44

Implications of a 'side chain' approach

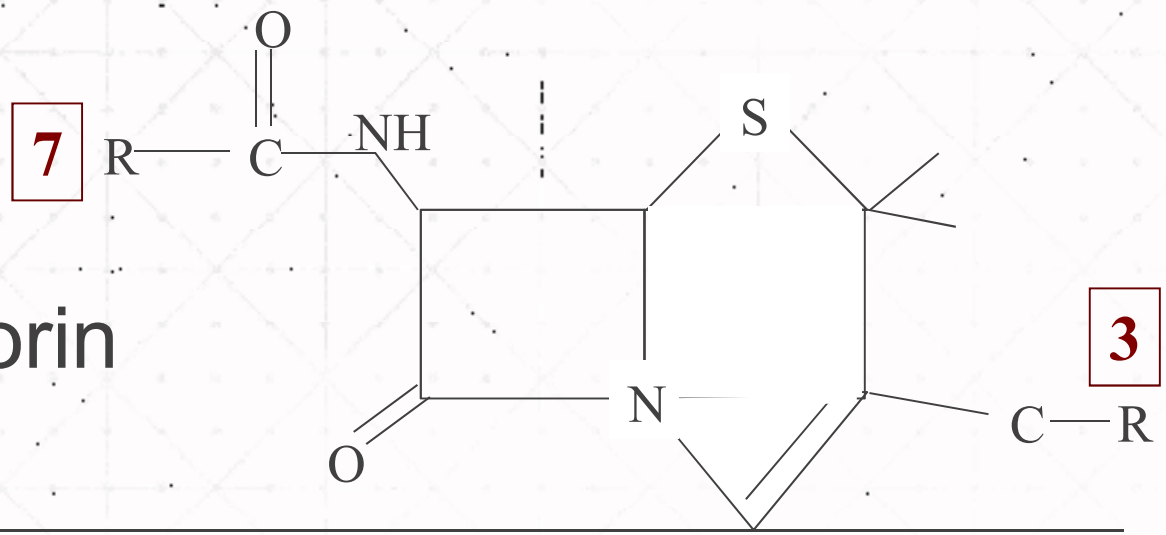
- Experimental and clinical data suggest role of side chain immunogenic epitopes & specific IgE antibodies

- If side chains drive IgE response:
  - Skin testing with benzylpenicillin may have negative response
  - Patients may tolerate penicillins not possessing the relevant side chain determinants

Silviu-Dan et al. J Allergy Clin Immunol 1993;91:694-701



Penicillin



Cephalosporin

Adapted from DePestel et al. J Am Pharm Assoc 2008;48:530-40

DePestel et al.

	Amox	Amp	Cefep	Ceftriax	Cefotax	Cephal
Amox		6				6/7
Amp	6					6/7
Cefep				7	7	
Ceftriax			7		7	
Cefotax			7			
Cephal	6/7	6/7				

Amox: amoxicillin; Amp: ampicillin; Cefep: cefepime; Ceftriax: ceftriaxone; Cefotax: cefotaxime; Cephal: cephalexin

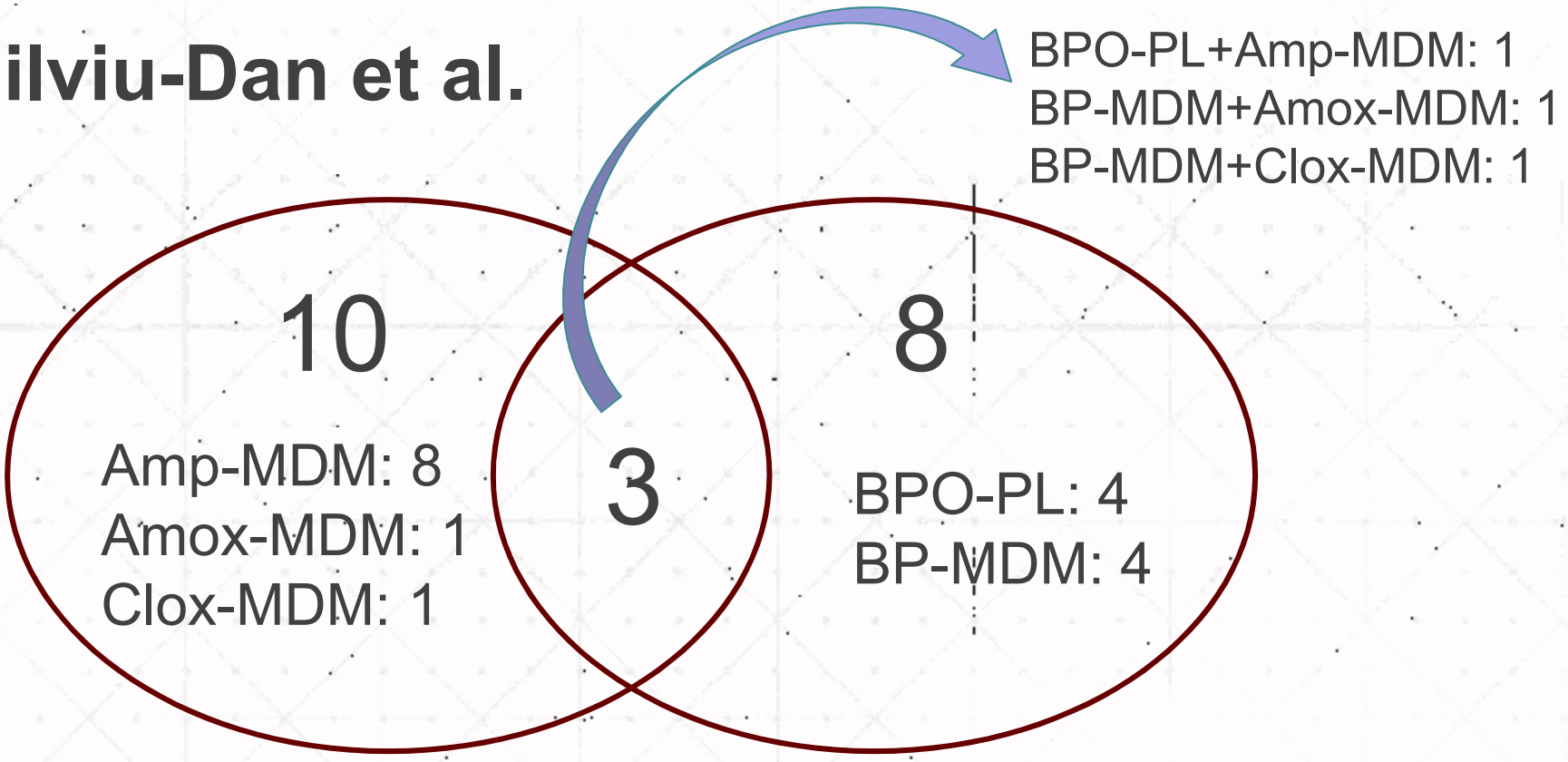
Adapted from DePestel et al. J Am Pharm Assoc 2008;48:530-40

Silviu-Dan et al. (1993)

- 112 patients in Allergy and Clinical Immunology Clinic (Winnipeg; 1981-1991)
  - Clearly defined allergy to penicillin or derivatives
- Intradermal testing: benzylpenicillin derivatives, >=1 semisynthetic penicillin

Silviu-Dan et al. J Allergy Clin Immunol 1993;91:694-701

Silviu-Dan et al.



Amp: ampicillin; Amox: amoxicillin; BP: benzylpenicillin; BPO-PL: benzylpenicilloyl polylysine; Clox: cloxicillin; MDM: minor determinant mixture (equal parts part drug, penilloate and penicilloate analogs)

Silviu-Dan et al. J Allergy Clin Immunol 1993;91:694-701

Silviu-Dan et al.

- Patients with Amp allergy: (+) skin test for Amp-MDM, (-) for Amox-MDM
  - Found in other studies too (Blanca et al., de Haan et al.)
  - Polymer lengths for these can vary → alter antigenicity?
- More (+) skin test with Amp-MDM than anticipated
  - Lyophilized semisynthetic preparations → more efficient mast cell degranulation?

Silviu-Dan et al. J Allergy Clin Immunol 1993;91:694-701

Take home points (don't forget the salt)

- PCN-1st, 2nd generation ceph: ≤10%
- PCN-3rd, 4th generation ceph: <2%

- Similar side chains: up to 40%
  - PCN-ceph
  - Ceph-ceph

Similar side chains:

- Pcn, amp, amox, cephalexin
- Ceftriax, cefurox, ceftaz, cefepime
- Ceftaz, aztreonam

Cefazolin = no similarities

Romano et al. Curr Allergy Asthma Rep 2016;16:24

PCN-carbapenem

- Immediate hypersensitivity (n=212): all (-) skin tests with imipenem/cilastatin, meropenem, ertapenem; 211 challenges all (-)
- T-cell mediated (n=57-204): 0-5%
- Cross reactivity: ~1% (imipenem, meropenem)
  - Similar with ceph-carbapenem (limited data)

Romano et al. Curr Allergy Asthma Rep 2016;16:24

NATIONAL PENICILLIN ALLERGY DAY

Assessment & management of allergies

- Patient history: specific agent, nature of event/severity, timing, onset, course/resolution, current meds, previous ADRs and outcomes
- Skin testing
- Desensitization (90-95% success rate) or graded dose challenge

Romano et al. Curr Allergy Asthma Rep 2016;16:24

Patient case #3

- 75 yo M presents w/ malaise, fevers x 2 days
- PMH: ESRD on HD, T2DM, chronic LE wound, CAD
- Allergies: penicillin (unknown)
- Empiric vancomycin & levofloxacin
- Blood cultures → GPC clusters → MSSA
- Antibiotics plan?

When assessing risk of beta-lactam cross-reactivity:

- Class to class risk assessments appear to be sufficient (Eg, penicillin and cephalosporins)
- Robust data are limited to within-class assessments (eg, penicillin to penicillin)
- Agent-specific assessments appear to be best (eg, amoxicillin and ceftriaxone)
- Data are insufficient to easily assess cross reactivity

Summary

- Limited data suggest that azithromycin and levofloxacin have comparable CV risks
  - Study limitations; patient factors appear to be most important
- Vancomycin & piperacillin/tazobactam carry an increased risk of AKI
  - Duration appears to be a prominent risk factor
- When assessing penicillin and cephalosporin cross-reactivity, a specific agent approach seems best
  - Class approach appears outdated, though penicillin-carbapenem seems okay