UNIVERSITY of MARYLAND

Goodbye excessive Fluoroquinolone use, hello decreased *C.difficile* rates

Emily Heil, PharmD, BCIDP, BCPS

Objectives

1) Describe the link between fluoroquinolone use and *C. difficile* infection (CDI)

2) Discuss strategies to decrease unnecessary use of fluoroquinolones as an antimicrobial stewardship initiative

3) Propose beta-lactam allergy management as a fluoroquinolone reduction strategy

Decreasing inappropriate use of fluoroquinolones is one of the most important interventions that a stewardship program can make for *C.difficile* reduction.

The primary risk factor for nosocomial CDI is antibiotic exposure

Cohen SH, et al. *Infect Control Hosp Epidemiol* 2010; 31:431-55; Chang et al. *Infect Control Hosp Epidemiol* 2007; 28:926-31.

All Antibiotics Are Not Created Equal

Clindamycin

3rd Generation Cephalosporins

Fluoroquinolones

Deshpande A et la. J Antimicrob Chemother 2013;68:1951-61.

NAP1/BI/027

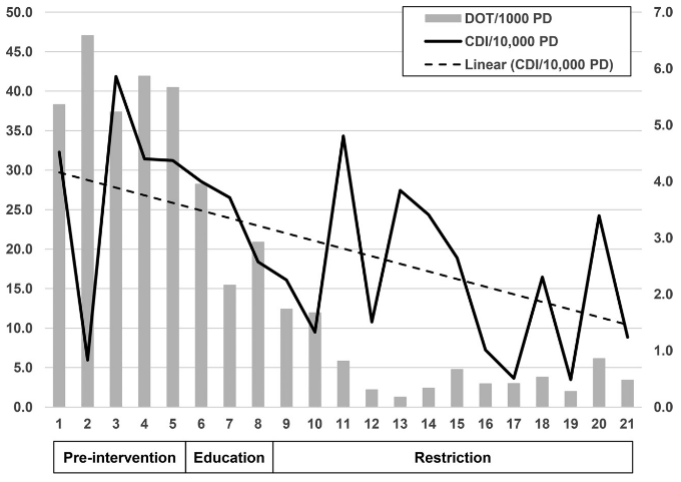
- Hypervirulent strain capable of producing higher levels of Toxin A & Toxin B
- High-level fluoroquinolone resistance
- Associated with:
  - Greater odds of severe disease (aOR 1.74; 95% CI, 1.36-2.22)
  - Severe outcomes (aOR 1.66; 95% CI, 1.09-2.54)
  - 14-day mortality (aOR 2.12; 95% CI, 1.22-3.68)

Lessa, FC, et al. *N Engl J Med*; 2015;372:825-34; McDonald LC, et al. *N Engl J Med.* 2005; 2005;353:2433-441; Stabler RA, et al. *Genome Biol 2009;* 10:R102. See I, et al. Clin Infect Dis 2014;58:1394-400.

✓

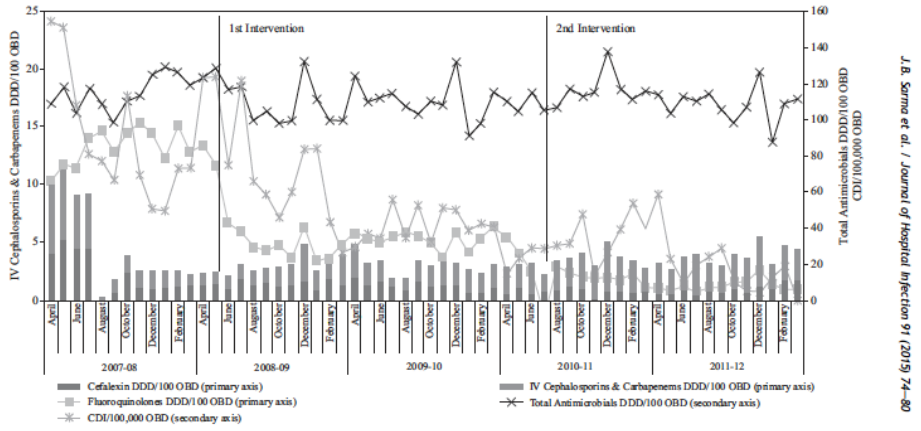
Are fluoroquinolones associated with CDI?

Does reducing fluoroquinolone use reduce CDI rates?



YES

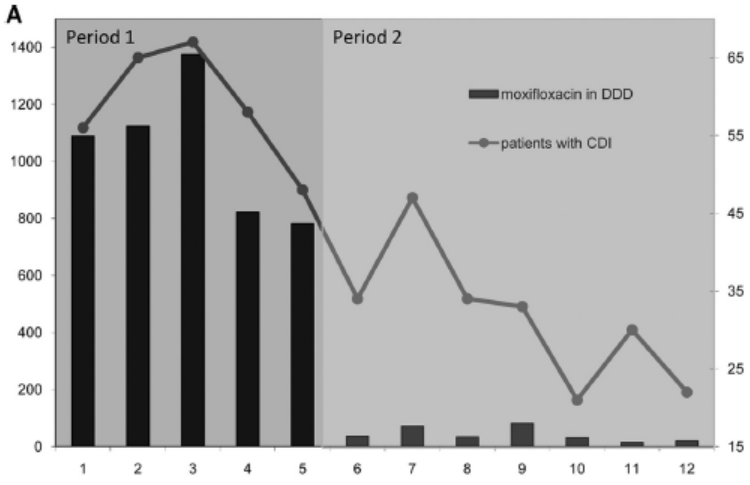
Shea KM, et al. Antimicrob Agents Chemother 2017. 61:e00125-17.



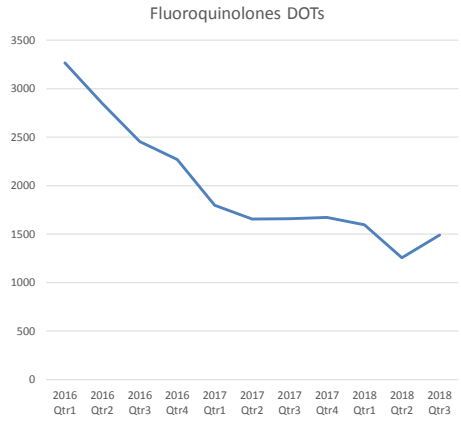
YES

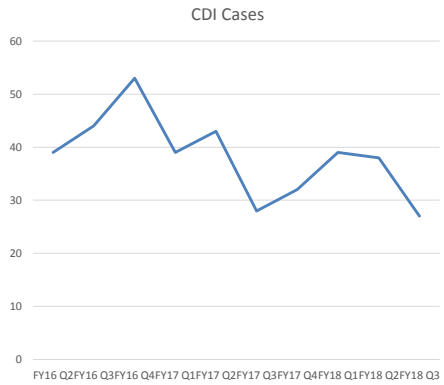
Sarma et al. J Hosp Infection 2015;91:74-80.

STILL YES



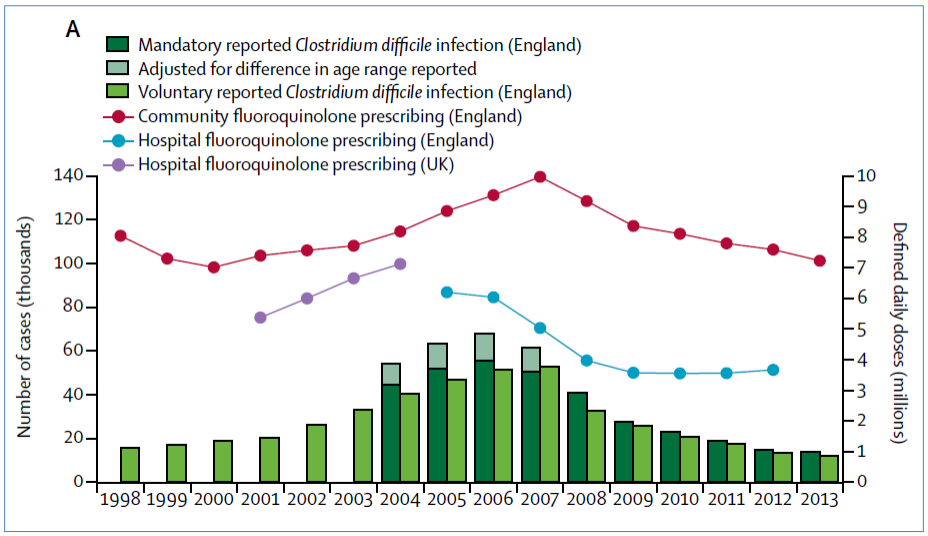
Wenisch JM, et al. Antimicrob Agent Chemother 2014;58:5079-84.



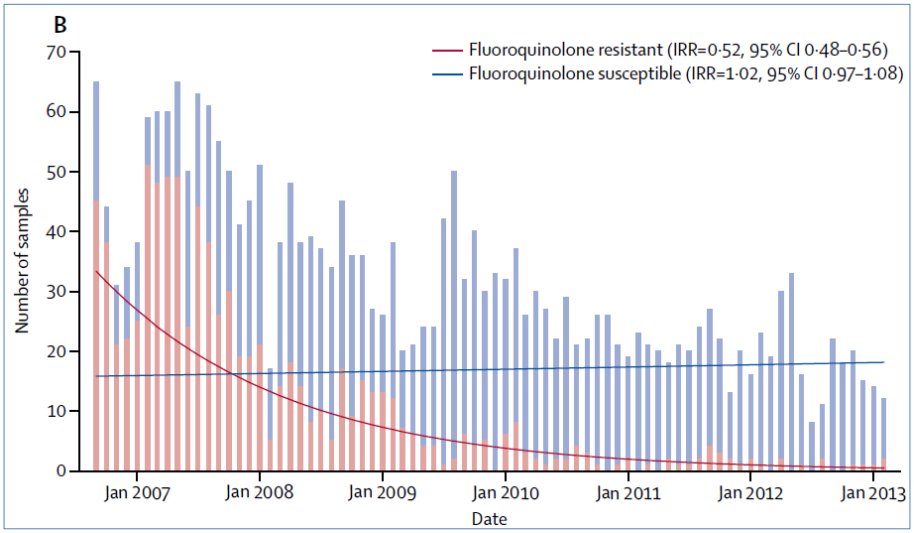


Ok, stop we get it

UMMC Internal Data



Dingle KE, et al. Lancet Infect Dis 2017;17: 411–21.



Dingle KE, et al. Lancet Infect Dis 2017;17: 411–21.

✓ Are fluoroquinolones associated with CDI?

✓ Does reducing fluoroquinolone use reduce CDI rates?

How can I reduce fluoroquinolone use at my institution?

Antimicrobial Stewardship Strategies

- Front end: Formulary restriction and preauthorization
- Back end: Interventions after antimicrobials have been prescribed
- BOTH: Prospective audit with intervention and feedback

Supplemental Strategies

- Education, guidelines, clinical pathways
- Dose optimization via PK-PD
- De-escalation/ Streamlining
- Combination therapy
- Antimicrobial order forms/order sets if CPOE
- IV-PO switch
- Computerized decision support
- ~~Antimicrobial cycling~~

Dellit TH, et al. CID 2007;44:159-77
Barlam T, et al. CID 2016;62:e51-77.
Hand K, et al Hospital Pharmacist 2004;11:459-64
Paskovaty A, et al IJAA 2005;25:1-10

Auditing/Feedback

- **Examples**
- Review all patients on fluoroquinolones and recommend alternatives as appropriate
- Utilize institution specific data to identify target service areas or prescribers with higher fluoroquinolone use for review

Virulence 2013;4:151-157
http://www.ahrq.gov/qual/cdifftoolkit/index.html

Auditing/Feedback

Pros	Cons
• Adaptable to many hospital environments • Can be done a few times a week versus daily • Can intervene in cases of inadequate therapy • Facilitates a team approach to patient care • Has been shown to improve antimicrobial use and outcomes • Provides educational opportunities • More easily accepted by physicians than restrictions/pre-authorization	• Can be labor intensive • Success depends on the effectiveness and skill of staff making the interventions • For maximal efficiency requires systems to identify patients to intervene on and how to best convey suggestions

http://www.ahrq.gov/qual/cdifftoolkit/index.html

Restrictions/Pre-authorization

- **Examples**
- Mandating ID consults or stewardship approval for fluoroquinolones
- Specific requirements that must be met for dispensing of fluoroquinolones (‘checklist’)

Restrictions/Pre-authorizations

Pros	Cons
• Effective in decreasing targeted antibiotics • Can influenced future prescribing practices – education built into the process of discussing therapy choice	• May shift prescribing to alternative agents • May be less acceptable to prescribers (loss of prescriber autonomy) • May delay time to therapy for patients • Effectiveness depends on skills of staff making recommendations and reviewing requests

http://www.ahrq.gov/qual/cdifftoolkit/index.html

Guideline Changes

Indication	Fluoroquinolone Substitution
Bronchitis	No antibiotics! If truly indicated, doxycycline
Infective Exacerbation of COPD – non-severe	Doxycycline Amoxicillin/Clavulanate
Community Acquired Pneumonia	Ampicillin/Sulbactam + Azithromycin Ceftriaxone + Azithromycin
Urinary Tract Infection – Cystitis	Nitrofurantoin
Urinary Tract Infection – Pyelonephritis	SMX/TMP
Intra-abdominal Infections	Ceftriaxone +/- Metronidazole Piperacillin/tazobactam (if *Pseudomonas* coverage needed)

Leverage the Electronic Medical Record (EMR)

- Remove fluoroquinolones from ordersets
- Build warning alert about the toxicities

Mang N, et al. ID Week 2018

Leverage the Electronic Medical Record (EMR)

- Suppress reporting of fluoroquinolone susceptibilities from the microbiology lab

Urine Culture: >100,000 CFU E. coli		
ANTIBIOTIC	ORGANISM: ESCHERICHIA COLI	
AMIKACIN	<=2	S
AMPICILLIN	>=32	R
AMPICILLIN/SULBACTAM	<=2	S
CEFAZOLIN	>=32	R
CEFTRIAXONE	<=2	S
NITROFURANTOIN	32	S
PIPERACILLIN/TAZOBACTAM	<= 4	S
TRIMETHOPRIM/SULFAMETHOXAZOLE	<= 20	S

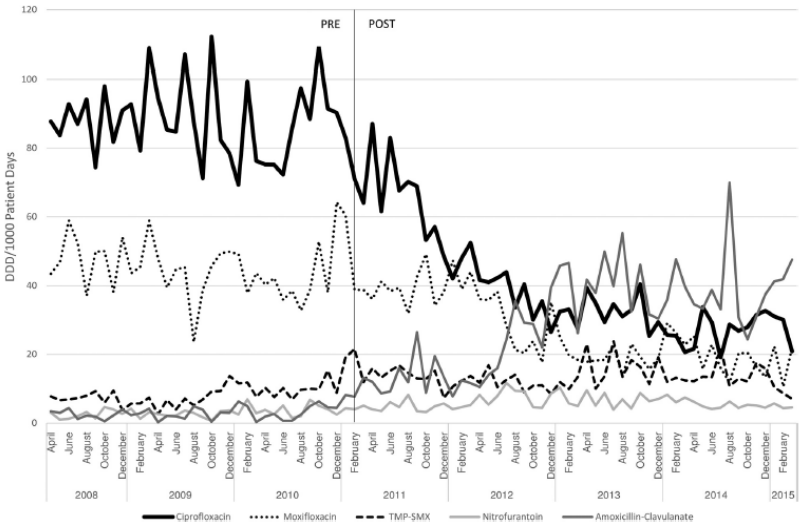


FIG 1 Antimicrobial utilization before and after ciprofloxacin selective reporting.

Goodbye Fluoroquinolones!

THE ROLE OF ALLERGIES

PCN Allergy – How common

- PCN & other beta-lactams are the most frequent cause of medication-induced anaphylaxis
- Up to 10% of patients report a penicillin allergy
  - Most reports reflect historical childhood events, family history, or non-allergic adverse effects
- Over a 2 year period, 6200 patients admitted to UMMC reported a PCN allergy

Salkind AR et al. JAMA 2001;285:2498-505.; Pichichero ME et al. Ann Allergy Asthma Immunol 2014;112:404-12.

PCN Allergy – Overstated?

- Even with a well documented allergy, hypersensitivity may not persist over time due to loss of anti-PCN IgE antibodies (up to 80% over 10 years)
- 9 out of 10 patients who claim to be allergic to penicillin are not truly allergic when assessed by skin testing
- Preferred beta-lactam therapy is avoided in >50% of patients even when a non-severe prior reaction is reported

Salkind AR et al. JAMA 2001;285:2498-505.; Pichichero ME et al. Ann Allergy Asthma Immunol 2014;112:404-12.
McFadden D et al. Clin Infect Dis 2016;63:904-10.

Implications of PCN "Allergy"

- Increased adverse effects
- Longer hospital stays, more readmissions
  - Approximately one-half day longer
  - 30,000 hospital days/65 million in expenditures
- Development of MDR infections
  - 23.4% increase in *C. difficile* infection
  - 14.1% more MRSA
  - 30.1% increased VRE

MacFadden DR et al. Clin Infect Dis. 2016;63:904-10.
Macy E et al. J Allergy Clin Immunol 2014;133:790-6.

Implications of PCN "Allergy"

- Increased usage of broad-spectrum antibiotics
  - FQ, Clindamycin, Vancomycin
- Increased antibiotic costs
  - 63% higher than those without reported allergy
- Antibiotic regimens deviate from standard of care (as defined by national guidelines, protocols or ID consults) in ~40% of patients with a reported PCN allergy

MacLaughlin EJ et al. Arch Fam Med 2009;9:722-6.; Charneski L et al. Pharmacother 2011;31:742-7.; Macy E. er al. J Allergy Clin Immunol 2014;133:790-6.

PCN Allergy - Documentation

- Allergy history documentation is poor
  - Often lack documentation of nature and severity of reaction
  - One retrospective cohort found only 39.8% of records had a specific allergen identified and only 22.7% had reaction characteristics identified
- Appropriate history can improve classification of mild versus life-threatening reactions
- Rechallange with beta—lactams is more likely when allergic reactions are well documented

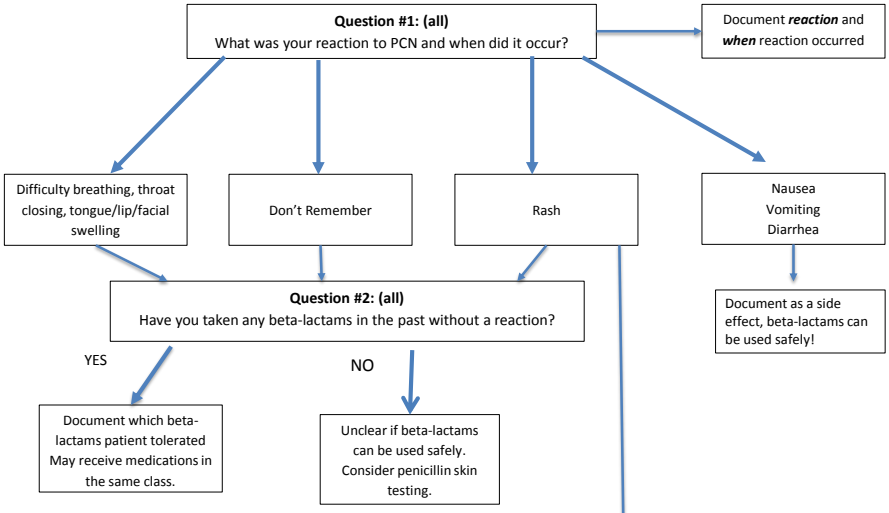
Shah N. PLoS One 2016;11(3):e0150514.

PCN Allergy - Documentation

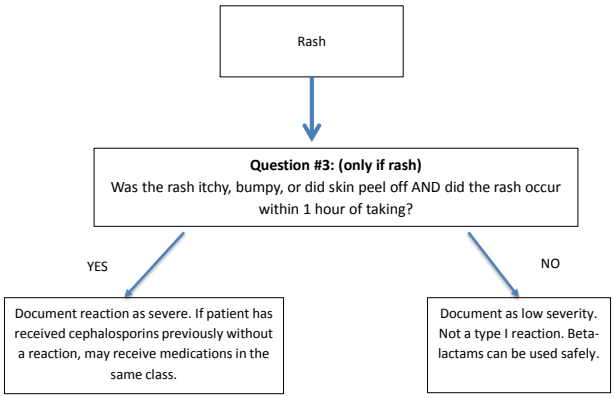
- Allergy records are rarely updated to demonstrate tolerance
  - ONLY 18% of patients with a documented penicillin allergy who received a penicillin antibiotic without incident had their records updated at UMMC
  - Rarely updated to indicate tolerance of other beta-lactams
- Algorithms to guide penicillin allergy histories can improve documentation

Oliver WD. JACI In Practice 2017;5:184-6.
Staicu ML. ID Week 2016

PCN Allergy - Documentation



PCN Allergy Documentation



Pharmacist Allergy Interviews on FQ Use

Table 2. Primary and Secondary Outcomes.

	Control Group (n = 43)	Prospective Group (n = 37)	*P* Value
Duration of fluoroquinolone, mean days (SD)	3.7 (2.2)	2.7 (1.7)	0.027
Duration of fluoroquinolones, mean hours (SD)	88.4 (52.2)	64.2 (42.0)	0.027
Length of stay, median days (IQR)	6 (3-9)	5 (4-8)	0.73
Patient switched to β-lactam antibiotic, n (%)	N/A	18 (49)	
Ceftriaxone, n (%)	N/A	16 (43)	
Cefdinir, n (%)	N/A	1 (3)	
Cefepime, n (%)	N/A	1 (3)	
Reason for switch from FQ to β-lactam, n (%)	N/A		
Pharmacy recommendation		17 (94)	
Physician switch without intervention		1 (6)	
Pharmacy recommendations accepted, n (percentage recommendations)	N/A	17/18 (94)	
Adverse reaction after switch to β-lactam, n	N/A	0	

Abbreviations: FQ, fluoroquinolone; IQR, interquartile range.

Covington.CW et al. Annals Pharmacother 2019, epub ahead of print

Management of Reported Type 1 PCN Allergy

- Desensitization
- Graded Challenges
- Direct Oral Challenges
- Penicillin skin testing

Challenges with Desensitization

- Time consuming
  - Pharmacy preparation
  - Nursing monitoring
- Requires exquisite compliance with antibiotic administration times
- Effects are not sustained

…Wouldn't it be better to just rule out the allergy?

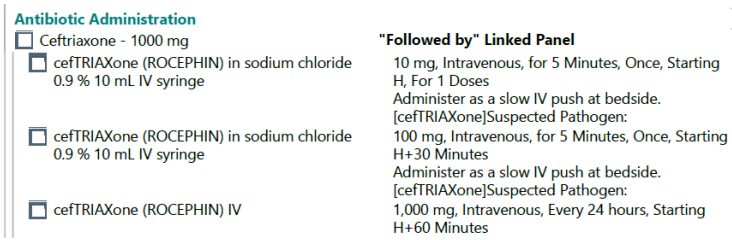
Direct Oral Challenges

- Administer 250-500 mg dose of amoxicillin and observe for 1 hour after dose
- Reserved for patients with a low suspicion for true anaphylactic allergy (e.g., history of mild childhood rash, nonurticarial rash, adverse events such as nausea or vomiting)

Aberer W. JACI Practice 2017;5:684

Graded Challenges

- Not intended to induce drug tolerance
- Demonstrates that administration of a specific drug will not result in an immediate reaction
- Give 1%, then 10%, then 100% of therapeutic doses at 30 minute intervals



Antibiotic Administration

	"Followed by" Linked Panel
☐ Ceftriaxone - 1000 mg	
☐ cefTRIAXone (ROCEPHIN) in sodium chloride 0.9 % 10 mL IV syringe	10 mg, Intravenous, for 5 Minutes, Once, Starting H, For 1 Doses Administer as a slow IV push at bedside. [cefTRIAXone]Suspected Pathogen:
☐ cefTRIAXone (ROCEPHIN) in sodium chloride 0.9 % 10 mL IV syringe	100 mg, Intravenous, for 5 Minutes, Once, Starting H+30 Minutes Administer as a slow IV push at bedside. [cefTRIAXone]Suspected Pathogen:
☐ cefTRIAXone (ROCEPHIN) IV	1,000 mg, Intravenous, Every 24 hours, Starting H+60 Minutes

Annals of allergy, asthma, & immunology 2010;105:259-73.

Antimicrobial Stewardship Guidelines

- Penicillin skin testing is now recommended
- “In patients with a history of B-lactam allergy, we suggest that ASPs promote allergy assessments and PCN skin testing when appropriate”
- Largely unstudied as primary ASP intervention
- Weak recommendation, low-quality evidence

Barlam TF, et al. Clin Infect Dis 2016;62:e51-77.

PCN Skin testing (PST)

- PCN & other beta-lactams spontaneously breakdown into reactive intermediates that bind with circulating carrier proteins forming haptens – these serve as the reactive allergenic major and minor determinants for skin testing
- Major determinant – benzylpenicilloyl polylysine accounts for 90% of PCN intermediates
- PST antigens react with IgE antibodies, if present, and the interaction results in a skin wheal, flare, or bleb at the injection site

Unger NR et al. Pharmacother 2013;33:856-67.

PCN Skin Testing

- When performed in the appropriate setting with proper technique and reagents, the skin test has a negative predictive value of 97-99% and a positive predictive value of 50%
- Patients with a negative skin test are at no greater risk of experiencing an allergic reaction to a beta-lactam than the general population

Unger NR et al. Pharmacother 2013;33:856. del Real GA et al. Ann Allergy Asthma Immunol 2007:98:355.
Sullivan TJ et al. J Allergy Clin Immunol 1981;68:171. Sogn DD et al. Arch Intern Med 1992;152:1025.

Who to test?

- Patients that based on history likely experienced an IgE-mediated allergic reaction
- Patients known to be extremely hypersensitive to penicillin (e.g., systemic or anaphylactic reactions) should not be skin tested
- Ensure patient has not been receiving any histamine blockers (H1 – diphenhydramine and H2 – ranitidine and famotidine) within last 24 hours!!

Models for PST

- Allergy (when available)
- Infectious Diseases Consultants
- Pharmacist-managed (state law dependent)
- Other physician specialties
  - Emergency Medicine
  - Hospitalist
- **Outpatient/Peri-operative**

Clinical Review & Education

JAMA | Review

Evaluation and Management of Penicillin Allergy
A Review

Erica S. Shenoy, MD, PhD; Eric Macy, MD, MS; Theresa Rowe, DO, MS; Kimberly G. Blumenthal, MD, MSc

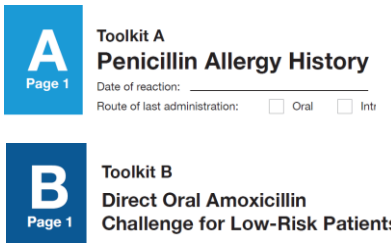


Table S2. Cephalosporin cross-reactivity, by R1 groups*

Common amino R1 group	Common methoxyimino R1 group
Ampicillin	Ceftriaxone
Amoxicilin	Cefotaxime
Cefaclor	Cefuroxime
Cephalexin	Cefepime
Cefadroxil	Ceftazidime
	Cefpodoxime

*Beta-lactam antibiotics have shared beta-lactam rings and may have R1 (6/7 position) and/or R2 (3 position) side chains that can be structurally identical or similar. Cross reactivity appears highest for beta-lactams that share identical R1 side chains. More comprehensive cephalosporin cross-reactivity matrices[2] may be used if avoiding identical and similar structures at both side chain locations is desired.

Shenoy ES et al. JAMA 2019;321:188-199.

WHAT ABOUT OVIVA AND POET?

It's not all bad….

- Highly bioavailable – facilitate PO option for the treatment of susceptible gram negative bacteremias
- Better bone penetration compared to other agents offering a PO option for the treatment of susceptible pathogens causing osteomyelitis
- Risk of CVCs often outweigh antibiotic risks
- Must weigh patient-specific risks of CDI vs potential benefits of PO FQ administration

Underwood J, JAC 2018;74(3)
Lee HK, NEJM 2019;380:5

Conclusions

- Fluoroquinolones (FQ) are one of the most prescribed antibiotic classes in the US.
- FQs are associated with a high risk of *C.difficile* compared to other classes of antibiotics
- Multiple observational studies have demonstrated reduced *C. difficile* rates through FQ restriction.
- Restriction of FQ is likely to have collateral benefits.

Questions?