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Antimicrobial Stewardship Strategies to Reduce Hospital-Acquired Clostridium Difficile Infections

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Disclosure

Lucas Schulz

Merck Health Solutions: Consultant; Theravance: Speaker's Bureau

Tristan Timbrook

Biofire Diagnostics, LLC: Consultant, Speaker's Bureau; GenMark Diagnostics, Inc.: Advisory Board, Consultant

All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

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SOCIETY OF INFECTIOUS DISEASES PHARMACISTS

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Antimicrobial Stewardship Is A Team Sport

Erin K. McCreary, Pharm.D., BCPS
Education & Development Coordinator
Infectious Diseases Clinical Pharmacist
UW Health
Madison, WI
@erinmccreary

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Learning Objective

- Design team-based antimicrobial stewardship initiatives to reduce Clostridium difficile infection (CDI) rates in an acute care setting.

Antimicrobial Stewardship Team

- Physicians
  - AMS physicians
  - ID fellows
  - MD representative from speciality areas
- Microbiology lab
  - Director
  - Fellows
  - Technicians
- Infection control team
- Epidemiologist
- Hospital leadership
- Environmental services
- Pharmacists
  - AMS pharmacists
  - Decentralized pharmacists
  - Drug policy program
  - Medication safety coordinator
  - Informatics
  - Residents
  - APPE and IPPE Students
- Nurses
- Patients and families

Clinical Infectious Diseases

INVITED ARTICLE

HEALTHCARE EPIDEMIOLOGY: Robert A. Weinstein, Section Editor

Expert Consensus on Metrics to Assess the Impact of Patient-Level Antimicrobial Stewardship Interventions in Acute-Care Settings

Rebekah W. Moehring,[1,2] Deverick J. Anderson,[1,2] Ronda L. Cochran,[3] Lauri A. Hicks,[3] Arjun Srinivasan,[3] and Elizabeth S. Dodds Ashley[1,2]; for the Structured Taskforce of Experts Working at Reliable Standards for Stewardship (STEWARDS) Panel

[1]Duke University Medical Center, Department of Medicine, Division of Infectious Diseases, and [2]Duke Antimicrobial Stewardship Outreach Network, Durham, North Carolina; [3]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

Antimicrobial stewardship programs (ASPs) positively impact patient care, but metrics to assess ASP impact are poorly defined. We used a modified Delphi approach to select relevant metrics for assessing patient-level interventions in acute-care settings for the purposes of internal program decision making. An expert panel rated 90 candidate metrics on a 9-point Likert scale for association with 4 criteria: improved antimicrobial prescribing, improved patient care, utility in targeting stewardship efforts, and feasibility in hospitals with electronic health records. Experts further refined, added, or removed metrics during structured teleconferences and re-rated the retained metrics. Six metrics were rated >6 in all criteria: 2 measures of *Clostridium difficile* incidence, incidence of drug-resistant pathogens, days of therapy over admissions, days of therapy over patient days, and redundant therapy events. Fourteen metrics rated >6 in all criteria except feasibility were identified as targets for future development.

Keywords. antimicrobial stewardship; patient safety; process measure; outcome measure; quality metrics.

CDI at UW Health

	No. of Infections Reported (A)	Number of Patient Days	Predicted No. Infections (B)	Standardized Infection Ratio (SIR) (A/B)	Evaluation
UNIVERSITY OF WI HOSPITALS & CLINICS AUTHORITY	217	162344	156.006	1.391	Worse than the National Benchmark

CDI at UW Health

	No. of Infections Reported (A)	Number of Patient Days	Predicted No. Infections (B)	Standardized Infection Rati (SIR) (A/B)	Evaluation
UNIVERSITY OF WI HOSPITALS & CLINICS AUTHORITY	217	162344	156.006	1.391	Worse than the National Benchmark

CDI at UW Health: Comparison

Peer Institutions	Reported Infections	Predicted Infections	SIR
Regional #1 (small community)	27	65	0.453
Regional #2 (large community)	23	47	0.48
Regional #3 (large academic)	210	151	1.391
Regional #4 (large academic)	172	174	0.99
Regional #5 (large academic)	199	166	1.19
National #1 (large academic)	95	118	0.80
National #2 (large academic)	78	119	0.66

CDI at UW Health – comparison

Peer Institutions			
Regional #1 (l			
Regional #2 (large co			
Regional #3 (l			
Regional #4 (large academic)			
Regional #5 (large academic)			1.19
National #1 (large academic)		1	0.80
National #2 (large academic)		119	0.66

Only 38 hospitals in the US have more hospital-onset cases of CDI than UW

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CDI at UW Health vs. Comparison

Peer Institutions			
Regional #1 (l			
Regional #2 (large co			
Regional #3 (l			
Regional #4 (large academic)			
Regional #5 (large academic)			1.19
National #1 (large academic)		1	0.80
National #2 (large academic)		119	0.66

94% of hospitals in the US have a <u>better SIR</u> than UW

CDI Reduction Efforts

- Testing algorithm redesign
- Admission screening in high-risk populations
- Nursing documentation of stool consistency
- Enhanced PPE requirements and education
- Enhanced hand-washing education and auditing
- Environmental services initiatives
- Post-prescription review and feedback
- Oral vancomycin prophylaxis
- Probiotics
- Proton pump inhibitor de-prescribing

Tamma PD, et al. Clin Infect Dis. 2017;64(5):537-543.
Carignan A, et al. Am J Gastroenterol. 2016;111(12):1834-1840.
Lewis PO, et al. Ann Pharmacother. 2017;51(10):848-854.

CDI Reduction Efforts

- Testing algorithm redesign – all patients
- Admission screening in high-risk populations – oncology and transplant
- Nursing documentation of stool consistency – all patients
- Enhanced PPE requirements and education – all patients
- Enhanced hand-washing education and auditing – all patients
- Environmental services initiatives – all patients
- Post-prescription review and feedback – all patients on antibiotics
- Oral vancomycin prophylaxis – oncology and transplant
- Probiotics – medicine units
- Proton pump inhibitor de-prescribing – all patients

Tamma PD, et al. Clin Infect Dis. 2017;64(5):537-543.
Carignan A, et al. Am J Gastroenterol. 2016;111(12):1834-1840.
Lewis PO, et al. Ann Pharmacother. 2017;51(10):848-854.

Image: https://emojipedia.org/face-palm/

Antibiotic Exposure and CDI Risk

- Clindamycin
- Cephalosporins
- Carbapenems
- Fluoroquinolones
- ß-lactam/ß-lactamase inhibitor combinations

Slimings C, Riley TV. J Antimicrob Chem. 2014;69:881-891.
Stevens V, et al. Clin Infect Dis. 2011;53(1):42-48.
McCusker ME, et al. Emerging Infectious Diseases. 2003;9(6):730-733.

Effects of control interventions on *Clostridium difficile* infection in England: an observational study

*Kate E Dingle, Xavier Didelot, T Phuong Quan, David W Eyre, Nicole Stoesser, Tanya Golubchik, Rosalind M Harding, Daniel J Wilson, David Griffiths, Alison Vaughan, John M Finney, David H Wyllie, Sarah J Oakley, Warren N Fawley, Jane Freeman, Kirsti Morris, Jessica Martin, Philip Howard, Sherwood Gorbach, Ellie J C Goldstein, Diane M Citron, Susan Hopkins, Russell Hope, Alan P Johnson, Mark H Wilcox, Timothy E A Peto, A Sarah Walker, Derrick W Crook, the Modernising Medical Microbiology Informatics Group**

Dingle KE, et al. Lancet Infect Dis. 2017;17:411-421.

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

Drug Safety Communications

FDA Drug Safety Communication: FDA updates warnings for oral and injectable fluoroquinolone antibiotics due to disabling side effects

Safety Announcement

[07-26-2016] The U.S. Food and Drug Administration (FDA) approved changes to the labels of fluoroquinolone antibacterial drugs for systemic use (i.e., taken by mouth or by injection). These medicines are associated with disabling and potentially permanent side effects of the tendons, muscles, joints, nerves, and central nervous system that can occur together in the same patient. As a result, we revised the *Boxed Warning*, FDA's strongest warning, to address these serious safety issues. We also added a new warning and updated other parts of the drug label, including the patient Medication Guide.

We have determined that fluoroquinolones should be reserved for use in patients who have no other treatment options for acute bacterial sinusitis (ABS), acute bacterial exacerbation of chronic bronchitis (ABECB), and uncomplicated urinary tract infections (UTI) because the risk of these serious side effects generally outweighs the benefits in these patients. For some serious bacterial infections the benefits of fluoroquinolones outweigh the risks, and it is appropriate for them to remain available as a therapeutic option.

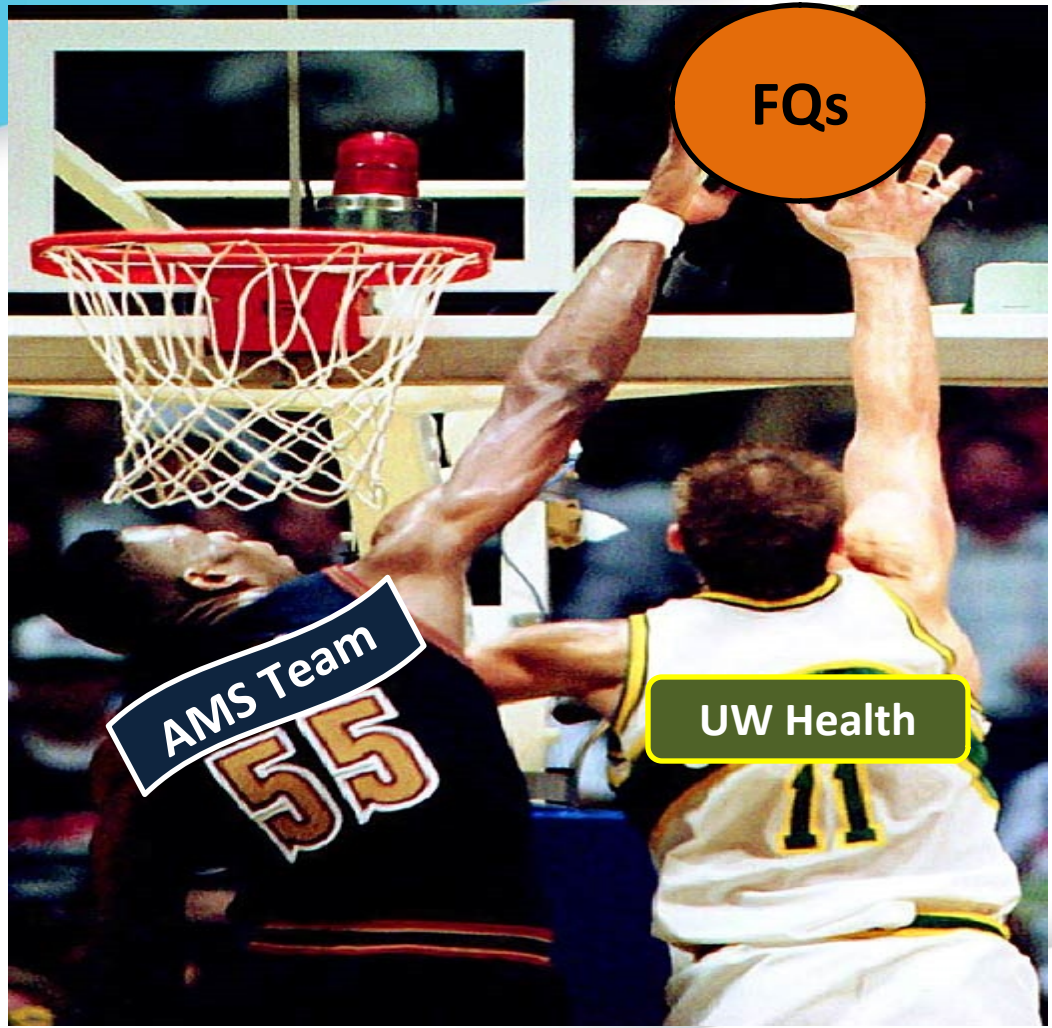


Image: https://solecollector.com/news/2014/05/flashback-dikembe-mutombo-blocks-record-31-shots-in-sonics-series-upset-20-years-ago

Image: https://www.emojibase.com/emoji/1f631/facescreaminginfear

Image: https://www.emojibase.com/emojilist/sos

Pilot: Who, What, When

- Transplant unit and MICU/SICU
  - Highest incidence of CDI
- FQs commonly prescribed for:
  - Lower respiratory tract infections
  - Abdominal infections
  - Urinary tract infections
  - Bloodstream infections
- July 2016

ICU

Diagnosis	Historical Empiric Therapy	Proposed New Empiric Therapy
Septic Shock – unknown origin empiric coverage of *Pseudomonas*	Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin	• Vancomycin[A] PLUS piperacillin/tazobactam PLUS tobramycin OR • Vancomycin[A] PLUS cefepime PLUS tobramycin OR • Vancomycin[A] PLUS meropenem PLUS tobramycin
		For patients with IgE-mediated or severe reaction to β-lactam: vancomycin[A] PLUS aztreonam PLUS tobramycin PLUS metronidazole
Community-acquired Pneumonia	Moxifloxacin	No risk factors for MDRO: ceftriaxone OR ampicillin/sulbactam If concern for atypical bacteria or Legionnaires' disease: ADD azithromycin
		For patients with IgE-mediated or severe reaction to β-lactam: vancomycin[A] AND aztreonam
Healthcare-associated Pneumonia	Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin	With risk factors for MDRO: vancomycin[A] PLUS piperacillin/tazobactam OR cefepime If patient in septic shock: ADD tobramycin If concern for atypical bacteria or Legionnaires' disease: ADD azithromycin
		For patients with IgE-mediated or severe reaction to β-lactam: vancomycin[A] PLUS aztreonam
Sepsis (without septic shock) of urinary origin/pyelonephritis	Vancomycin AND/OR ciprofloxacin	No risk factors for MDRO: ceftriaxone With risk factors for MDRO: vancomycin[A] PLUS cefepime For patients with IgE-mediated or severe reaction to β-lactam: vancomycin[A] PLUS tobramycin
Intraabdominal infection – with or without septic shock[B]	Ciprofloxacin AND metronidazole	No risk factors for MDRO: • ceftriaxone AND metronidazole OR • cefoxitin OR • piperacillin/tazobactam
	Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin	With risk factors for MDRO: • vancomycin[A] PLUS piperacillin/tazobactam PLUS tobramycin OR • vancomycin[A] PLUS cefepime PLUS tobramycin PLUS metronidazole OR • vancomycin[A] PLUS meropenem with or without tobramycin
		For patients with IgE-mediated or severe reaction to β-lactam: vancomycin[A] PLUS aztreonam PLUS tobramycin PLUS metronidazole

TRANSPLANT

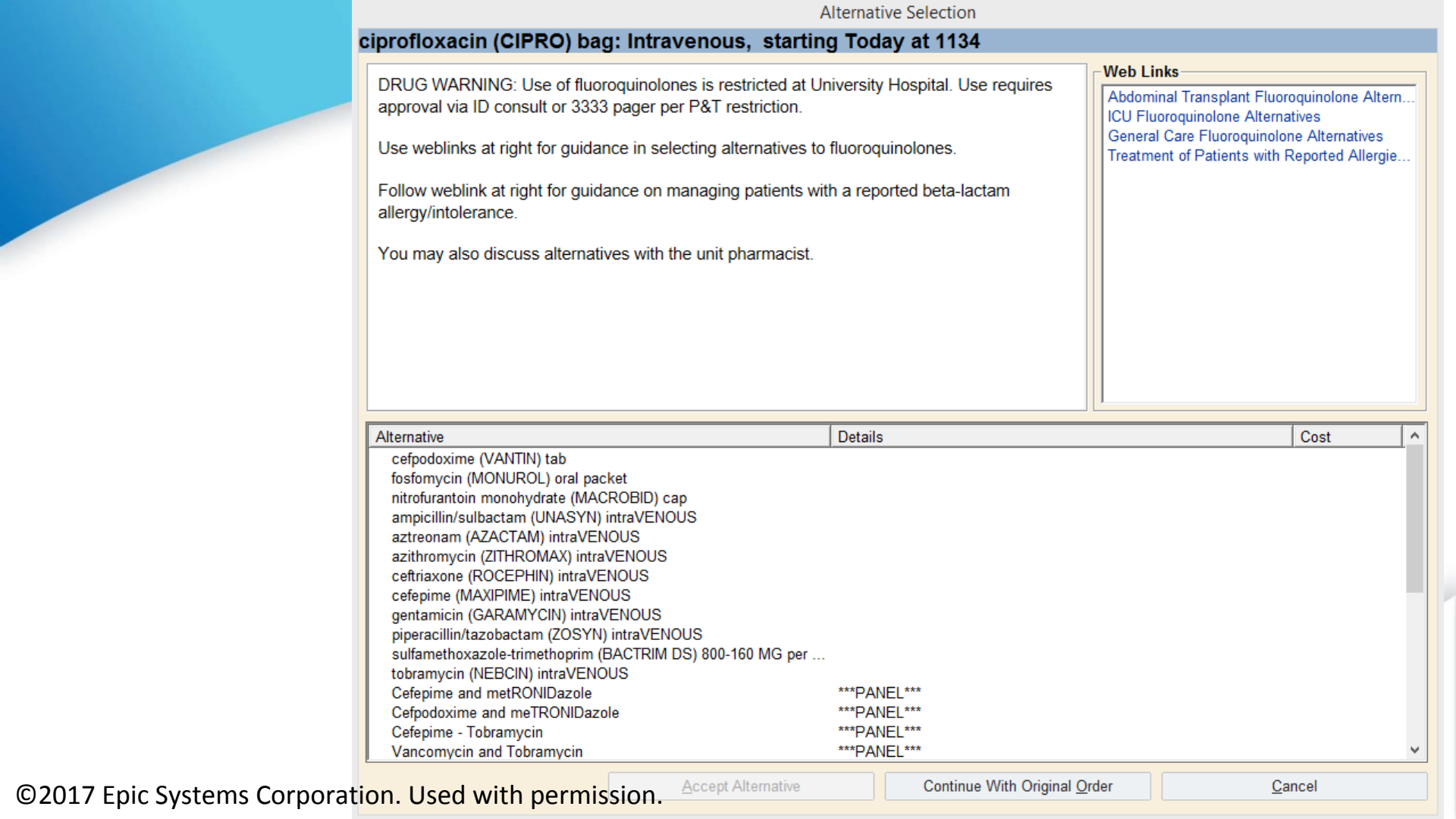
Diagnosis	Historical Empiric Therapy	Proposed New Empiric Therapy		Comments/Step Down Therapy[A]
Cystitis or Uncomplicated Urinary Tract Infection (non-renal transplant)	Ciprofloxacin OR Levofloxacin	Nitrofurantoin Fosfomycin Cefpodoxime		Base on final culture results: nitrofurantoin, fosfomycin, cefpodoxime
Positive urine culture in the deceased renal transplant donor	Ciprofloxacin *ADD Vancomycin IF concern for Gram-positive organisms*	No risk factors for MDRO: ceftriaxone Concern for extended spectrum Gram-negative rods: cefepime or piperacillin/tazobactam		Base on final culture results Ceftriaxone susceptibility predicts activity for cefpodoxime If no oral options, page 3333 for fluoroquinolone approval
		For patients with IgE-mediated or severe reaction to β-lactam: tobramycin or aztreonam[B]		
Cystitis in renal transplant patient	Ciprofloxacin	ASYMPTOMATIC <3 months post renal transplant	No empiric antibiotic. Await final culture results to start therapy. If treatment started, provide 5-7 day therapy course	Base on final culture results Ceftriaxone susceptibility predicts activity for cefpodoxime If no oral options, page 3333 for fluoroquinolone approval
		ASYMPTOMATIC >3 months post renal transplant	No treatment, unless associated rise in creatinine	
		SYMPTOMS present	Nonsystemic therapies • nitrofurantoin if CRCL >40 mL/min • fosfomycin if CRCL <40 mL/min or concern for drug resistant isolates	Continuation of empiric, non-systemic therapies or based on final culture results
Pyelonephritis in renal transplant patient	Ciprofloxacin *ADD Vancomycin IF concern for Gram-positive organisms*	No risk factors for MDRO: ceftriaxone Concern for extended spectrum Gram-negative rods: cefepime or piperacillin/tazobactam For patients with IgE-mediated or severe reaction to β-lactam: tobramycin (while awaiting pathogen identification) OR aztreonam[B]		Base on final culture results Ceftriaxone susceptibility predicts activity for cefpodoxime If no oral options, page 3333 for fluoroquinolone approval

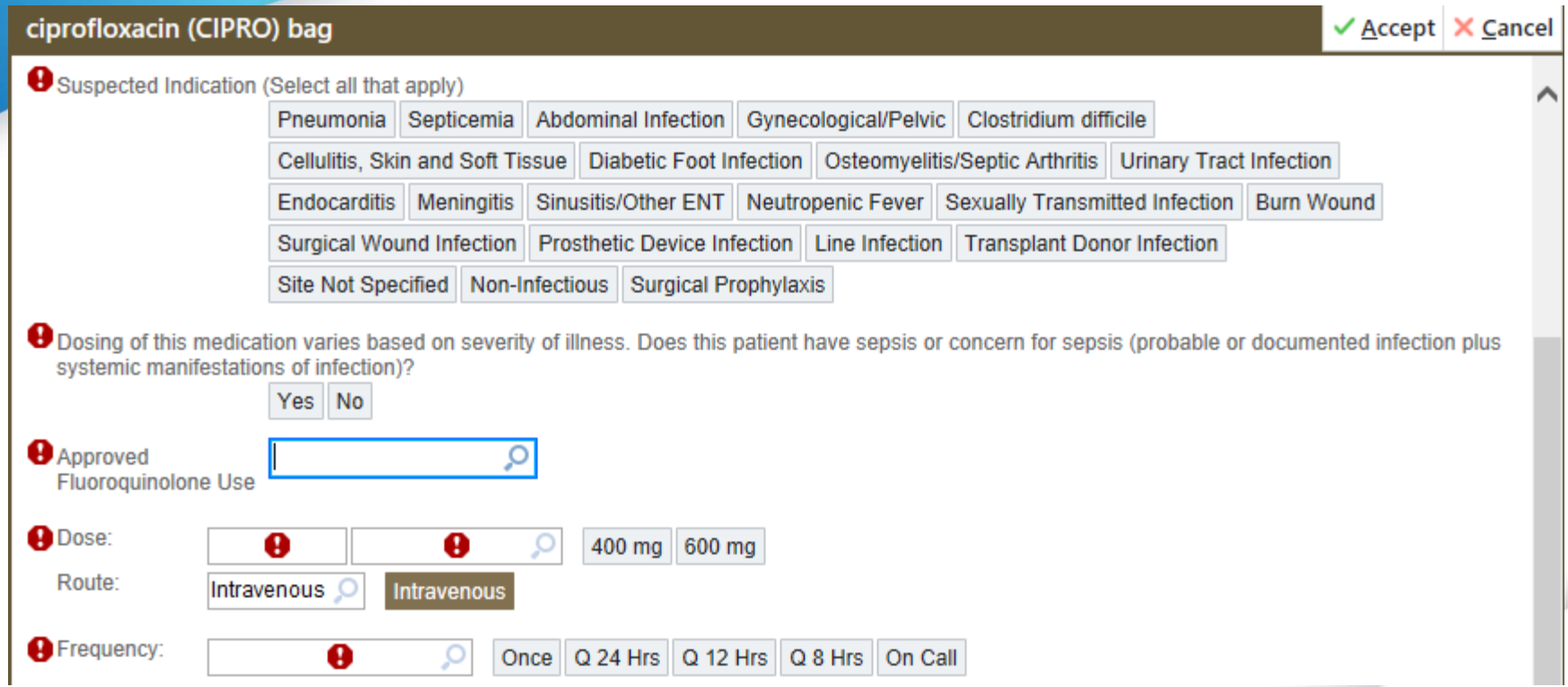
TRANSPLANT

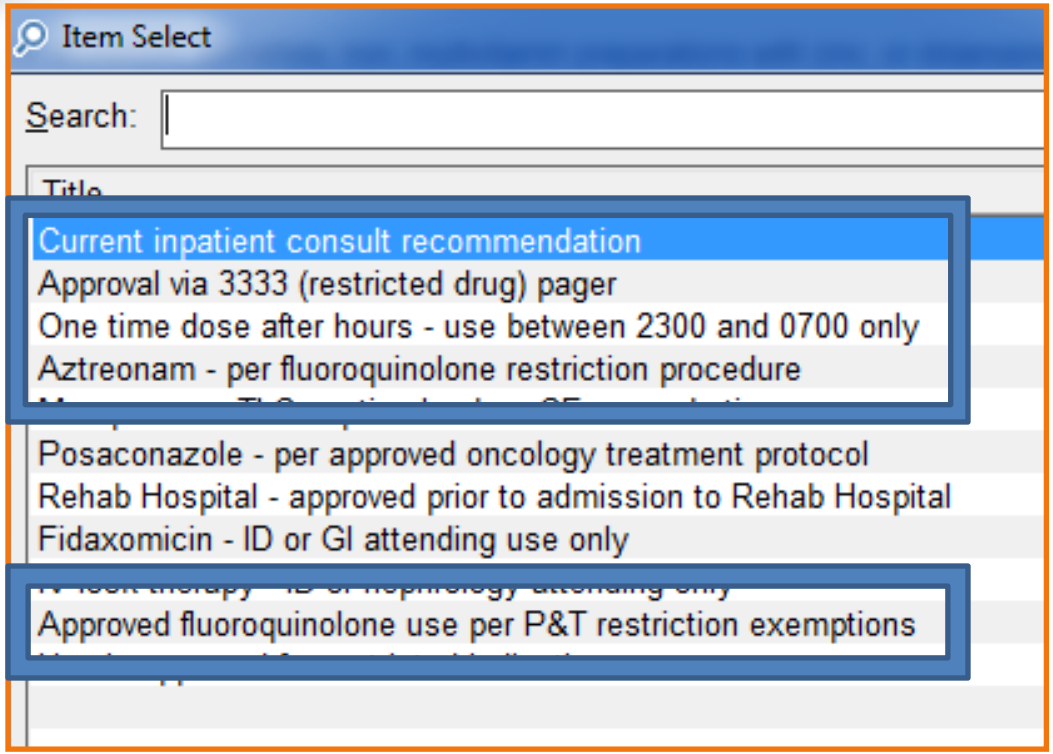
Diagnosis	Historical Empiric Therapy	Proposed New Empiric Therapy	Comments/Step Down Therapy[A]
Cholangitis in the historical liver transplant recipient	Ciprofloxacin PLUS amoxicillin OR moxifloxacin	• Piperacillin/tazobactam PLUS metronidazole OR • Cefepime PLUS metronidazole For patients with IgE-mediated or severe reaction to β-lactam: • vancomycin (trough goal 10-20 mcg/mL) PLUS tobramycin OR • vancomycin (trough goal 10-20 mcg/mL) PLUS aztreonam	Cefpodoxime OR cefuroxime PLUS amoxicillin (*Enterococcus* coverage) If no oral options, page 3333 for fluoroquinolone approval
Intra-abdominal infection – Other community or healthcare associated	Ciprofloxacin AND metronidazole	No risk factors for MDRO: ceftriaxone AND metronidazole	Base on final culture results, some examples of potential oral options: • cefpodoxime OR cefuroxime PLUS metronidazole • amoxicillin/clavulanic acid If final culture results require fluoroquinolone step down (e.g. *Pseudomonas*) single oral dose prior to discharge is acceptable
	Vancomycin PLUS Piperacillin/ tazobactam AND Ciprofloxacin	With risk factors for MDRO: • vancomycin[C] PLUS piperacillin/tazobactam OR • vancomycin[C] PLUS meropenem With risk factors for MDRO and IgE-mediated or severe reaction to β-lactam: vancomycin[C] PLUS aztreonam PLUS metronidazole	
Community-acquired Pneumonia[D]	Moxifloxacin OR Levofloxacin	No risk factors for MDRO: • ceftriaxone PLUS doxycycline OR • ceftriaxone PLUS azithromycin	Potential oral options: cefpodoxime OR cefuroxime PLUS azithromycin OR doxycycline If no oral options, page 3333 for fluoroquinolone approval
		For patients with IgE-mediated or severe reaction to β-lactam: vancomycin[C] PLUS aztreonam[B]	
Healthcare-associated Pneumonia[D]	Vancomycin PLUS Cefepime AND Ciprofloxacin	With risk factors for MDRO: vancomycin[B] PLUS cefepime If patient in septic shock: ADD tobramycin (pending transfer to higher care level) If concern for atypical bacteria: ADD azithromycin	Double coverage for *Pseudomonas* is not required in clinically stable, general care patient If no oral options, page 3333 for fluoroquinolone approval
		For patients with IgE-mediated or severe reaction to β-lactam: vancomycin[B] PLUS aztreonam[C]	

Pilot: How

- Aminoglycoside safety
- Cross-table antibiogram
- Physician support
- Pharmacist education
- Nursing and resident education
- Electronic decision support







Existing Restriction Modification

- “Aztreonam may be used without Infectious Disease approval for up to 72 hours of empiric use. After 72 hours, ID approval required through ID consult or Restricted Antimicrobial Pager (*3333)”

Pilot Results: August 2016

- Pilot Units
  - MICU/SICU FQ use ↓ 70.5%
  - Transplant FQ use ↓ 65.8%
- Non-pilot Units
  - General Medicine and Hospitalist FQ use ↓ 39.7%
  - Overall FQ use at University Hospital ↓ 29.6%
  - Overall FQ use at The American Center ↓ 33.3%

Results: Alternative Tables

Indication	Order Set Utilization N	Alternative compliance N (%)
Cholangitis	6	4 (67)
Community-acquired pneumonia	7	7 (100)
Cystitis	4	2 (50)
Healthcare-associated pneumonia	24	13 (54)
Intraabdominal infection	26	21 (81)
Positive donor culture (renal transplant)	5	4 (80)
Pyelonephritis	8	6 (75)
Sepsis (urinary tract source)	10	4 (40)
Septic shock – unknown origin	7	3 (43)
Other infection	41	40 (98)

104/138 = 75% overall compliance

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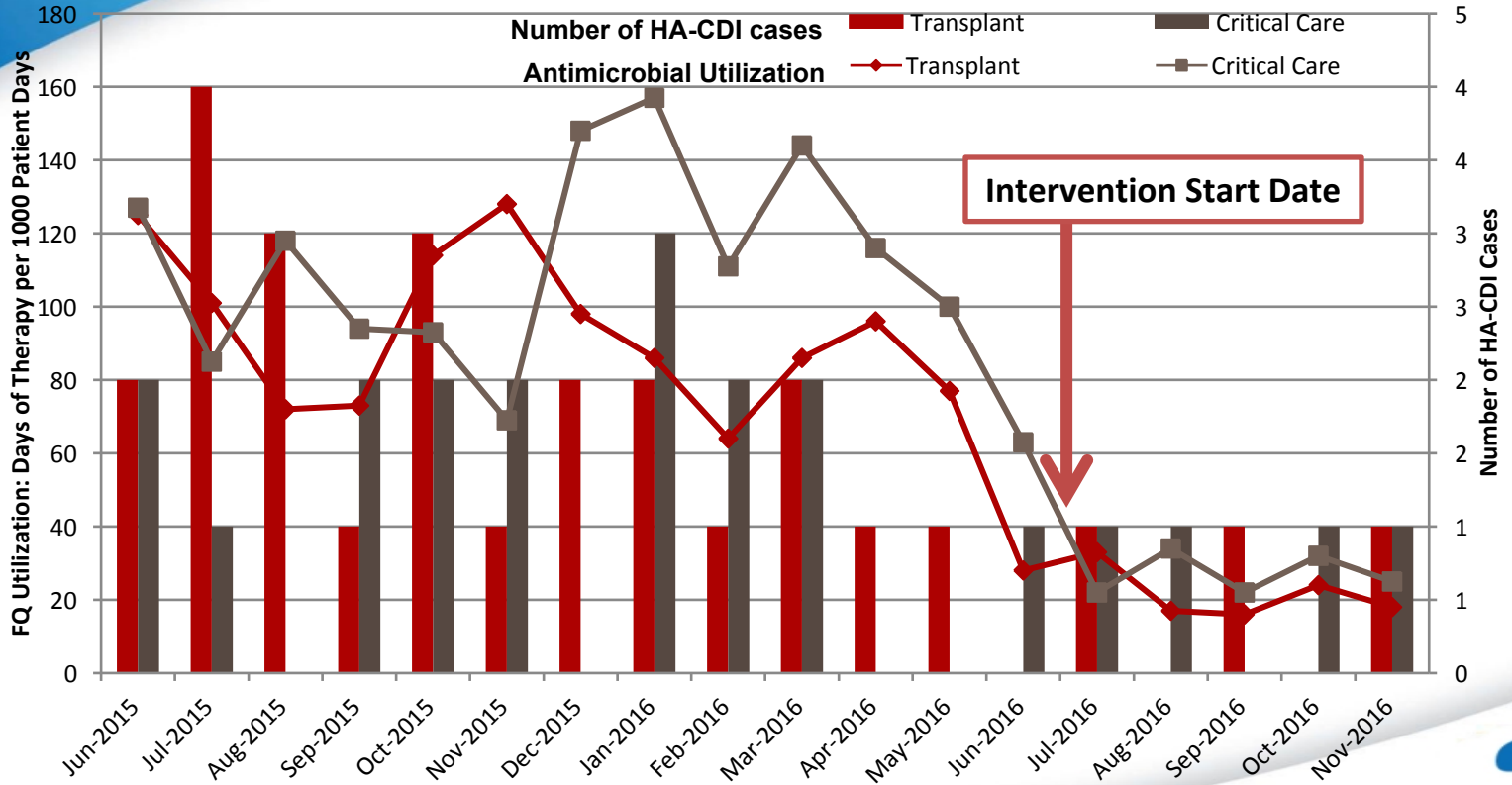
Results: Safety & Efficacy

- Safety
  - 7/138 treatment courses used AG
    - 2 patients developed AKI
- Efficacy
  - 5/124 patients readmitted for same infection
    - 3 intraabdominal
    - 2 cellulitis

Pilot Results: November 2016



Results: November 2016

HA-CDI Cases Per 10,000 Patient Days	Pre-intervention	Post-intervention	
University Hospital	8.36	5.65	*p=0.05*
Pilot Units	16.8	7.7	*p=0.12*

House-Wide Expansion

- March 15th, 2017
- Create general medicine/surgery alternative tables
- Update 66 order sets containing FQs
- Education via institutional Lexicomp®
- Exclusions: Children's Hospital, Emergency Department, Regional hospitals

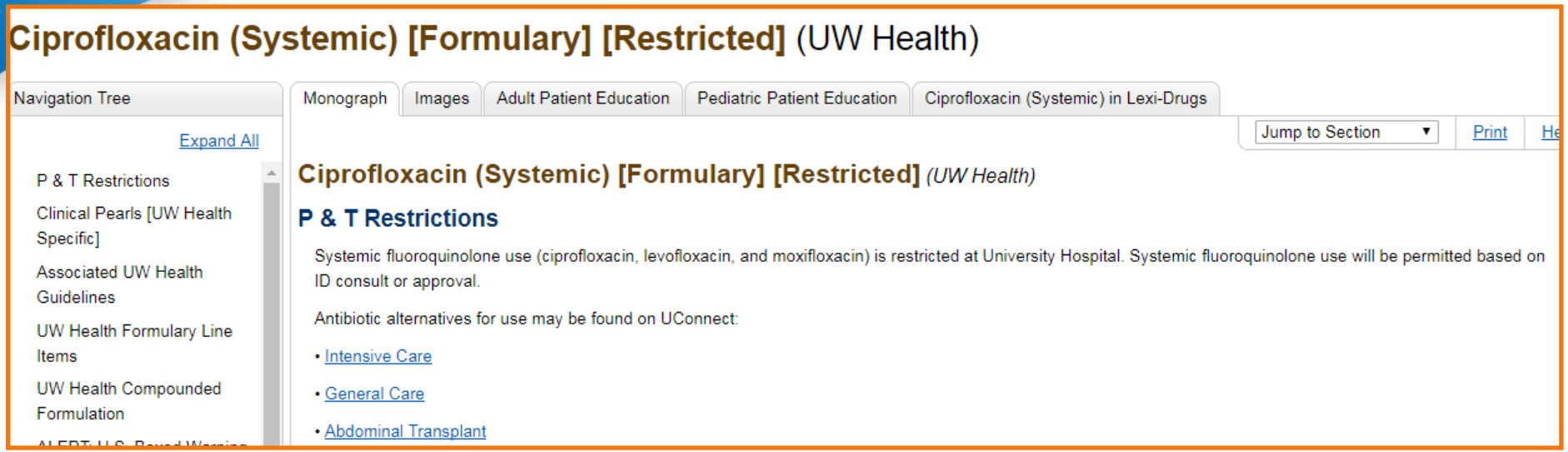
GENERAL

Diagnosis	Historical Empiric Therapy	Proposed New Empiric Therapy	Comments/Step Down Therapy[A]
Cystitis or Uncomplicated Urinary Tract Infection	Ciprofloxacin OR Levofloxacin	Nitrofurantoin Fosfomycin Cefpodoxime	Do not treat asymptomatic bacteruria Base on final culture results: nitrofurantoin, fosfomycin, TMP/SMX, cefpodoxime Ceftriaxone susceptibility predicts activity for cefpodoxime
Pyelonephritis	Ciprofloxacin OR Levofloxacin	No risk for MDRO: cefpodoxime or ceftriaxone	If no oral options, page 3333 for fluoroquinolone approval Tailor therapy based on final culture results Ceftriaxone susceptibility predicts activity for cefpodoxime
		With risk factors for MDRO: cefepime and vancomycin[B]	
		With risk factors for MDRO and IgE-mediated or severe reaction to β-lactam: gentamicin OR TMP/SMX	
Spontaneous bacterial peritonitis (SBP) prophylaxis	Ciprofloxacin	Oral therapy: TMP/SMX OR cefpodoxime Intravenous therapy: ceftriaxone	May transition to oral equivalent of empiric regimen OR to ciprofloxacin at discharge
Intra-abdominal infection – community or healthcare associated	Ciprofloxacin AND metronidazole	No risk factors for MDRO: • cefpodoxime AND metronidazole OR • ceftriaxone AND metronidazole	Base on final culture results, some examples of potential oral options: • cefpodoxime OR cefuroxime PLUS metronidazole • amoxicillin/clavulanic acid If final culture results require fluoroquinolone step down (e.g. *Pseudomonas*) single oral dose prior to discharge is acceptable
	Vancomycin PLUS Piperacillin/ tazobactam AND Ciprofloxacin	With risk factors for MDRO or severe community-acquired infection: • vancomycin[B] PLUS piperacillin/tazobactam OR • vancomycin[B] PLUS cefepime AND metronidazole With risk factors for MDRO and IgE-mediated or severe reaction to β-lactam: vancomycin[B] PLUS aztreonam PLUS metronidazole	

GENERAL

Diagnosis	Historical Empiric Therapy	Proposed New Empiric Therapy	Comments/Step Down Therapy[A]
Community-acquired Pneumonia[D]	Moxifloxacin OR Levofloxacin	No risk factors for MDRO: • ceftriaxone PLUS doxycycline OR • ceftriaxone PLUS azithromycin For patients with IgE-mediated or severe reaction to β-lactam: vancomycin[B] PLUS aztreonam[C]	Potential oral options: cefpodoxime OR cefuroxime PLUS azithromycin OR doxycycline If no oral options, page 3333 for fluoroquinolone approval
Healthcare-associated Pneumonia[D]	Vancomycin PLUS Cefepime AND Ciprofloxacin	With risk factors for MDRO: vancomycin[B] PLUS cefepime If patient in septic shock: ADD tobramycin (Pending transfer to higher care level) If concern for atypical bacteria: ADD azithromycin For patients with IgE-mediated or severe reaction to β-lactam: vancomycin[B] PLUS aztreonam[C]	Double coverage for *Pseudomonas* is not required in clinically stable, general care patient If no oral options, page 3333 for fluoroquinolone approval
Sepsis (without septic shock) of urinary origin/pyelonephritis	Vancomycin AND/OR ciprofloxacin	No risk factors for MDRO: ceftriaxone With risk factors for MDRO: vancomycin[B] PLUS cefepime For patients with IgE-mediated or severe reaction to β-lactam: vancomycin[B] PLUS tobramycin	
Septic Shock – unknown origin empiric coverage of *Pseudomonas*	Vancomycin PLUS Piperacillin/tazobactam AND Ciprofloxacin	• Vancomycin[B] PLUS piperacillin/tazobactam PLUS tobramycin OR • Vancomycin[B] PLUS cefepime PLUS tobramycin For patients with IgE-mediated or severe reaction to β-lactam: Vancomycin[B] PLUS aztreonam[C] PLUS tobramycin PLUS metronidazole	

Ciprofloxacin (Systemic) [Formulary] [Restricted] (UW Health)



Exemptions

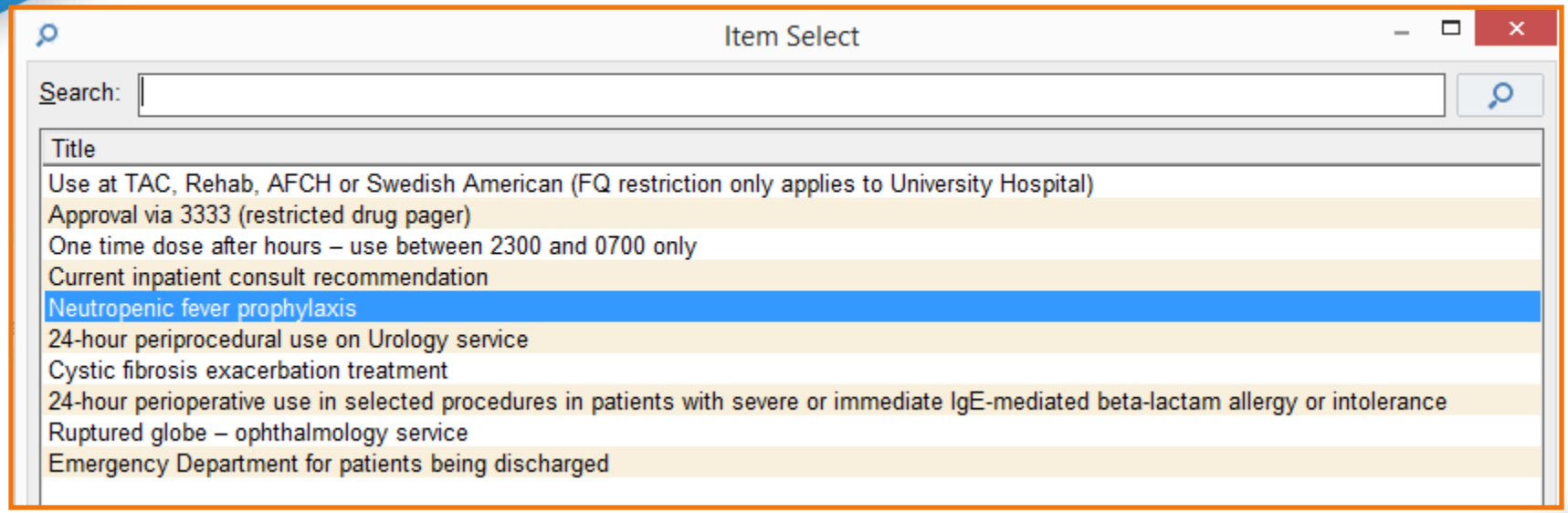
- Fever and neutropenia prophylaxis (oncology)
- 24-hour periprocedural use (urology)
- Cystic fibrosis exacerbation treatment (pulmonary)
- 24-hour perioperative use in selected procedures in patients with severe or immediate IgE-mediated beta -lactam allergy or intolerance

Audience Participation

Image: http://www.iemoji.com/view/emoji/840/smileys-people/woman-raising-hand

You Live and You Learn

- Cefepime shortage
- Allergies
- Prior-to-admission medications
- Readmissions
- Facilitating discharge
- Renal transplant / Nephrology
- GI clinic
- Pulmonary
- Emergency Department
- Ophthalmology
- Leeches
- Ebola



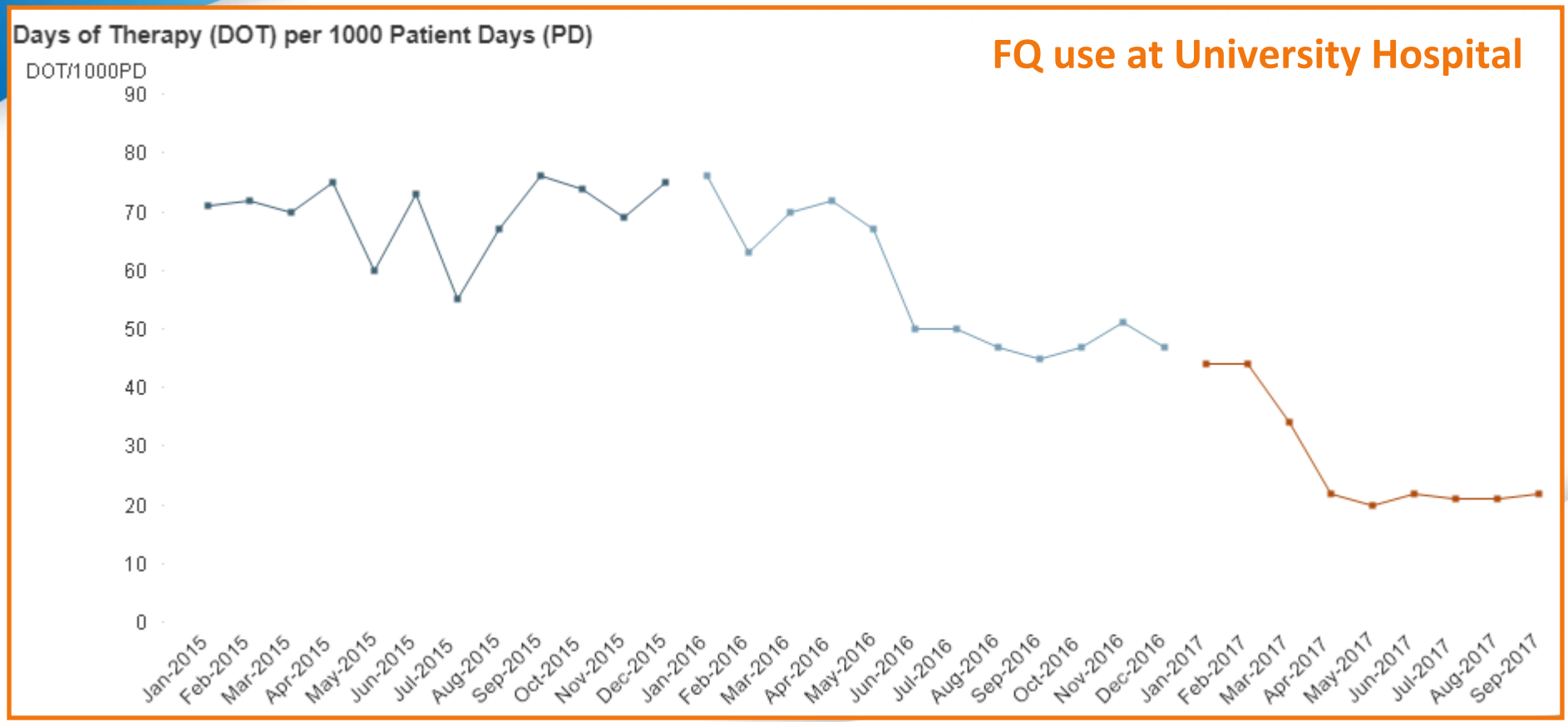
Expansion Results

Month	HA-CDI Cases 2017
April	5
May	5
June	3

Expansion Results

Expansion Results

Expansion Results



Key Takeaways

- It take’s a lot to steer a big ship
- Antimicrobial stewardship is a team effort
- “It’s not whether you get knocked down, it’s whether you get up.”
- Fluoroquinolones aren’t great and you can live without them

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Evolution of *Clostridium difficile* Testing and Implications for Antimicrobial Stewardship

Tristan T. Timbrook, Pharm.D., M.B.A., BCPS
Antimicrobial Stewardship Pharmacist
University of Utah Health Care
Salt Lake City, Utah
@TimbrookTT

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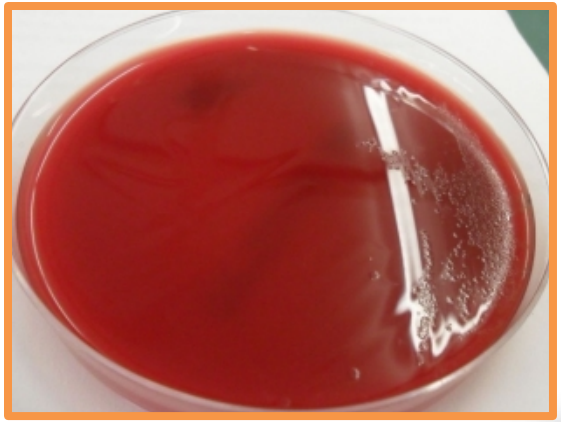
Learning Objectives

- Recognize the differences between rapid diagnostic tests for *Clostridium difficile* infection (CDI) and impact on diagnosis.
- Use various approaches, including multi-step testing algorithms, to potentially improve diagnosis of CDI.

CDI Testing 101: *Gold Standard*

Anaerobic Toxigenic Culture (TC)

- Isolation of *C. difficile* via culture incubation of 2-7 days
- Not routinely used due to labor and time intensity
- Requires additional test to confirm toxin production

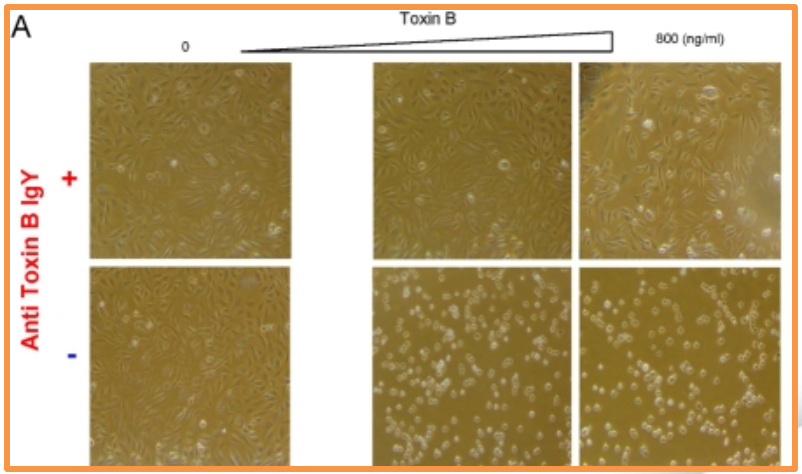


Burnham CD, et al. CMR. 2013. ▪ Image: commons.wikimedia.org/wiki/File:Clostridium_difficile.jpg

CDI Testing 101: *Gold Standard*

Cell culture cytotoxicity neutralization assay (CCNA)

- Confirms *in vivo* toxin production
- Requires 24-48h test time
- Not routinely used due to labor and time intensity

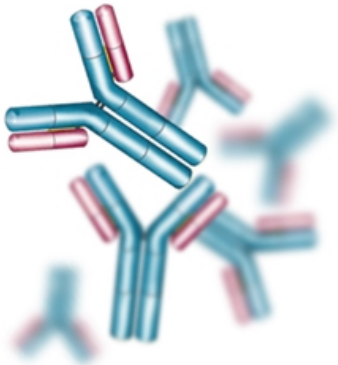


Burnham CD, et al. CMR. 2013. ▪ Image: Lei X, et al. Plos One. 2013. (Creative Commons License)

CDI Testing 101:

Toxin Enzyme-linked immunosorbent assay (EIAs)

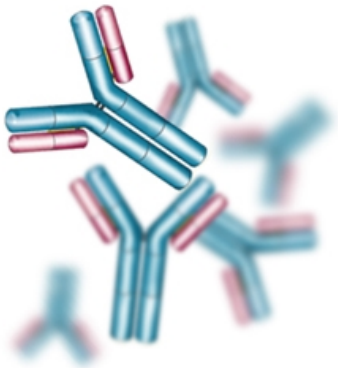
- Utilizes antibodies directed against *C. difficile* antigens (e.g. proteins) to detect toxins
- Toxin A and B
  - Sensitivity 70%
  - Specificity 98%



Burnham CD, et al. CMR. 2013. ▪ AHRQ 2017 ▪ Image: upload.wikimedia.org/wikipedia/commons/e/e5/Antibody1.jpg

CDI Testing 101:
Glutamate Dehydrogenase (GDH) EIAs

- Enzyme produced by both toxogenic **and** non-toxin producing *C. difficile*
- May require toxin identification by another test
- Sensitivity 90%, specificity 94%



Burnham CD, et al. CMR. 2013. ▪ AHRQ 2017 ▪ Image: upload.wikimedia.org/wikipedia/commons/e/e5/Antibody1.jpg

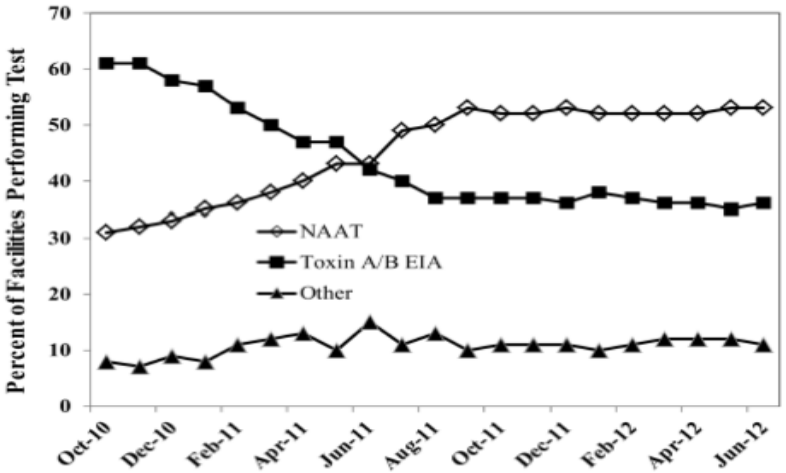
CDI Testing 101:
Nucleic Acid Amplification Techniques (NAAT/PCR)

- Detects gene for toxin B (*tcd*B) and/or toxin A (*tcd*A)
- Advantages
  - Limited labor
  - Approximately 1 hour turn-around time
  - Sensitivity 95%, specificity 97%
- Does **not** detect toxin production and therefore **may reflect colonization** rather than active disease

Burnham CD, et al. *CMR*. 2013. ▪ AHRQ 2017 ▪ Image: upload.wikimedia.org/wikipedia/commons/e/e5/DNA_Double_Helix.png

Evolution of CDI Testing: A Messy Endeavor

CDI Test Type at 132 VA Facilities



- Increased utilization of NAAT due to **high sensitivity**
- CDI rates often reported to **double** after switching to PCR
- When screening all hospitalized patients, 72% of **positive** CDI tests may be in **colonized/ asymptomatic** patients

Burnham CD, et al. CMR. 2013. ▪ Koo HL, et al. ICHE. 2014;35(6):667-673. ▪ Image: Evans ME, et al. ICHE. 2014 (public domain)

Which type of CDI testing may promote over-diagnosis of CDI?

A. Glutamate Dehydrogenase (GDH) Enzyme-linked immunosorbent assay (EIAs)
B. Nucleic Acid Amplification Techniques (NAAT/PCR)
C. Toxin A&B Enzyme-linked immunosorbent assay (EIAs)
D. A&B

Strategies to Improve CDI Diagnosis

- Creating a "**laboratory test utilization committee**" can optimize diagnostic test use by **involving key stakeholders** akin to P&T committees optimization of medication use
- Areas for optimization
  - **Pre-analytical:** Ensuring appropriate test ordering
  - **Analytical:** Optimal testing
  - **Post-analytical:** Improved communication of results

Messacar K, et al. *JCM.* 55(3):715-723.▪ Banerjee R, et al. *Clin Infect Dis*. 2016;63(10):1332-1339.
Image: commons.wikimedia.org/wiki/File:Federal_Open_Market_Committee_Meeting.jpg ▪ Hawkins R. *Ann Lab Med.* 2012;32(1):5-16.

Pre-analytical

Increasing Pre-Test Probability of CDI

EMR Modification Study

- Methods: EMR modified to enforce testing criteria
  - ≥ 3 unformed stools in 24h, absence of laxative use in prior 48h
- Results: In 1 year, 16.2% (375/2,321) of tests canceled for not meeting criteria
- Conclusion: EHR enforced criteria for testing to decrease inappropriate *C. difficile* testing

Truong CY, et al. *JCM.* 2017. ▪ Image: pixabay.com/p-1476525/?no_redirect

Pre-analytical

Does Pre-test Probability Correlate to CDI?

CDI Test to Pre-test Probability Study

- Methods: low, medium, and high pre-test probability compared to EIA and TC results
- Results: Of 111 patients, 65% had low pre-test probability. None had + EIA, four had + TC and none developed CDI in following 30 days
- Conclusion: Pre-test probability of disease should be considered when ordering CDI testing

Kwon JH, et al. *JCM.* 2017;55(2):596-605. ▪ Image: pixabay.com/p-1476525/?no_redirect

Analytical

European Diagnostic Recommendations on CDI Testing

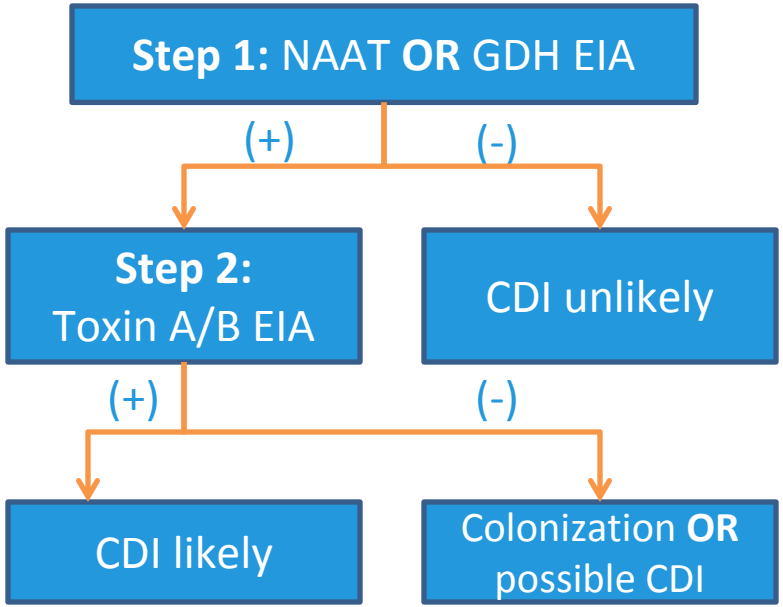


Figure adapted from Crobach MJT, et al. CMI. 2016

- Multi-step algorithm
  - High **sensitivity** test for **negative** predictive value
  - High **specificity** test for **positive** predictive value
  - Combination increases clinical utility of testing

Analytical: Value in Toxin Identification?

Study	Population	Methods	Outcomes
Polage et al. *JAMA Intern Med*. 2015	• 1,416 adults • Single academic center	• Testing: EIA Tox, PCR • PCR reported, tox **not** reported • Outcomes: CDI related complications, CDI related mortality	• 21% PCR+ (44.7% of those Tox+) • **No CDI-related complications** in Tox−/PCR+ v.s 10 Tox+/PCR+ ($p < 0.01$)

Analytical: Value in Toxin Identification?

Study	Population	Methods	Outcomes
Planche et al. *Lancet Infect Dis.* 2013	• 12,420 fecal samples • 4 UK laboratories	• Testing: TC, CCNA, GDH, EIA, PCR • Outcomes: Mortality (adj. for confounding)	• **Increased mortality** associated with detection of toxin production (p=0.04) but **not** in detection of organism w/o toxin

Analytical: Is There an Optimal Approach?

- Overall, the issue of testing methods is still an evolving subject
  - ECCMID supporting multiple step algorithms
  - IDSA new guidelines will likely support multiple step algorithm
- **Take home**:
  - Know your labs methods and use with clinical judgement
  - CDI is a clinical diagnosis supported, not defined, by laboratory data

Burnham CD, et al. CMR. 2013. ▪ Fang FC, et al. JCM. 2017.
Dubberke ER, Burnham CD. JAMA Intern Med. 2015;175(11):1801-2

Using sample multistep in handout, how should a positive PCR be used?

A. CDI is likely, initiate CDI therapy
B. Follow-up test with GDH EIA
C. Follow-up test with Toxin A/B EIA
D. Follow-up test with TC

Post-analytical

Communicating & Interpreting Results

- *Clostridium difficile* detected by PCR, EIA Toxin A/B negative

VS

- *Clostridium difficile* detected by PCR, EIA Toxin A/B negative
- Results suggestive of colonization or possible CDI

Which facilitates interpretation for clinicians?

Image: pixabay.com/en/communication-phone-call-message-1015376/

Post-analytical

Communicating & Interpreting Results

- **RDT Mock Case Study**
  - Interpretation and prescribing of 156 physicians based on mock cases with rapid diagnostic testing (RDT) results
  - 14-48% incorrect RDT interpretation
- Stewardship teams should work with labs to develop results communications in addition to providing clinician education on interpretation

Donner LM, et al. *JCM*. 2017;55(5):1496-1507. ▪ Image: pixabay.com/en/communication-phone-call-message-1015376/

Key Takeaways

- Work with IT and educate clinical staff on strategies to **increase pre-test probability of disease** (e.g. no laxatives in last 48h)
- Determine your **current testing standards** and discuss with micro lab and other stakeholders if **multi-step testing** is right for your facility
- **Educate** clinical staff on facility specific **testing methods and result interpretation**, provide prospective audit and feedback on positive testing

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Pharmacologic and Non-Pharmacologic Interventions That Improve CDI Rates and Patient Outcomes

Jerod Nagel, Pharm.D., BCPS-AQ ID
Clinical Team Lead, Infectious Diseases
Clinical Assistant Instructor
University of Michigan Health System
University of Michigan, College of Pharmacy

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Overview

- **Primary vs Secondary Treatment and Prevention**
  - Infection control for pharmacists
    - Going beyond hand hygiene
  - Pharmacologic treatment options
    - Focus on newer options
  - Non-pharmacologic treatment options
    - Probiotics and FMT
  - Multi-faceted approach

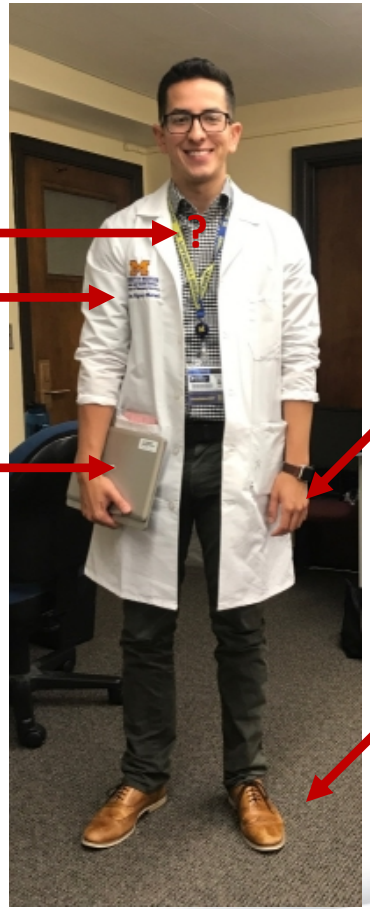
Infection Control Practices for Pharmacists

Neck Tie

Lab Coat

- Wash at least weekly with on hot cycle

Computer



Hands

-Most common source for spread of CDI spores

Shoes

-10-40% of shoes have CDI spores and other pathogens

- Shoe covers can reduce spread

ashp 75 CELEBRATING YEARS

Predicting and Possibly Preventing Patients From Acquiring CDI

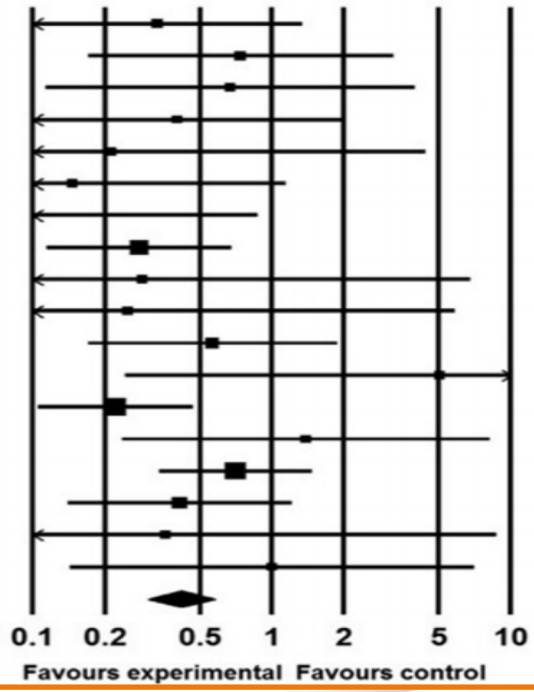
- **Traditional Risk Factors:**
  - Age >65, antibiotics, PPIs, previous CDI, length of hospitalization
- **Targeted Risk Factors:**
  - ICU: SICU admission, ICU length of stay, COPD, mechanical ventilation
  - Oncology: salvage lymphoma chemotherapy
  - Transplant: neutropenia in BMT
- **Screen for Colonization with Toxigenic *C. difficile***
  - Incidence ranges from 2% to 35% depending on population

Prevention Options for Patients at High-Risk

- **Practice Good Hand Hygiene and Infection Control Practices**
- **Evaluate and Minimize Modifiable Risk Factors**
  - Avoid antimicrobials (FQs, clindamycin, ceftriaxone, carbapenems)
  - Minimize use of acid suppression with proton pump inhibitors
- **Prophylaxis with Anti-CDI Agent for Select Patients**
  - Ongoing studies for patients colonized with toxigenic CDI
- **Vaccination**
  - Currently being developed
- **Probiotics for High-risk Patients**

Probiotics in Patient Taking Antibiotics

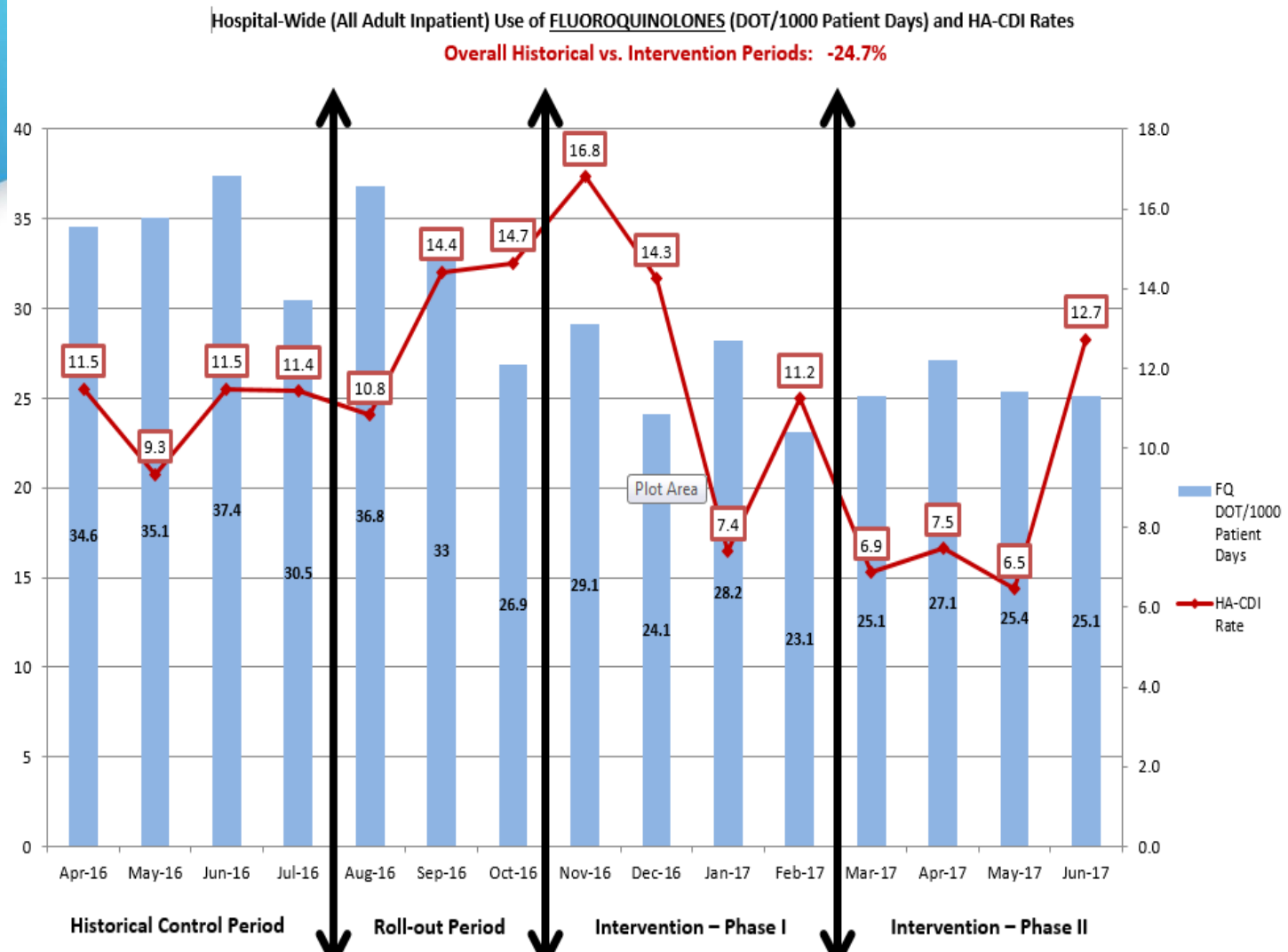
Study name	Events / total		Relative weight	Risk ratio
	Probiotics	Control		
Surawicz 1989	3 / 116	5 / 64	5.30	0.33
McFarland 1995	3 / 97	4 / 96	4.80	0.74
Thomas 2001	2 / 133	3 / 134	3.30	0.67
Plummer 2004	2 / 69	5 / 69	4.02	0.40
Can 2006	0 / 73	2 / 78	1.14	0.21
Beausoleil 2007	1 / 44	7 / 45	2.46	0.15
Hickson 2007	0 / 57	9 / 56	1.30	0.05
Rafiq 2007	5 / 45	22 / 55	13.16	0.28
Wenus 2008	0 / 34	1 / 29	1.04	0.29
Safdar 2008	0 / 23	1 / 17	1.05	0.25
Miller 2008a	4 / 95	7 / 94	7.26	0.57
Miller 2008b	2 / 157	0 / 159	1.13	5.06
Gao 2010	9 / 171	20 / 84	18.82	0.22
Pozzoni 2012	3 / 106	2 / 98	3.32	1.39
Allen 2013	12 / 1470	17 / 1471	19.16	0.71
Ouwehand 2014	6 / 304	7 / 146	9.01	0.41
Wong 2014	0 / 76	1 / 82	1.02	0.36
Ehrhardt 2016	2 / 146	2 / 146	2.74	1.00
Summary estimate				0.42

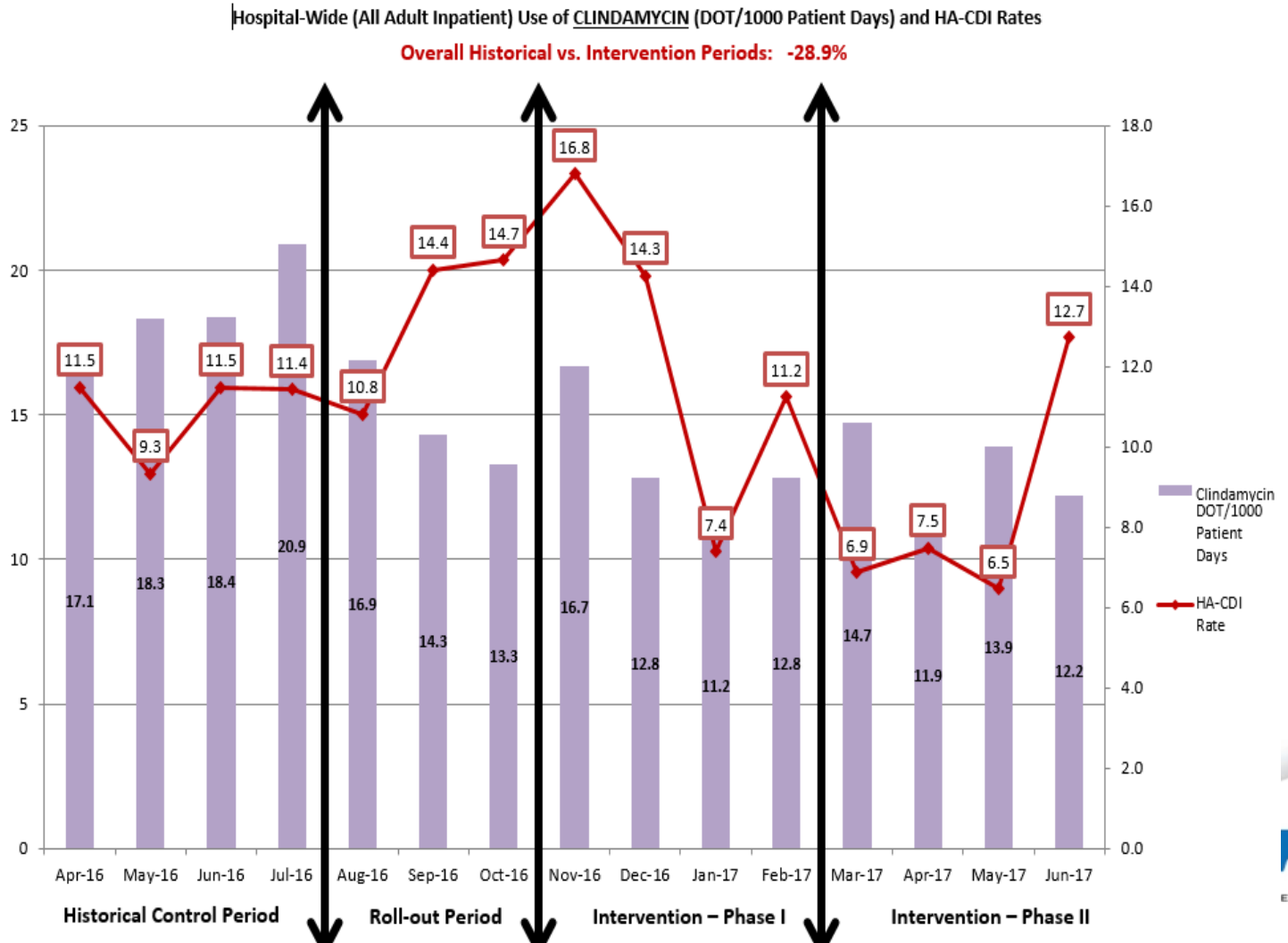


Gastroenterology. 2017 Jun;152(8):1889-1900

University of Michigan Experience with Reducing High-Risk Antibiotics

- **Focused on Providing Service-Specific Feedback to Pharmacy Teams on Performance and Outcomes Metrics**
  - Antibiotic utilization reports for FQs, clindamycin, and ceftriaxone
  - Appropriate prescribing reports
  - Hospital acquired CDI rates by service and pharmacy team
- **Evaulated utilization and CDI during 4 periods:**
  - Historic control
  - Education session on appropriate utilization of antibiotics and workflow expectations
  - Monthly reports, plus daily stewardship team coaching and feedback to clinical pharmacists
  - Monthly reports without stewardship oversight


Hospital-Wide (All Adult Inpatient) Use of FLUOROQUINOLONES (DOT/1000 Patient Days) and HA-CDI Rates
Overall Historical vs. Intervention Periods: -24.7%
40
35
30
25
20
15
10
5
0
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
11.5
9.3
11.5
11.4
10.8
14.4
14.7
16.8
14.3
7.4
11.2
6.9
7.5
6.5
12.7
34.6
35.1
37.4
30.5
36.8
33
26.9
29.1
24.1
28.2
23.1
25.1
27.1
25.4
25.1
Plot Area
FQ DOT/1000 Patient Days
HA-CDI Rate
Apr-16
May-16
Jun-16
Jul-16
Aug-16
Sep-16
Oct-16
Nov-16
Dec-16
Jan-17
Feb-17
Mar-17
Apr-17
May-17
Jun-17
Historical Control Period
Roll-out Period
Intervention – Phase I
Intervention – Phase II


Hospital-Wide (All Adult Inpatient) Use of CLINDAMYCIN (DOT/1000 Patient Days) and HA-CDI Rates
Overall Historical vs. Intervention Periods: -28.9%
25
20
15
10
5
0
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
11.5
9.3
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16.8
14.3
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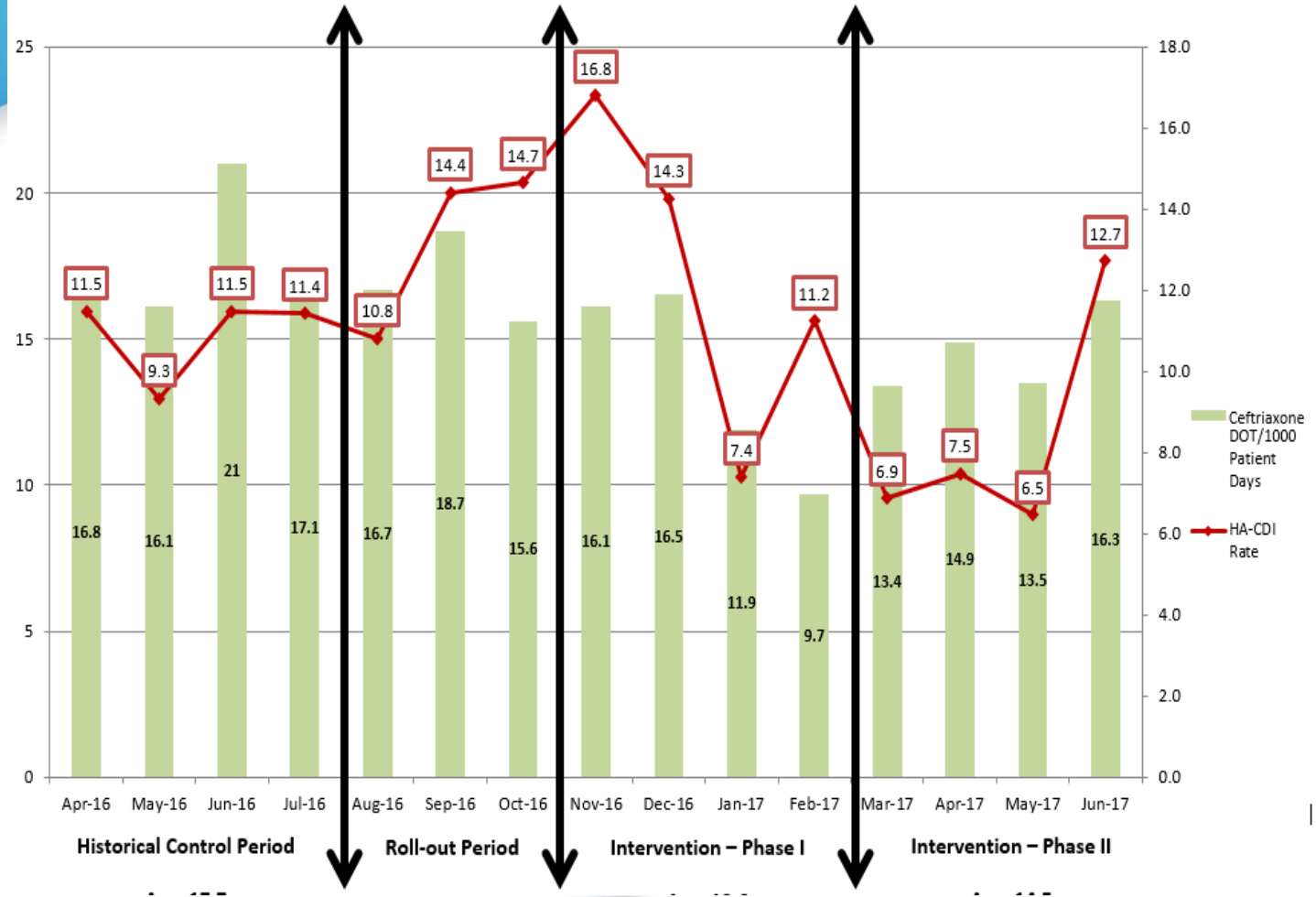
11.2
6.9
7.5
6.5
12.7
17.1
18.3
18.4
20.9
16.9
14.3
13.3
16.7
12.8
11.2
12.8
14.7
11.9
13.9
12.2
Apr-16
May-16
Jun-16
Jul-16
Aug-16
Sep-16
Oct-16
Nov-16
Dec-16
Jan-17
Feb-17
Mar-17
Apr-17
May-17
Jun-17
Historical Control Period
Roll-out Period
Intervention – Phase I
Intervention – Phase II
Clindamycin DOT/1000 Patient Days
HA-CDI Rate

Hospital-Wide (All Adult Inpatient) Use of CEFTRIAXONE (DOT/1000 Patient Days) and HA-CDI Rates

Overall Historical vs. Intervention Periods: -20.9%



Pharmacy Driven Intervention to Minimize PPIs and Promote Probiotics

	Historic Group	Intervention Group	Difference	P-value
Total PPI (doses/1,000 pt days)	677	581	-14.2%	0.0002
IV PPI (doses/ 1,000 pt days)	229	158	-31.1%	0.0008
Total Probiotic (doses/1,000 pt days)	97	223	+129.6%	0.0006
Hospital CDI (cases/1,000 pt days)	0.49	0.39	-20%	0.04

Ann Pharmacother. 2017 Oct;51(10):848-854.

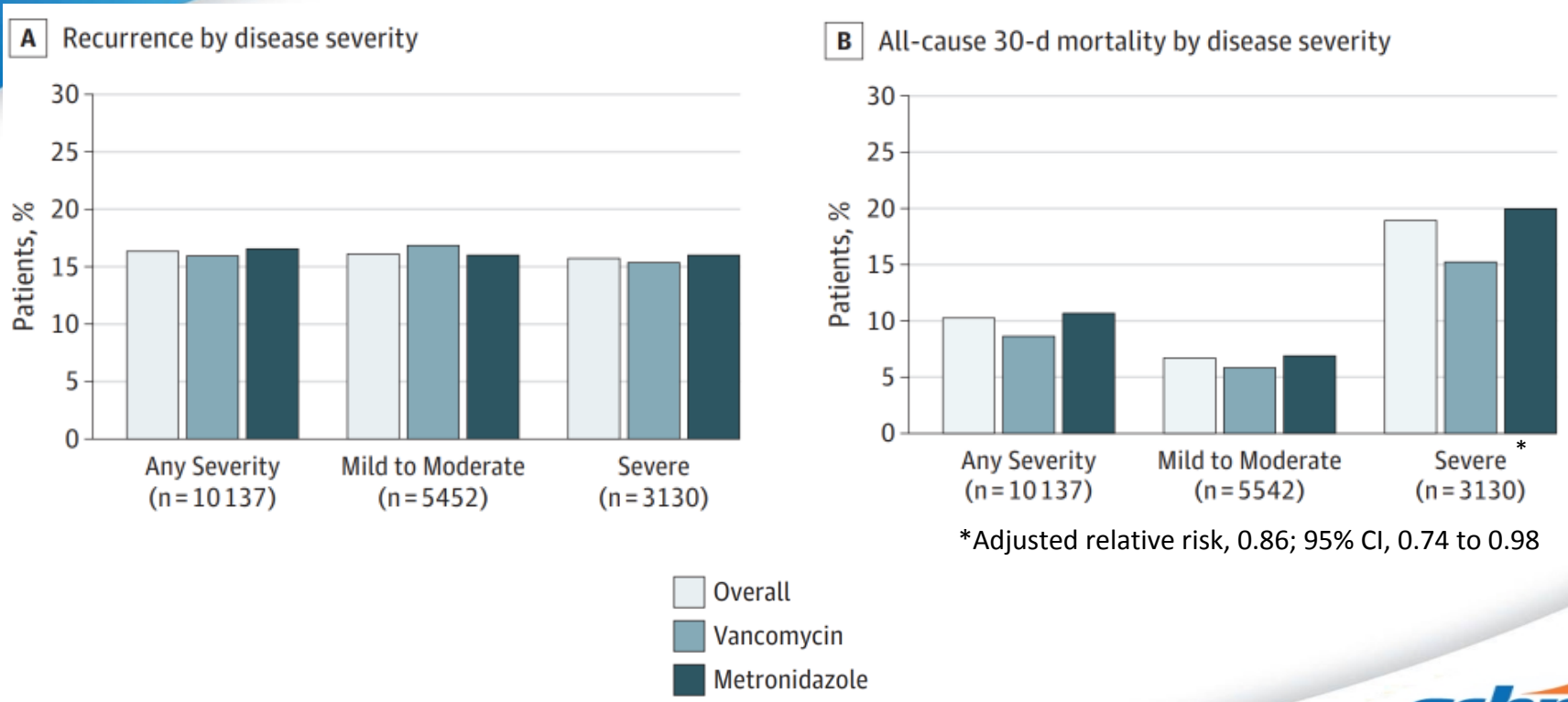
IDSA/SHEA CDI Treatment Guidelines

Disease Severity	Recommendation
Mild-moderate	Oral Metronidazole
Severe	Oral Vancomycin
Severe and complicated	Oral Vancomyciin +/- IV Metronidazole + PR Vancomycin if ileus or obstruction

- Treatment recommendations are same for index and first recurrence,
  but metronidazole should be avoided past first recurrence
- No guidance is provided for treatment of multiple recurrences
- Guidelines were published in 2010 and do not mention role for fidaxomicin, bezlotoxumab, or fecal microbiota transplant (FMT)

Infection Control and Hospital Epidemiology, 31(5), 431-455

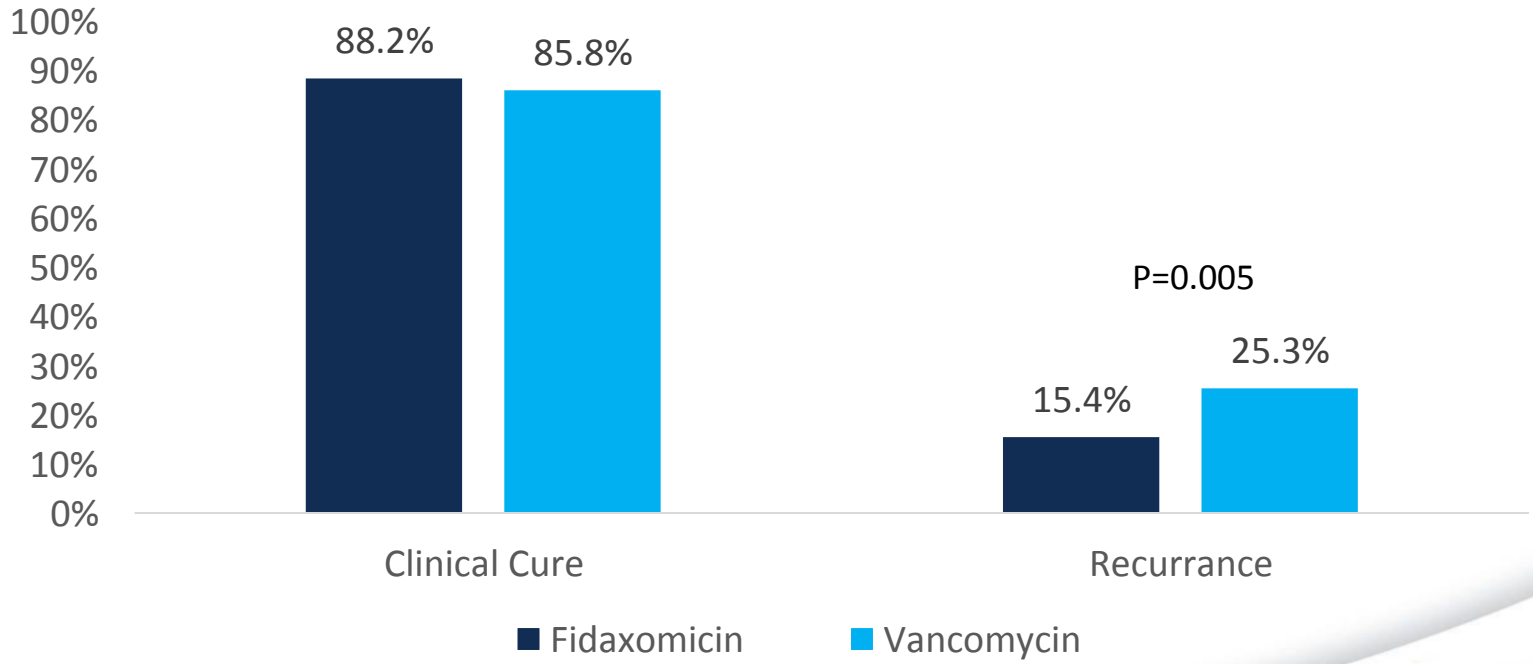
Vancomycin vs. Metronidazole



*Adjusted relative risk, 0.86; 95% CI, 0.74 to 0.98

JAMA Intern Med. 2017;177(4):546-553

Fidaxomicin vs. Vancomycin

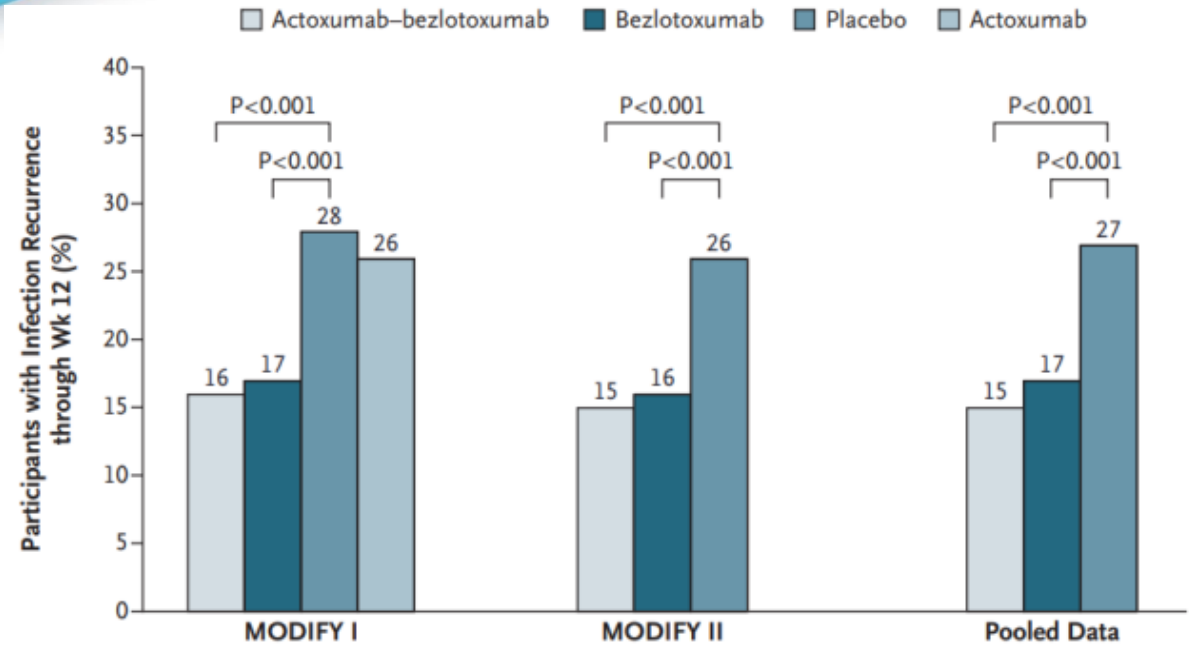


N Engl J Med 2011;364:422-31.

Bezlotoxumab

- Monoclonal antibiotic against toxin B
- Prescribed as adjunct therapy with anti-CDI therapy
- Given as a single IV dose of 10 mg/kg infused over 1 hour
- Long half-life of approximately 19 days
- Average wholesale price: $4,560 per 1 gm vial

Bezlotoxumab



- No difference in clinical cure: 80% vs. 73% vs. 80%

N Engl J Med 2017;376:305-17

Multifaceted CDI Initiative

- Real-time notification of CDI result to stewardship team
- Recommend timely appropriate CDI therapy, based on severity
- ID and Surgical consults, for patients with severe disease with complications or multiple recurrences
- Discontinue or de-escalate concomitant antibiotics
- Discontinue or change PPIs
- Education regarding proper testing

Am J Infect Control. 2016 Dec 1;44(12):1539-1543.

Multifaceted CDI Initiative

Interventions			
	Pre-Intervention (231)	**Intervention (227)**	**P-value**
PPI Stopped	13.9%	28.6%	**0.0292**
ID Consulted within 72 hours	10.4%	17.2%	**0.0349**
Vancomycin order, Severe Disease	59%	87%	**<0.0001**
Days to Vanco order (mean)	1.70	1.05	**0.03**

Clinical Outcomes			
	Pre-Intervention (231)	**Intervention (227)**	**P-value**
Attributable 30-day mortality	3.0%	3.1%	0.97
Attributable 30-day ICU admission	5.6%	5.3%	0.87
Attributable 30-day surgery	1.7%	0.0%	0.12
Recurrence	8.7%	8.4%	0.91

Am J Infect Control. 2016 Dec 1;44(12):1539-1543.

Pharmacists Interventions to Improve Prescribing & Outcomes for Patients with CDI

Author (n)	Intervention	Outcomes
Jury (n=146)	- Clinician education - Micro contacted AST, who recommend therapy - Order set implementation	- Improved guideline compliance - Improved time to appropriate therapy - Clinical outcomes were not evaluated
Jardin (n=256)	- Pharmacy prescribing authority for severe CDI	- Improved compliance with guideline for severe CDI
Yeung (n=424)	- Treatment algorithm - Pharmacist consult - Education	- Improved algorithm adherence rates - No difference in mortality - Decrease LOS (30 days vs 21 days, p=0.01)
Brumley (n=169)	- Develop guideline and order set (bundle) - Education - Recommend bundle interventions	- Improved overall bundle compliance: • Improved adherence to treatment recommendations • Discounted concomitant antimicrobials - No difference in mortality, readmission with CDI or LOS
Abbett (n=NR)	- Education - Prevention and treatment bundle development	- Process measures not reported - No Difference in mortality
Hammond (n=24)	- Education - Treatment guideline	- Improved algorithm adherence rates - No difference in hospital LOS - Reduction in ICU LOS (1.5 days vs. 3.5 days, p= 0.01)
Knaus (n=351)	- Education - Treatment guideline	- Improved algorithm adherence rates - No difference in mortality or LOS

Treatment Options for Patients with Multiple Recurrences

- **No Guideline Recommendations or Clear Delineation from Published Literature, and Each Option Has Pros and Cons**
  - Vancomycin pulse or taper regimen
  - Fidaxomicin taper regimen (following vancomycin or fidaxomicin)
  - Adjunct therapy with bezolotoxumab
  - Fecal microbiota transplant
    - Fresh vs. Frozen
    - GI vs. PR administration

Fidaxomicin Chaser or Taper

- **Potential option, but limited comparative data**
- **18 patient case series in patients with at least 3 previous CDI, received of various fidaxomicin chaser or taper regimens:**
  - 38% recurrence rates with 10-day chaser
  - 18% recurrence rate with 14-33 day taper following treatment
  - Taper resulted in longer time between episodes for patients with recurrence (257 vs. 25 days, $p<0.001$)

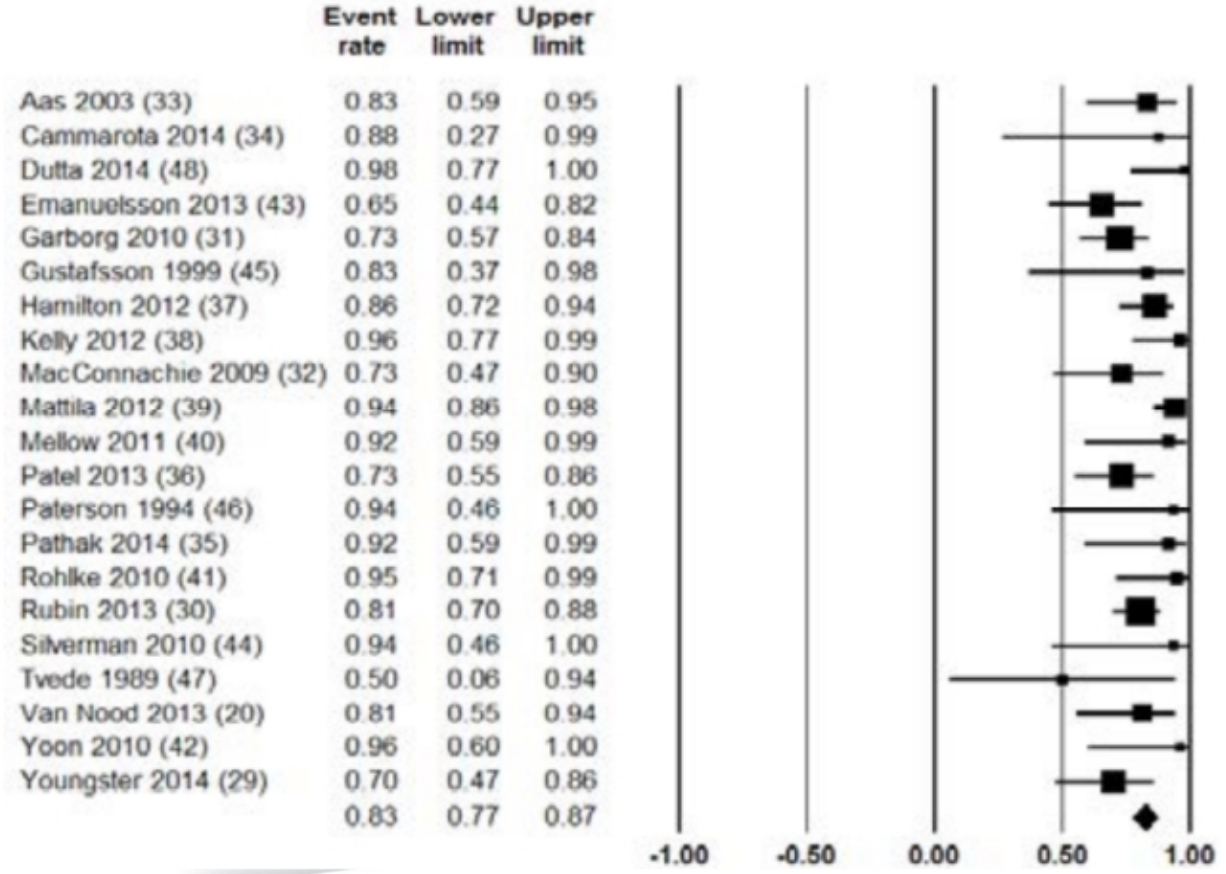
Open Forum Infect Dis. 2014 Aug 25;1(2)

Fecal Microbiota Transplant (FMT)

- **Primarily for patients with multiple recurrences failing standard therapy**
  - Otherwise, need FDA Investigational New Drug Application
- **Several options for getting product:**
  - Patient brings in product
    - Auto (self)
    - Donor
  - Purchase screened product from vendor
    - OpenBiome (Medford, MA)
    - AdvancingBio (Sacramento, CA)

Fecal Microbiota Transplant (FMT)

- 83% success rate for patients with multiple recurrences
- 53% success for patients with refractory disease



Ann Intern Med 2015;162(9):630–8.

FMT Preparation

Author	Design (sample size)	Intervention	Outcomes
Youngster, 2014	• Randomized controlled trail • n=20	Frozen FMT via NG tube vs. Frozen FMT via colonoscopy	Success with 1 treatment: -60% vs. 80% Success with >1 treatment: -80% vs. 100%
Lee, 2016	• Double blind, randomized, non-inferiority trail • n=232	Frozen FMT via enema vs. Fresh FMT via enema	Success: 83.5% vs. 85.1%
Kelly, 2016	• Multi-center, Double blind, randomized controlled trial • n=46	Fresh FMT via Donor vs. Fresh FMT via Auto (self)	Success: 91% vs. 63%

FMT vs. Vancomycin Taper for Recurrent CDI

Author	Design (sample size)	Intervention	Outcomes
van Nood, 2013	• Open label, randomized trial • n=43	Donor FMT via NG, plus bowel lavage vs. Vancomycin x 14 days vs. Vancomycin x 14 days, plus bowel lavage	<u>No recurrence within 10 weeks:</u> -81% FMT plus lavage -31% Vancomycin -23% Vancomyicn plus lavage
Cammarota, 2015	• Open label, randomized trial • n=20	Vancomycin treatment & taper (minimum 3 weeks) vs. Donor FMT via colonoscopy	<u>No recurrence within 10 weeks:</u> -90% FMT vs. 26% vancomycin
Hota, 2017	• Single-center, open label, randomized trial • n=30	Vanco x 14D, then Fresh donor FMT vs. Vanco treatment and 6 week taper	<u>No recurrence within 120 days:</u> -56.2% vanco plus FMT -41.7% vanco taper

Key Takeaways

- **Efforts to Decrease High-Risk Antibiotics are Strongly Associated with Reductions in Hospital-Acquired CDI Rates**
  - FQ, Clindamycin, Cephalosporins and Carbapenems
- **Pharmacists Initiatives to Improve Management of CDI have Consistently Resulted in Significant Improvements:**
  - Starting prompt anti-CDI therapy
  - Starting the correct anti-CDI therapy
  - Decreasing unnecessary antibiotics
  - Stopping unnecessary PPIs

Key Takeaways

- **Vancomcyin should be first line for severe disease**
  - Only CDI treatment option that has demonstrated improvements in clinical cure compared to metronidazole
  - Does not reduce recurrence compared to metronidazole
- **Bezlotoxumab and fidaxomicin have demonstrated reductions in recurrence for patients with initial and/or first recurrence, but limited data for patients with multiple recurrences**
- **Vancomycin taper/pulse dose, bezlotoxumab, fidaxomicin and fecal microbiota transplant are options for patients with multiple recurrences**

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Antimicrobial Stewardship Strategies to Reduce Hospital-Acquired *Clostridium Difficile* Infections

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