Overcoming Barriers to Successful Outcomes in *Clostridium difficile* & Antimicrobial-Resistant Gram-Negative Infections

Balancing the Old with the New

Supported by an educational grant from Merck & Co.

Jointly provided by Center for Independent Healthcare Education and Vemco MedEd

Understanding *C. difficile* Infections and Gram-Negative Infections: Are We There Yet?

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Antimicrobial-Resistant Bacteria are a Global Threat

World Health Organization

GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

CDC

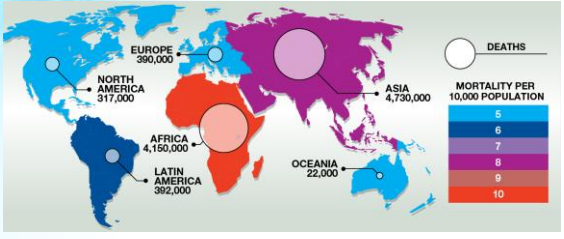
ANTIBIOTIC RESISTANCE THREATS in the United States, 2013

NIAID's Antibacterial Resistance Progra
Current Status
Future Dire
2014

Faces of IDSA ANTIMICROBIAL RESISTANCE

10,000,000 Deaths Annually by 2050

Annual deaths attributable to antimicrobial resistance by 2050



Review on Antimicrobial Resistance. Tackling a Crisis for the Future Health and Wealth of Nations. December 2014. Available at: https://amr-review.org/Publications.html.

Greatest Threats

CDC

- Urgent
  - *Clostridium difficile*
  - Carbapenem-resistant Enterobacteriaceae
  - *Neisseria gonorrhoeae*
- Serious
  - Multidrug-resistant (MDR) *Acinetobacter*
  - Drug-resistant *Campylobacter*
  - Fluconazole-resistant *Candida*
  - ESBL
  - VRE
  - MDR *Pseudomonas*
  - Drug-resistant *Salmonella*
  - Drug-resistant *Shigella*
  - Methicillin-resistant *S. aureus* (MRSA)
  - Drug-resistant Pneumococcus
  - Drug-resistant tuberculosis
- Concerning
  - Vancomycin-resistant *S. aureus*
  - Erythromycin-resistant Group A Strep
  - Clindamycin-resistant Group B Strep

WHO

- Critical
  - Carbapenem-resistant *Acinetobacter*
  - Carbapenem-resistant *Pseudomonas*
  - Carbapenem-resistant Enterobacteriaceae
- High
  - VRE
  - Vancomycin-intermediate MRSA
  - Clarithromycin-resistant *H. pylori*
  - Fluoroquinolone-resistant *Campylobacter*
  - Fluoroquinolone-resistant *Salmonella*
  - *Neisseria gonorrhoeae*
- Medium
  - Penicillin-non-susceptible Pneumococcus
  - Ampicillin-resistant *H. influenzae*
  - Fluoroquinolone-resistant *Shigella*

CDC. Available at: https://www.cdc.gov/drugresistance/biggest_threats.html.
WHO. Available at: http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/.

Treatment and Prevention of Infections Due to Resistant Bacteria is an Ongoing Challenge

- Population vs. patient
  - Antimicrobial stewardship: prevent development/promotion of resistant bacteria
  - Need effective antibiotics if resistant bacteria causing infection
- Need not be mutually exclusive

Current Therapeutic Options for Antimicrobial-Resistant Gram-Negative Infections

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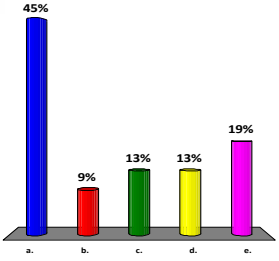
Audience Question

Which of the following songs sums up your entire professional career to date?

a. "I Will Survive"
b. "Chariots of Fire"
c. "Friends in Low Places"
d. "Mo Money"
e. "Flight of the Bumblebee"



Antimicrobial Resistance Threats: CDC

Urgent Threats	Serious Threats
C. difficile	MDR *P. aeruginosa* and *Acinetobacter*
Carbapenem-resistant Enterobacteriaceae	ESBL-producing Enterobacteriaceae
Drug-resistant gonococcal gonorrhea	MRSA and VRE

CDC. Antibiotic Resistance Threats in the United States, 2013.
Available at: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.

WHO Establishes Priority Level for Resistant Gram-Negative Bacteria (2017)

Priority 1: CRITICAL

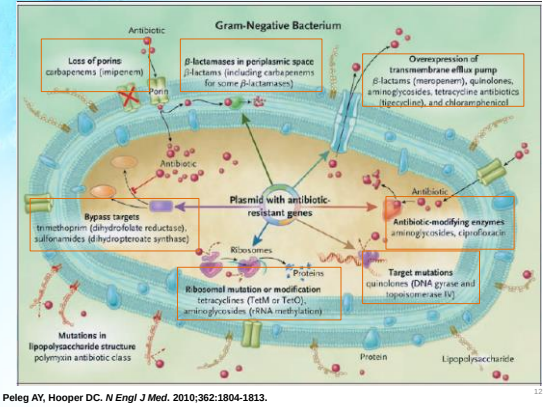
- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- Enterobacteriaceae*, carbapenem-resistant
- Enterobacteriaceae*, 3rd-generation cephalosporin-resistant

World Health Organization

*Enterobacteriaceae include *K. pneumoniae*, *E. coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., *Providencia* spp., *Morganella* spp.
WHO. Available at: http://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en/.

GRAM-NEGATIVE ANTIMICROBIAL RESISTANCE MECHANISMS AND TRENDS

Mechanisms of Antibiotic Resistance in Gram-Negative Bacteria



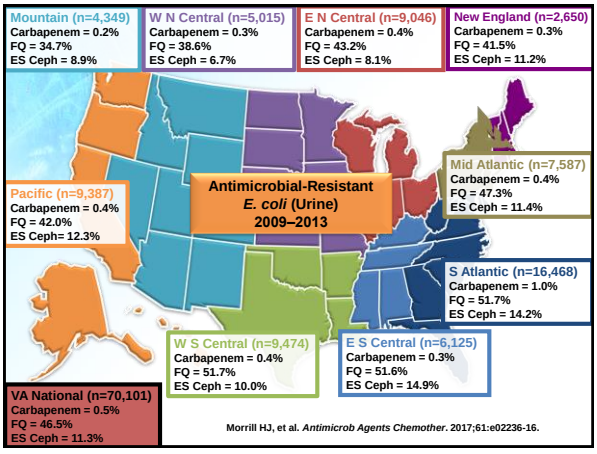
Peleg AY, Hooper DC. *N Engl J Med.* 2010;362:1804-1813.

Classes of β-Lactamases in Gram-Negative Bacteria

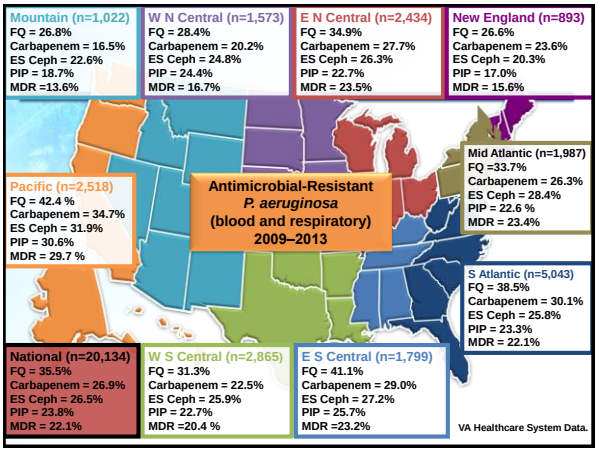
Ambler Classification	Description or Characteristics	Examples of Enzymes	Bacterial Strains
Class A (serine β-lactamase)	Cephalosporinases (ESBLs) **Usually clavulanic acid susceptible, except for KPC**	TEM, SHV, CTX-M, KPC, VEB	Enterobacteriaceae, *Pseudomonas* spp.
Class B (metallo-β-lactamase or MBL)	Contain metal ion (Zn) Carbapenemases **Not inhibited by clavulanic acid** Inhibited by aztreonam	IMP, VIM, NDM	Enterobacteriaceae, *Acinetobacter* spp., *Pseudomonas* spp.
Class C (AmpC β-lactamase – serine β-lactamase)	**Resistant to clavulanic acid** Intrinsic in certain species of Gram-negatives	CMY, DHA	Enterobacteriaceae *Pseudomonas spp.*
Class D (serine β-lactamase)	Oxacillinases **Susceptible to clavulanic acid** Carbapenemase	OXA	Enterobacteriaceae (OXA-48 like), *Acinetobacter* spp.

Note: Enzymes underlined are carbapenemases.

Sidjabat HE, et al. *Microbiology Australia*. 2013;34:43-46.



Morrill HJ, et al. *Antimicrob Agents Chemother*. 2017;61:e02236-16.



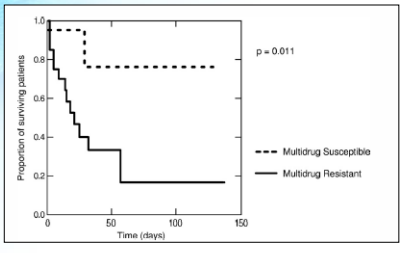
VA Healthcare System Data.

Antimicrobial-Resistant *P. aeruginosa*, All HAIs 2011–2014

Resistance type	Overall	2011	2012	2013	2014
Carbapenem (N=22,593)	19.3%	20.0%	17.8%	20.4%	19.2%
Cephalosporin (N=26,772)	10.3%	11.7%	9.9%	10.8%	9.5%
Fluoroquinolone (N=26,897)	21.6%	23.5%	20.8%	22.3%	20.7%
Aminoglycoside (N=27,197)	9.7%	10.6%	9.1%	9.8%	9.6%
Piperacillin/ tazobactam (N=23,662)	10.0%	12.8%	10.0%	10.1%	9.0%
Multidrug-Resistant (N=27,289)	14.2%	15.7%	13.3%	14.8%	13.5%

CDC. Antibiotic Resistance Patient Safety Atlas. Available at: http://gis.cdc.gov/grasp/PSA/MapView.html.

MDR *Pseudomonas* – Impact



Tam VH, et al. *Antimicrob Agents Chemother*. 2010;54:3717-22.

Patient Case

Patient Case: Mr. Z

CC: 76-year-old man residing in LTCF with a history of complicated UTIs presents to the ED complaining of painful urination and slight hematuria

HPI: April 10th hospitalization for UTI. No indwelling urinary catheter present, patient performs self-catheterization

PMHx: Diabetes, PVD, prostrate CA

ROS: Fever 38.9°C (102.2°F); WBC 18K

PE: Acute costovertebral angle pain

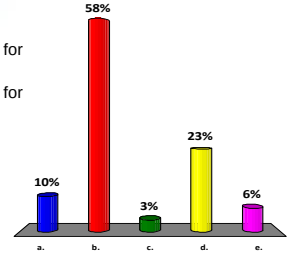
Patient Case: Mr. Z (cont'd)

- **Management plan:**
  - Patient is empirically given imipenem 500 mg IV q6h
- **New information:**
  - AMS Team reviews records from his last admission (~30 days prior); urine culture grew *P. aeruginosa,* previously treated with IV then PO levofloxacin 750 mg × 10 days (4/10 to 4/20/2017)
  - Blood and urine culture from current admission shows Gram-negative rods

Audience Question

Before recommending a change in therapy, what would you consider?

a. Imipenem may be overly broad, recommend narrowing therapy
b. Recommend to empirically cover for MDR *P. aeruginosa*
c. Recommend to empirically cover for KPCs
d. Recommend nothing, stay the course and await C&S
e. Make a phone call to the primary team to discuss further



Assessing Patient Risk for MDR Infection to Guide Empiric Therapy

- **Identify patients** who have received substantial previous broad-spectrum antimicrobial therapy, had prolonged hospitalizations, undergone multiple invasive interventions, or known to have been colonized or infected with a resistant Gram-negative organism, or at risk for infection from a resistant Gram-negative pathogen.
- **Consult local epidemiologic data and antibiograms** for assistance in selecting empiric antimicrobial therapy in patients considered at risk for infection with resistant Gram-negative pathogens.

Mazuski JE, et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. *Surg Infect (Larchmt).* 2017;18:1-76.

Risk Factors for Infection with MDR Gram-Negative Pathogens

Risk Factors
• Previous hospitalization
• Previous antibiotic exposure
• Previous stay in ICU
• Residence in LTC facilities
• Infection or colonization with Gram-negative pathogens in the previous year
• Comorbidities
• Immunocompromised states
• Older age (>65)
• Previous invasive procedures and/or presence of devices
• Mechanical ventilation

Hirsch EB, et al. *Expert Rev Pharmacoecon Outcomes Res.* 2010;10:441-451.
Obritsch MD, et al. *Pharmacotherapy.* 2005;25:1353-1364.
Trecarichi EM, et al. *Future Microbiol.* 2012;7:1173-1189.

Over Half of *P. aeruginosa* Isolates Non-susceptible to Pip-Tazo Also Non-susceptible to a Carbapenem

	Pip-Tazo (% PTZ-NS)	Meropenem (% MER-NS)	MDR (% of PTZ-NS also MER-NS)
New England	19	17	44
Mid-Atlantic	27	20	52
East North Central	21	18	51
West North Central	14	10	50
South Atlantic	25	20	49
East South Central	22	18	57
West South Central	26	25	68
Mountain	22	25	64
Pacific	20	12	40

PTZ, piperacillin/tazobactam; MER, meropenem; MDR–% of PTZ-NS isolates that were also MER-NS.
2012 INFORM Surveillance data, *Pseudomonas aeruginosa* resistance. Forest Laboratories, LLC.

NEWER ANTIMICROBIAL AGENTS IN THE MANAGEMENT OF INFECTIONS CAUSED BY MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

Newer Agents for Antibiotic-Resistant Gram-Negative Bacteria

Antibiotic	Class (Mechanism of action)	Status	Spectrum of Activity
Ceftolozane-tazobactam	Anti-pseudomonal cephalosporin/BLI combination Tazobactam active against penicillinases & cephalosporinases	Approved: ▪ cUTI, including pyelonephritis ▪ cIAI (with metronidazole)	Gram-negatives, including MDR *P. aeruginosa* and ESBL-producing strains
Ceftazidime-avibactam	Anti-pseudomonal cephalosporin/BLI combination	Approved: ▪ cUTI, including pyelonephritis ▪ cIAI (with metronidazole)	Gram-negatives, including MDR *P. aeruginosa*, ESBL-producing strains, KPCs

BLI, beta-lactamase inhibitor; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; ESBL, extended-spectrum beta-lactamase; HAP, hospital-acquired pneumonia; MDR, multi-drug resistant; KPC, *K. pneumoniae* carbapenemase.

Boucher et al. *Clin Infect Dis* 2013;56:1685–94.

Ceftolozane-Tazobactam (ZERBAXA®)

Class/MOA	Novel cephalosporin/established β-lactamase inhibitor combination
Approval	• Complicated urinary tract infections (cUTIs), including pyelonephritis • Complicated intra-abdominal infections (cIAIs)
Investigational	• Ventilator-associated bacterial pneumonia (VABP) and ventilated hospital-acquired bacterial pneumonia (HABP) with dose of 3 g q8h (2000 mg ceftolozane and 1000 mg tazobactam)
Dose & Adjustment*	• cUTIs dose: 1.5 g q8h (1000 mg ceftolozane and 500 mg tazobactam) • cIAIs dose 1.5 g q8h (1000 mg ceftolozane and 500 mg tazobactam) plus meropenem 500 mg q8h
Spectrum	• Activity against multidrug-resistant Gram-negative bacilli. • Tazobactam extends the activity to include most ESBLs & anaerobic species • Potent activity versus ***Pseudomonas aeruginosa***, including drug-resistant phenotypes such as carbapenem, piperacillin/tazobactam, and ceftazidime-resistant isolates, as well as MDR strains
Does not cover	• MSSA, MRSA, enterococcus

*Label includes a warning about decreased efficacy seen in patients with renal impairment

ZERBAXA® (ceftolozane and tazobactam) Prescribing Information. Merck & Co., Inc. Whitehouse Station, NJ. October 2016. www.clinical trials.gov. Accessed May 2, 2017; Clinicaltrials.gov.

Ceftolozane-Tazobactam: Activity Against *P. aeruginosa*

- Demonstrated *in vitro* activity against *P. aeruginosa* isolates tested that had:
  - Chromosomal AmpC *or*
  - Loss of outer membrane porin (OprD) *or*
  - Up-regulation of efflux pumps (MexXY, MexAB)
- Not active against bacteria producing metallo-β-lactamases

Current FDA susceptibility interpretive criteria:

	Minimum Inhibitory Concentrations (μg/mL)		
Pathogen	Susceptible (S)	Intermediate (I)	Resistant (R)
Pseudomonas aeruginosa	≤4 / 4*	8 / 4*	≥16 / 4*

*Ceftolozane-tazobactam susceptibility testing performed with a fixed 4 μg/mL concentration of tazobactam

Takeda S, et al. *Int J Antimicrob Agents*. 2007;30:443-445.
Takeda S, et al. *Antimicrob Agents Chemother*. 2007;51:826-830.
Castanheira M, et al. *Antimicrob Agents Chemother*. 2014;58:6844-6850.

Ceftolozane-Tazobactam: In Vitro Activity

Ceftolozane-tazobactam activity tested against *P. aeruginosa* isolates from patients hospitalized with pneumonia (USA - 2012)

	Cumulative (%) inhibited at MIC in μg/mL of:			MIC_{50} / MIC_{90} (μg/mL)
	4	8	16	
Pseudomonas aeruginosa (n=1019)	92.6	94.1	94.6	0.5 / 4
Ceftazidime-non-S (n=269)	72.1	77.7	79.6	4 / >32
Cefepime-non-S (n=239)	70.7	77.0	79.1	4 / >32
Meropenem-non-S (n=268)	75.7	78.0	79.9	2 / >32
Piperacillin-tazobactam-non-S (n=311)	76.5	81.4	83.0	2 / >32
CAZ & MEM & P/T-non-S (n=158)	60.1	63.9	67.1	4 / >32
Levofloxacin-non-S (n=307)	81.4	82.7	84.4	2 / >32
Gentamicin-non-S (n=197)	71.6	73.1	75.1	2 / >32
Multidrug-resistant (MDR) (n=246)	72.4	75.6	77.6	2 / >32
Extensively drug-resistant (XDR) (n=174)	63.2	66.1	69.0	4 / >32

Farrel DJ, et al. *Int J Antimicrob Agents*. 2014;43:533-539.

Phase 3 Clinical Trials: Ceftolozane-Tazobactam for cUTIs

- **Primary endpoint - composite of microbiological eradication and clinical cure rate (composite cure rate) at 5–9 days after end of therapy—TOC visit.**
- **Of 1083 patients enrolled, 800 (73.9%), of whom 656 (82.0%) had pyelonephritis, were included in the microbiological MITT population.**

cUTI treatment	Ceftolozane-tazobactam 1.5g q8h	Levofloxacin 750mg q24h	Difference
microbiological modified intent-to-treat patients	76.9%	68.4%	8.5%; 95% CI, 2.3–14.6*
microbiologically evaluable patients	83.3%	75.4%	8%; 95% CI, 2–14*

*"as the lower bound of the two-sided 95% CI around the treatment difference was positive and greater than zero, superiority was indicated"

Wagenlehner FM, et al. *Lancet*. 2015;385:1949-56.

Ceftazidime-Avibactam (AVYCAZ®)

Class/MOA	Established cephalosporin/novel non-beta-lactam beta-lactamase inhibitor
Approval *Based upon two Phase 2 trials	• Complicated urinary tract infections (cUTIs) • Complicated intra-abdominal infections (cIAIs) "New treatment for serious infections in patients who have limited or no alternative treatment options "
Investigational	• Nosocomial pneumonia, including those with ventilator-associated pneumonia with dose of 2.5 g q8h (2000 mg ceftazidime and 500 mg avibactam
Dose & Adjustments*	• cUTI: 2.5 g q8h (2000 mg ceftazidime and 500 mg avibactam) • cIAI: 2.5 g q8h (with metronidazole)
Spectrum	Gram-negative infections, including extended-spectrum beta-lactamases (ESBLs; Ambler class A, B, C, and D) and *Klebsiella pneumoniae* carbapenemases (KPCs), including CTX-M types
Does not cover	MRSA, MSSA, enterococcus
Safety	The most common adverse reactions (incidence of >10% in either indication) were vomiting, nausea, constipation, and anxiety
Monitoring	Monitor CrCl at least daily in patients with changing renal function and adjust dose accordingly

*Label includes a warning about decreased efficacy seen in patients with renal impairment.

AVYCAZ® (ceftazidime and avibactam) Prescribing Information. Allergan USA, Inc., Irvine, CA. January 2017.
www.clinical trials.gov. Accessed May 2, 2017; Clinicaltrials.gov.

Ceftazidime-Avibactam: Activity Against *P. aeruginosa*

- Demonstrated *in vitro* activity against *P. aeruginosa* in the presence of:
  - some AmpC beta-lactamases *or*
  - certain strains lacking outer membrane porin (OprD)
- Not active against bacteria producing metallo-β-lactamases and may not have activity against Gram-negative bacteria that overexpress efflux pumps or have porin mutations

Current FDA susceptibility interpretive criteria:

	Minimum Inhibitory Concentrations (µg/mL)	
Pathogen	Susceptible (S)	Resistant (R)
Pseudomonas aeruginosa Enterobacteriaceae	≤8 / 4*	≥16 / 4*

* Ceftazidime-avibactam susceptibility testing performed with a fixed 4 µg/mL concentration of avibactam

AVYCAZ® (ceftazidime and avibactam) Prescribing Information. Allergan USA, Inc., Irvine, CA. January 2017.

Ceftazidime-Avibactam: In Vitro Activity

Ceftazidime-avibactam activity tested against *P. aeruginosa* isolates from patients hospitalized in USA (2012–2013)

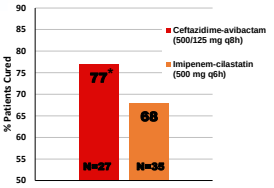
	Cumulative (%) inhibited at MIC in µg/mL of:		MIC_{50} / MIC_{90} (µg/mL)
	8	16	
Pseudomonas aeruginosa (n=3082)	97.0	99.0	2 / 4
non-ICU (n=2240)	97.5	99.2	2 / 4
ICU (n=842)	95.6	98.3	2 / 4
VAP (n=185)	97.3	100.0	2 / 4
Ceftazidime-non-S (n=482)	80.7	93.4	4 / 16
Meropenem-non-S (n=537)	87.0	95.3	4 / 16
Multidrug-resistant (MDR) (n=436)	80.7	93.1	4 / 16
Extensively drug-resistant (XDR) (n=247)	74.5	89.1	8 / 32

Sader HS, et al. *Int J Antimicrob Agents*. 2015;46:53-59.

Ceftazidime-Avibactam: Phase II Trial Results, cUTIs

- 3rd-generation antipseudomonal cephalosporin, non-beta-lactam beta-lactamase inhibitor[1]
  - Inhibits Ambler class A, C and some D beta-lactamases (ESBL, AmpC, KPC)
  - Extends spectrum to include most Enterobacteriaceae including AmpC, ESBL, KPC and OXA-type carbapenemases; *P. aeruginosa* with high MICs to ceftazidime
  - NOT active against *Acinetobacter* or metallo-beta-lactamases
  - Indications: cIAI, cUTI [1]
  - Efficacy may be less with renal impairment (est CrCl <50 mL/min)

Microbiological Response for cUTIs[2] (Phase II trial; N=62 in ME Population)



*Response seen in 6/7 (85.7%) with ceftazidime-resistant pathogens

1. AVYCAZ® (ceftazidime and avibactam) Prescribing Information. Allergan USA, Inc., Irvine, CA. January 2017.
2. Vazquez JA, et al. *Curr Med Res Opin*. 2012;28:1921-31.

Clinical Infectious Diseases
INVITED ARTICLE
CLINICAL PRACTICE: Ellie J. C. Goldstein, Section Editor

Emerging Resistance, New Antimicrobial Agents … but No Tests! The Challenge of Antimicrobial Susceptibility Testing in the Current US Regulatory Landscape

R. M. Humphries and J. A. Hindler
Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California, Los Angeles

Table 3. Newly Approved Antimicrobial Agents and Availability on Commercial Antimicrobial Susceptibility Testing Systems

Antimicrobial	Year Drug Approved by FDA	RUO Disk Available	RUO Etest Available	FDA-Cleared Test Available*	Surrogate Agent Available for Predicting Susceptibility
Ceftazidime-avibactam	2015	Yes	Yes	Sensititre® (in progress)	No
Ceftolozane-tazobactam	2014	Yes	Yes	Sensititre	No
Dalbavancin	2014	No	No	Sensititre (in progress)	Vancomycin [14]
Oritavancin	2014	No	No	Sensititre	Vancomycin [15]
Telavancin	2014	Yes	Yes	Sensititre	Vancomycin [16]
Tedizolid	2014	No	No	Sensititre	Linezolid [17]
Ceftaroline (*Staphylococcus aureus*)	2013			BD Phoenix MicroScan Sensititre Vitek 2	No

Goldestein EJC. *Clinical Infectious Diseases;* 2016;63(1):83–8.

Current Availability of Ceftolozane-Tazobactam Susceptibility Tests

Disks

- MAST Disk – Distributed by Hardy Diagnostics, commercially available FDA approved diameters for:
  - Enterobacteriaceae: >21mm (S), 18-20mm (I), and <17mm (R),
  - *P. aeruginosa*: >21mm (S), 17-20mm (I), and <16mm (R),

Gradient Strips

- Breakpoints published in the package insert and latest CLSI M100 document
  - Etest (Biomérieux) Research use only, Etests can be ordered from IHMA (http://mist-ruo.com). Approval anticipated in June/July 2017.
  - MIC test strip (Liofilchem) C/T test strips can be ordered directly from Liofilchem (http://www.liofilchem.net/en/pdf/mic_brochure.pdf). Approved in US, Europe and Canada.

Panels

- Vitek 2 (Biomérieux) card approved and will undergo beta-testing; anticipate commercial availability in May/June 2017, software updates started in March 2017
- Microscan (Beckman Coulter) expect commercial availability in late 2017/2018
- Phoenix (BD) expect commercial availability late 2017/2018
- Trek Panel (ThermoFisher Scientific) commercially available since Q1 2016

Status and availability on April 18, 2017.

Current Availability of Ceftazidime-Avibactam Susceptibility Tests

Approved Tests
- KB Disks from Hardy Diagnostic and BD
- Custom Sensititre (ThemoFisher)

Tests in Development
- Etest – RUO only available at www.avycazeval.com
- Etest expected approval Q3-4 2017

Automated Tests
- Vitek 2 – Software validation Q1 2017, expected approval Q2 2018
- Phoenix – FDA approved, but not available yet
- MicroScan – Expected to be available mid 2018

Status and availability on May 8, 2017.

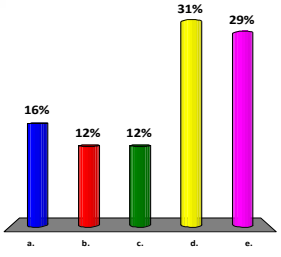
Patient Case: Mr. Z (cont'd)

- **Management plan:**
  - Patient remains on imipenem 500 mg IV q6h
- **New information:**
  - After 2 days, patient remains febrile with positive urine and blood cultures
  - C&S reveals *P. aeruginosa* with resistance to ceftazidime, pip/tazo, ciprofloxacin, and imipenem; susceptible to tobramycin and colistin

Audience Question

Given the susceptibility profile, what is your choice of therapy?

a. Colistin monotherapy
b. Polymixins + Tobramycin
c. BL/BLI combination
d. Request susceptibility testing of BL/BLI combination
e. New BL/BLI combination + colistin or tobramycin



ANTIMICROBIAL STEWARDSHIP STRATEGIES TO MINIMIZE THE BURDEN OF SERIOUS BACTERIAL INFECTIONS IN HEALTHCARE INSTITUTIONS

TJC Standard: CDC's Core Elements of ASP

1. **Leadership Commitment is critical to success of ASPs**
   - Dedicating necessary personnel, financial and information technology resources
2. **Accountability**
   - Appoint single leader responsible for program outcomes
   - Physician involvement demonstrated to be highly effective
3. **Drug Expertise**
   - Appointing a single pharmacist leader responsible for working to improve antibiotic use
4. **Education**
   - Educating healthcare providers about resistance and encouraging optimal prescribing patterns
5. **Action**
   - Implement policies and Interventions to Improve antibiotic use
6. **Tracking**
   - Monitoring the antimicrobial stewardship program, which may include information on antibiotic prescribing and resistance patterns
7. **Reporting**
   - Regularly report findings to healthcare providers and other relevant staff

The Joint Commission recommends that organizations use this document when designing their antimicrobial stewardship program

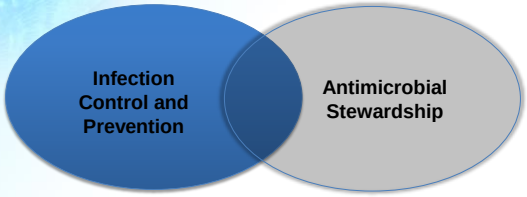
The Effect of Molecular Rapid Diagnostic Testing on Clinical Outcomes in Bloodstream Infections

Meta-analysis

Thirty-one studies (n=5920 patients)
- Mortality significantly lower with mRDT than conventional micro (OR, 0.66; 95% CI, 0.54-0.80),
- Mortality risk mRDT in studies with AMS (OR, 0.64; 95% CI, 0.51-0.79),
- **Non-ASP studies failed to demonstrate a significant decrease in mortality risk (0.72; .46-1.12)**
- Significant decreases in mortality risk were observed with:
  - Gram-positive (OR, 0.73; 95% CI, 0.55-0.97)
  - Gram-negative organisms (0.51; 0.33-0.78)
  - Yeast (0.90; 0.49-1.67)
- Time to effective therapy decreased (weighted mean difference) of 5.03 hours (95% CI, -8.60 to -1.45 hours)
- Length of stay decreased by 2.48 days (-3.90 to -1.06 days)

mRDT, molecular rapid diagnostic testing
Timbrook TT. *Clin Infect Dis*. 2016;64(1):15-23.

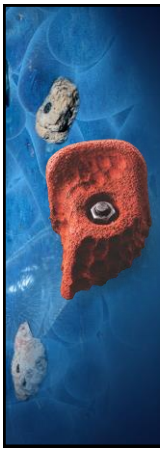
Infection Control and Antimicrobial Stewards Working Together to Prevent HAIs, including *C. difficile*



MUST HAVE Leadership support, protected workload & resources

Summary

- Antibiotic resistance is extremely high and is receiving global (WHO) and national (CDC) priority levels
- Newer antimicrobial agents are part of the armamentarium in the management of infections caused by MDR Gram-negative bacteria
- Antimicrobial stewardship strategies minimize the burden of serious bacterial infections and MDROs in healthcare institutions



Applying the Latest Approaches in the Management of *C. difficile* Infection and Recurrence

Erik R. Dubberke, MD, MSPH, FSHEA
Associate Professor of Medicine
Director, Section of Transplant ID
Washington University School of Medicine
St. Louis, MO

Mystery Product Profile

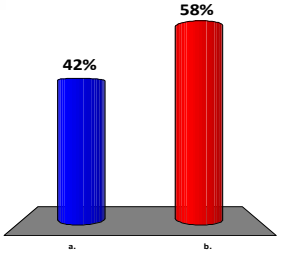
Indication	**Treatment of *C. difficile* infection (CDI)**
Product description / Mechanism of action	**It inhibits nucleic acid synthesis by binding to and disrupting the DNA of microbial cells; activity against anaerobic bacteria**
Pharmacokinetics / dynamics	**Oral, 100% absorbed, re-excreted into colon when inflamed; *C. difficile* MIC_{50}=0.5 mcg/mL, MIC_{90}=2.0 mcg/mL; Stool concentration: 1.9–77.3 mcg/gm, 40% <10 mcg/gm, 30% <5 mcg/gm**
Efficacy (double-blind RCTs only)	**Initial cure (vs. vancomycin): 72% (81%)* to 84% (97%)* Recurrence (vs. vancomycin): 23% (21%) to 14% (7%)**
Metabolism	**Hepatic metabolites cleared in urine; inhibits CYP2C9 and CYP3A4, may interfere with medications metabolized by these enzymes (e.g. warfarin, tacrolimus)**
Common adverse reactions	**Nausea (12%) sometimes accompanied by headache, anorexia, and occasionally vomiting; diarrhea; epigastric distress; and abdominal cramping**
Warnings	**Convulsive seizures and peripheral neuropathy; contraindicated in first trimester of pregnancy**

RCT = randomized controlled trial *p<0.05

Audience Question

Would you prescribe this product?

a. Yes
b. No



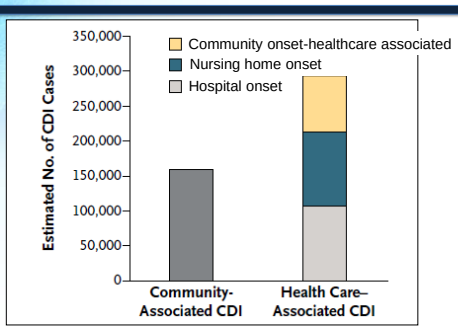
C. difficile is an "Urgent Threat"

- Over 450,000 cases per year
  - Over 29,000 associated deaths
- Most common cause of healthcare-associated infections in US

Pathogen	All Health Care–Associated Infections (N = 504)†	
	no. (%)	rank
Clostridium difficile	61 (12.1)	1
Staphylococcus aureus	54 (10.7)	2
Klebsiella pneumoniae or *K. oxytoca*	50 (9.9)	3
Escherichia coli	47 (9.3)	4
Enterococcus species‡	44 (8.7)	5
Pseudomonas aeruginosa	36 (7.1)	6
Candida species§	32 (6.3)	7
Streptococcus species¶	25 (5.0)	8
Coagulase-negative staphylococcus species	24 (4.8)	9
Enterobacter species	16 (3.2)	10

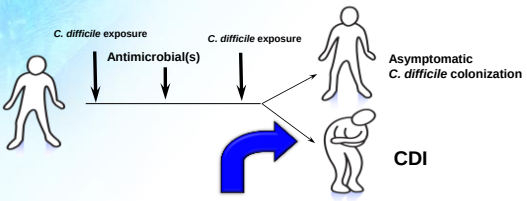
Lessa CF, et al. *N Engl J Med*. 2015;372:825-34.
Magill SS, et al. *N Engl J Med*. 2014;370:1198-1208.

CDI in the Community



Lessa CF, et al. *N Engl J Med*. 2015;372:825-34.

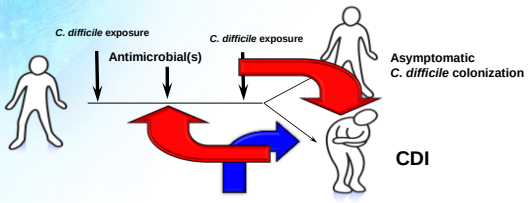
Current Pathogenesis Model for CDI



Acquisition of a toxigenic strain of *C. difficile* and failure to mount an anamnestic antibody response results in CDI.

Johnson S, Gerding DN. *Clin Infect Dis*. 1998;26:1027-34.
Kyne L, et al. *N Engl J Med*. 2000;342:390-7.

Current Pathogenesis Model for CDI



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Johnson S, Gerding DN. *Clin Infect Dis*. 1998;26:1027-34.
Kyne L, et al. *N Engl J Med*. 2000;342:390-7.

CDI Risk: The Host

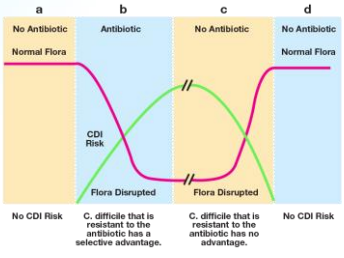
- Immune response to toxins
  - Severity of underlying illness
    - >70% CDI cases with recent unexpected hospitalization
  - Physiological age vs. chronological age
  - Immunosuppression

Variable	Univariate [Odds ratio (p-value)]	Multivariate [Odds ratio (p-value)]
Age ≥65	3.93 (.009)	3.76 (0.24)
Female	1.02 (.971)	
Horn index >1	4.20 (.077)	
Concomitant antibiotics	2.20 (.095)	2.06 (.19)
Gastric acid suppression	0.92 (.870)	
Prior CDI	2.70 (.041)	2.58 (.09)
Anti-toxin A	0.40 (.401)	
Anti-toxin B	0.12 (.045)	0.11 (.05)

Olsen M, et al. Presented at IDWeek 2015. San Diego, CA, October 7-11, 2015. Abstract #69. Available at: https://idsa.confex.com/idsa/2015/webprogram/Paper52013.html ; Gupta SB, et al. *Clin Infect Dis*. 2016;63:730-4.

Microbiota Disruption, Antibiotics, and *C. difficile* Exposure Timing

- *Firmicutes* and *Bacteroidetes*
  - Likely combination of metabolic pathways more important than individual organisms
  - ? Bile salt metabolism



Rupnik M, et al. *Nat Rev Microbiol*. 2009;7:526-36.

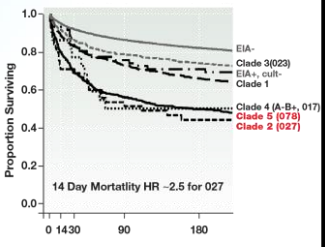
Antibiotics and CDI Risk

Very Commonly Related	Less Commonly Related	Uncommonly Related
Clindamycin	Beta-lactam inhibitors	Aminoglycosides
Ampicillin	Macrolides	Metronidazole
Amoxicillin	Carbapenems	Rifampin
Cephalosporins	Tigecycline	Tetracyclines
Fluoroquinolones		Daptomycin
		Sulfonamides
		Trimethoprim

Adapted from: Bouza E, et al. *Med Clin North Am*. 2006;90:1141-1163.
Loo VG, et al. *N Engl J Med*. 2005;353:2442-2449.

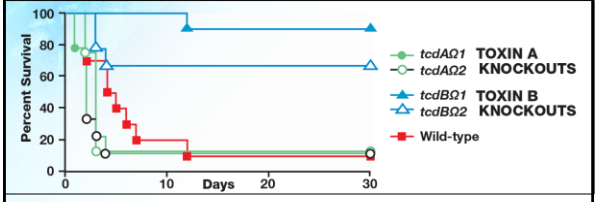
CDI Risk: *C. difficile* Strain

- Current epidemic strain: BI / NAP1 / ST1 / 027
  - Higher attack rate
    - NAP1: 55%
    - Non-NAP1: 29%
  - More severe disease
  - 50% higher recurrence rate
- Natural history of CDI
  - Predominant / more virulent strains emerge



Loo VG, et al. *N Engl J Med*. 2011;365:1693-703.
Walker AS, et al. *Clin Infect Dis*. 2013;56:1589-600.
Petrella LA, et al. *Clin Infect Dis*. 2012;55:351-7.

Toxin B is Key



- Virulence no different between wild-type and toxin B only strains
- Virulence significantly reduced for toxin A only strains

Carter GP, et al. *Gut Microbes*. 2010;1:58-64.

Patient Case

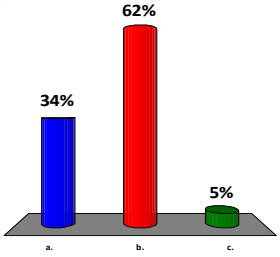
- 86-year-old female with hypertension
  - Recently completed a course of ciprofloxacin for a UTI
  - 2 days of abdominal cramping, 5–7 diarrheal bowel movements per day
  - BP 96/52 mm Hg, but responded to IV fluids
  - Her creatinine was at its baseline; WBC was 14,700/mm^3, and stool was positive for *C. difficile* toxins by EIA.

Audience Question

How would you treat her CDI?

a. Metronidazole 500 mg PO every 8 hours*
b. Vancomycin 125 mg PO every 6 hours*
c. Fidaxomicin 200 mg PO every 12 hours*

*all regimens are for 10 days



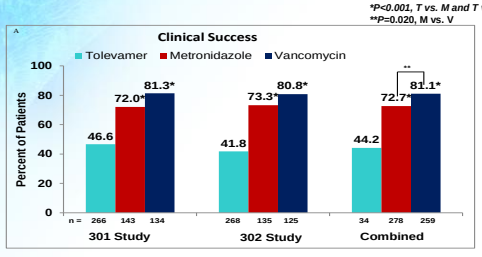
CDI Treatment Stratified by Severity: First CDI Episode (2010 Guidelines)*

Clinical scenario	Supportive clinical data	Recommended treatment
Mild to moderate	Leukocytosis (WBC <15,000 cells/mL) or SCr level <1.5 × premorbid level	Metronidazole 500 mg 3 times per day PO for 10-14 days
Severe	Leukocytosis (WBC ≥15,000 cells/mL) or SCr level ≥1.5 × premorbid level	Vancomycin 125 mg 4 times per day PO for 10-14 days
Severe, complicated	Hypotension or shock, ileus, megacolon	Vancomycin 500 mg 4 times per day PO or by nasogastric tube plus metronidazole 500 mg IV q 8 hrs

*Updated IDSA/SHEA *C. difficile* guidelines expected in Summer 2017.

Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31(5):431-455.

Metronidazole Also Inferior For Non-Severe CDI

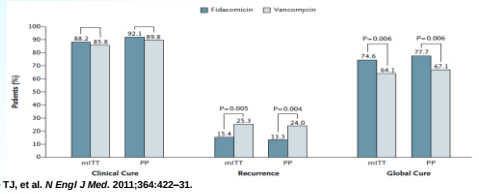


Vancomycin superior to metronidazole on multivariable analysis, including controlling for clinical severity (p=0.013)

Johnson S, et al. *Clin Infect Dis*. 2014;59:345-354.

Fidaxomicin for CDI

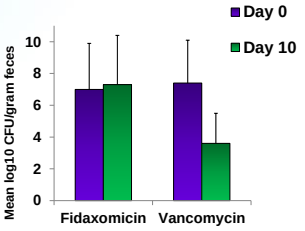
- Novel antimicrobial: macrocyclic
- Narrow spectrum: No activity against Gram-negatives
  - Sparing of *Bacteroides* spp., bifidobacterium, clostridial clusters IV and XIV
- Decrease in recurrences
  - Studies included patients with first and second CDI episodes
  - Role of dysbiosis?



Louie TJ, et al. *N Engl J Med*. 2011;364:422–31.

Impact on Microbiome: Fidaxomicin vs. Vancomycin

Bacteroides **group counts in feces before and after 10 days of treatment with: Fidaxomicin** (200 mg bid) **or Vancomycin** (125 mg qid)



Louie TJ, et al. *Clin Infect Dis*. 2012;55 Suppl 2:S132-142.

Mystery Product Profile

METRONIDAZOLE

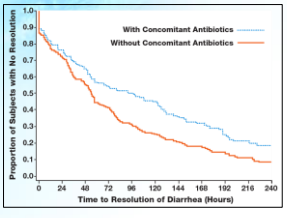
- Poor / inconsistent penetration to site of infection
- More side effects
- Inferior efficacy compared to vancomycin in double-blinded randomized controlled trials

Zar FA, et al. *Clin Infect Dis*. 2007;45:302-7.
Johnson S, et al. *Clin Infect Dis*. 2014;59:345-54.

Should Treatment of Initial CDI Focus on Recurrence Risk?

- If metronidazole is inferior for mild/moderate CDI, no need to select treatment based on CDI severity
- Major differentiators in currently available treatments
  - Impact of concomitant antibiotics
  - Recurrence

Impact of Concomitant Antibiotics on Response to CDI Treatment



No CA	Fidaxo N=391	Vanco N=416	*P*
Clinical cure	92%	93%	0.80
Recurrence	12%	23%	<0.001
Sustained response	81%	69%	<0.001

CA	Fidaxo N=90	Vanco N=102	*P*
Clinical cure	90%	79%	0.04
Recurrence	17%	29%	0.05
Sustained response	72%	59%	0.02

CA = concomitant antibiotics

Mullane KM, et al. *Clin Infect Dis*. 2011;53:440-7.

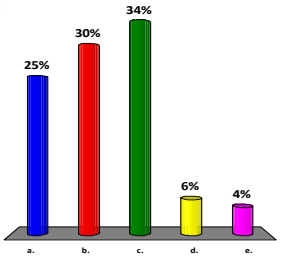
Back to the Case

- The patient responded appropriately to a 10-day course of vancomycin. One month later, she complained of foul smell to her urine
  - She was prescribed another course of ciprofloxacin for a "UTI"
  - Three days later, she developed clinically significant diarrhea, and she tested positive for *C. difficile* toxins again

Audience Question

How would you treat this patient?

a. Vancomycin 125 mg PO QID for 10 days
b. Vancomycin 125 mg PO QID for 10 days, followed by a taper
c. Fidaxomicin 200 mg PO BID for 10 days
d. Vancomycin 125 mg PO QID for 10 days, followed by fecal microbiota transplantation
e. Vancomycin 125 mg PO QID for 10 days, followed by bezlotoxumab 10 mg/kg IV x1



Recurrent CDI

- Recurrence risk after first episode 10% to 30%
  - Risk increases with additional recurrences
- Associated with worse outcomes
  - Readmissions (RR=2.5; 95% CI, 2.2–2.9)
  - Costs ($11,631; 95% CI, $8,937–$14,588)
  - Mortality (HR=1.3; 95% CI, 1.1–1.6)

Olsen MA, et al. *Am J Infect Control*. 2015;43:318-22.
Olsen MA, et al. *Clin Microbiol Infect*. 2015;21:164-70.
Dubberke ER, et al. *Infect Control Hosp Epidemiol*. 2014;35:1400-7.

Risk Factors Associated with CDI Recurrence

Findings from Selected Key Publications

Increasing Age	Antibiotic Use	Past Hospital / Healthcare Exposure	Host Immunity/ Underlying Disease Severity	CDI Experience
Per 1 year increment	Systemic concomitant ab use or continued use of non *C.difficile* abs	2+ Hospitalizations in the previous 60 days	Antibody to *C.difficile* toxin	CDI diagnosed at admission
>65 or advanced age	High risk antibiotic use at CDI onset	Total inpatient duration before admission* or long hospital stays	Albumin >35/ 26-35 / <=25	Stool frequency >3 unformed stools per day
60-69 70-79 >=80	Fluoroquinolone use at CDI onset	CO-HCFA (onset in community and discharged in last 12 weeks)	Horn's Index severe or fulminant	Previous CDI diagnosis or CDI in the past 3 months
>40 years of age	Treatment with vancomycin (vs. fidaxomicin)	Previous gastrointestinal ward admission	ER admittance + previous MRSA and previous dialysis or chemotherapy	C-reactive protein at the time of dx <35, 85-<160, >=160
		Inpatient vs. outpatient at CDI diagnosis**	ICU at CDI onset**	
			Co-Morbidities: cardiovascular or liver disease, upper GI abnormality**	
			CCR[***] at dx <80mL/minute	

* any past admission, >2-13 weeks, >13 weeks
** protective against CDI recurrence *** creatinine clearance rate

Courtesy S. Gupta (modified)

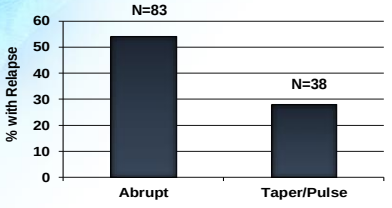
Recurrent CDI: 2010 IDSA/SHEA Guidelines*

Clinical scenario	Recommended treatment
First recurrence	Treat as first episode according to disease severity
Second recurrence	Treat with oral vancomycin taper and/or pulse dosing
Third recurrence	-SHEA/IDSA: challenging, consider FMT/rifaximin taper/IVIG -ACG**: FMT

FMT = fecal microbiota transplantation

*Updated IDSA/SHEA *C. difficile* guidelines expected in Summer 2017.
**Surawicz CM, et al. *Am J Gastroenterol*. 2013;108:478-98.
Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31(5):431-455.

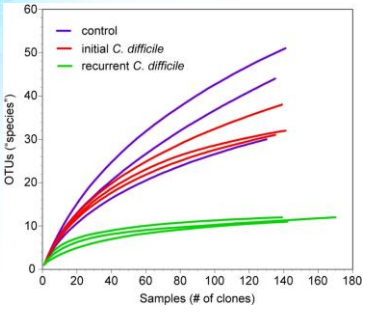
Abrupt Stop vs. Taper or Pulse of Vancomycin



- Mean number of CDI episodes: 3 ± 2.1 (range 1–14)
- Relative Risk of Relapse = 0.51 (95% CI, 0.29–0.90)

McFarland LV, et al. *Am J Gastroenterol*. 2002;97:1769-75.

Ten Days of Fidaxomicin May Not Be Enough for Recurrent CDI: Potential Role for Chaser or Taper



Chen X, et al. *Gastroenterology*. 2008;135:1984-92.

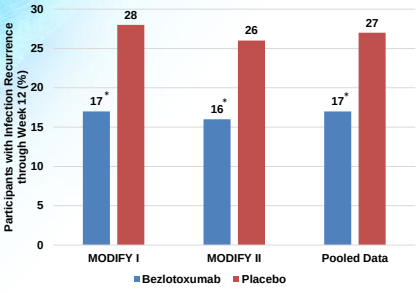
FMT Prospective Trials: Single Dose FMT Efficacy 60%–70%

Study	Single dose	Second dose
Youngster (n=20)	70%	90%
Hirsch (n=19)	68%	89%
Orenstein (n=34)	52%	79%
Youngster (n=14)	70%	90%
Van Nood (n=16)	81%	94%
Lee (PP n=178, mITT n=219)	62% / 51%	84% / 73%
Khanna (n=30)*	87%	97%
Press release (n=59)*	56%	NA
Combined (n=371)	65% / 60%	

*Same product

Youngster I, et al. *Clin Infect Dis*. 2014;58:1515-22.
Orenstein R, et al. *Clin Infect Dis*. 2016;62:596-602.
Van Nood E, et al. *NEJM*. 2013;368:407-15.
Khanna S, et al. *J Infect Dis*. 2016;214:173-81.
Hirsch BE, et al. *BMC Infect Dis*. 2015;15:191.
Youngster I, et al. *JAMA*. 2014;312:1772-8.
Lee CH, et al. *JAMA*. 2016;315:142-9.
Press Release. Available at: http://ir.serestherapeutics.com/phoenix.zhtml?c=254006&p=irol-newsArticle&ID=2190006.

Bezlotoxumab
Human Anti-toxin B Monoclonal Antibody



*p<0.001

Wilcox MH, et al. *N Engl J Med*. 2017;376:305-17.

When the Cardiologists Start to Demand Bezlotoxumab…

- No difference in resolution of CDI
  - 80% bezlotoxumab vs. 80% placebo
- Caution with congestive heart failure
  - Serious adverse events
    - 15/118 (13%) bezlotoxumab vs. 5/104 (5%) placebo
  - Death
    - 23/118 (20%) bezlotoxumab vs. 13/104 (13%) placebo

ZINPLAVA™ (bezlotoxumab) Prescribing Information. Merck & Co., Inc. Whitehouse Station, NJ. October 2016.

Bezlotoxumab: 30-day Readmission

Data compiled from MODIFY I and MODIFY II comparing bezlotoxumab (BZO) or placebo, both with standard of care antibiotics.

	BZO n/N (%)	Placebo n/N (%)	Difference (95% CI)
30-day all-cause readmissions	123/530 (23.2)	140/520 (25.9)	-3.7% (-9.0, 1.5)
30-day CDI-associated readmissions	21/530 (4.0)	50/520 (9.6)	-5.7% (-8.8, -2.7)
Age ≥65 years	11/298 (3.7)	37/308 (12.0)	-8.3% (-12.6, -4.2)
CDI in prior 6 months	8/127 (6.3)	18/122 (14.8)	-8.5% (-16.6, -0.9)
Immunocompromised	5/131 (3.8)	9/112 (8.0)	-4.2% (-11.2, 1.8)
Severe CDI	2/113 (1.8)	12/116 (10.3)	-8.6% (-15.7, -2.7)
027 ribotype	7/87 (10.4)	14/81 (17.3)	-6.8% (-18.2, 4.9)

Golan Y, Dubberke ER, et al. Presented at ASM Microbe 2016, June 16-20, 2016, Boston, MA.. Abstract #MONDAY-449.

Conclusions

- Risk of CDI and recurrent CDI related to:
  - Host (immune response)
  - Microbiome (antimicrobial exposures)
  - *C. difficile* strain
- Metronidazole IS no longer first-line treatment
  - Treatment selection based on recurrence risk, not severity
- Current approach to prevent recurrence is with microbiome preservation / restoration
- Immune restoration approach now available