Learning Objectives

- Discuss epidemiological trends of multidrug-resistant Gram-negative bacterial infections
- Utilize the latest evidence-based strategies for the management of serious bacterial infections based on patient and pathogen factors
- Evaluate the role of newer therapeutic approaches when managing serious infections caused by Gram-negative bacteria

Bacterial Pathogens Representing a Threat (CDC 2013)

- **Urgent Threats**
  - ***Clostridium difficile***
  - **Carbapenem-resistant Enterobacteriaceae**
  - **Drug-resistant *Neisseria gonorrhoeae***
- **Serious Threats**
  - **MDR *P. aeruginosa* and *Acinetobacter***
  - **ESBL-producing Enterobacteriaceae**
  - **MRSA and VRE**
  - **Various drug-resistant species (*Campylobacter*, *S. pneumoniae*, *Salmonella*, tuberculosis, *Shigella*)**

CDC. Available at: http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.

HAI: A Major Threat

- **In 2011, there were ≈722,000 HAIs[1]**
  - **≈75,000 patients died**
  - **> Half of HAIs occurred outside the ICU**
- **Up to 75% of HAIs are due to organisms resistant to 1st-line antimicrobials[2]**

Estimates of HAI Occurring in Acute Care Hospitals in US, 2011[1]

Major Site of Infection	Est. N
Pneumonia	157,500
Gastrointestinal illness	123,100
Urinary tract infections	93,300
Primary bloodstream infections	71,900
Surgical site infections from inpatient surgery	157,500
Other types of infections	118,500
ESTIMATED TOTAL INFECTIONS, N	721,800

HAI, healthcare-associated infection; ICU, intensive care unit

1. CDC Data and Statistics: Antimicrobial Use Prevalence Survey. http://www.cdc.gov/HAI/surveillance. Accessed April 13, 2016. To read the full report, please visit: CDC HAI Prevalence Survey. Magill SS, et al. *N Engl J Med.* 2014;370:1198-1208.
2. Lautenbach E, et al. *Infect Control Hosp Epidemiol.* 2014;35(4):333-335.

Resistant Gram-Negative Pathogens Are Common and Deadly

Incidence and Mortality of Antibiotic-resistant Gram-negative Pathogens in the United States

Organism	Annual # Cases	Annual Deaths
Carbapenem-resistant Enterobacteriaceae	9300	610
Extended-spectrum beta-lactamase–producing Enterobacteriaceae	26,000	1700
Multidrug-resistant *Acinetobacter* species	7300	500
Multidrug-resistant *P. aeruginosa*	6700	440

Adapted from CDC 2013.
Mehrad B, et al. *Chest.* 2015;147(5):1413-1421.

Audience Question

At your institution, which of the following is the greatest concern for surgical site infections?

1. ESBL-producing Enterobacteriaceae
2. Carbapenem-resistant Enterobacteriaceae
3. Multidrug-resistant *P. aeruginosa*
4. Multidrug-resistant *Acinetobacter* spp.

Antibiotic-Resistant Threat Pathogens

Acute Care Hospitals

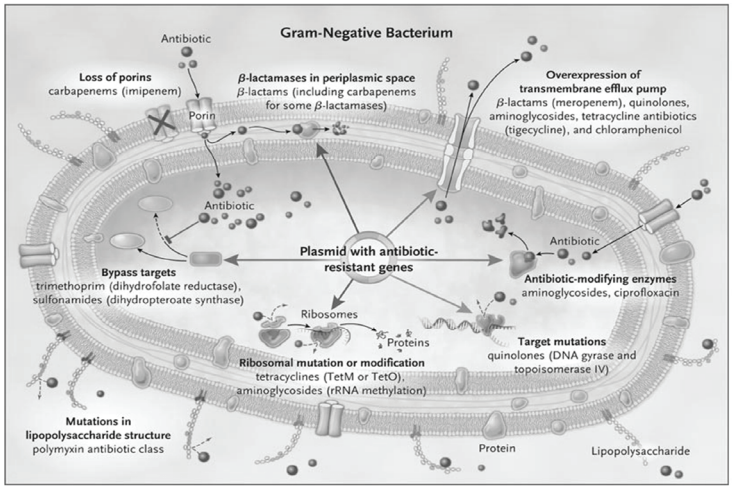
Pathogen	Surgical Site Infection No. tested (% resist)	CLABSI No. tested (% resist)
MRSA	3212 (44)	2556 (47.3)
VRE	3427 (18)	3079 (44.6)
ESBL Enterobacteriaceae	**4184 (12.6)**	**2804 (21.1)**
Carbapenem-R Enterobacteriaceae	**4441 (1.3)**	**3199 (4.9)**
MDR *Pseudomonas*	**1061 (6.5)**	**810 (15.7)**
MDR *Acinetobacter*	**63 (47.6)**	**369 (36.6)**

CLABSI, central line-associated bloodstream infection; MRSA, methicillin-resistant S. aureus; VRE, vancomycin-resistant Enterococci; MDR, multidrug-resistant
Weiner LM, et al. *MMWR.* 2016;65(9):235-241.

The Impact of Antimicrobial Resistance

- Multiple mechanisms of resistance
- Affects clinical outcomes[1]
  - Associated with higher mortality
    - Pt with resistant infection is 15% more likely to die
  - Results in higher costs
- Increased challenge for appropriate management[1]
  - Empiric therapy
  - Directed therapy

1. File TM, Jr. *Chest.* 1999 Mar;115(3 Suppl):3S-8S.



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

The NEW ENGLAND JOURNAL of MEDICINE

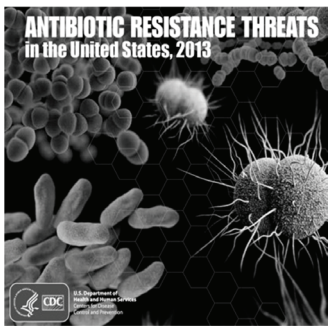
Antimicrobial Resistance: Public Health Crisis

- The discovery of potent antimicrobial agents was one of the greatest contributions to medicine in the 20th century.
- Now THREATENED due to Resistance

World Health Organization

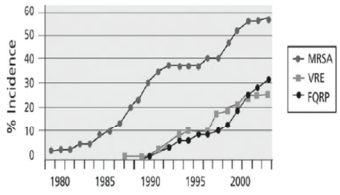
- **Antibiotic resistance: a threat to global health security**

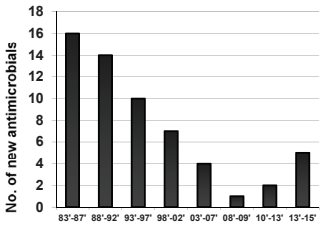
  May, 2013



IDSA Call-to-Action: Bad Bugs, No Drugs

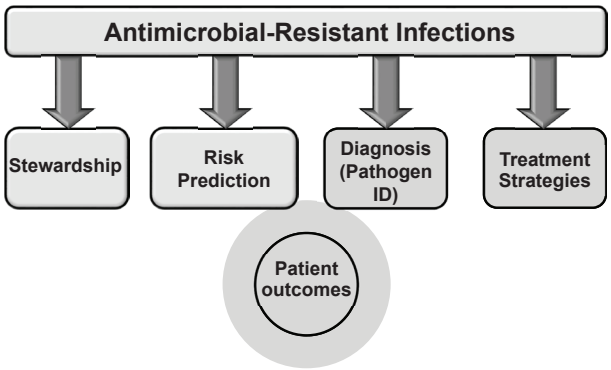
As resistance increases . . . number of new antimicrobials diminishes





IDSA. Infectious Diseases Society of America: Bad Bugs, No Drugs. Available at: http://www.idsociety.org/BBND/. Accessed April 13, 2016.

Addressing the Management of MDR Gram-Negative Infections



Part of Solution

Antimicrobial Stewardship: Importance for Patient and Public Health

Thomas M. File Jr,[1] Arjun Srinivasan,[2] and John G. Bartlett[3]

[1]Summa Health System, Akron, Ohio; [2]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; and [3]Johns Hopkins University School of Medicine, Baltimore, Maryland

Keywords. antimicrobial stewardship programs; public health.

"If best infection control practices and antibiotic stewardship were nationally adopted, more than 600,000 infections and 37,000 deaths could be prevented over 5 years."

— MMWR Aug 2015

File, TM Jr, et al. *Clin Infect Dis*. 2014;59(Suppl 3):S93-96.
CDC. *MMWR*. 2015;64(31):837-864.

Managing MDR Gram-Negative Infections

Basic Principles

- Recognize variability in bacteriology from hospital to hospital, and modify therapy to local data
- Avoid untreated or **inadequately**-treated patients by using prompt and **appropriate** therapy
- Avoid the over-usage of antibiotics: accurate diagnosis, tailor therapy to culture data, shorten duration of therapy as much as possible
    - De-escalation

Stratify for Risk of Gram-Negative MDR
Predicting MDRO

- **RISK SCORE: Shorr A, et al (*CID*. 2012;54:193)**
    - Recent hospitalization in preceding 90 days – 4 points
    - Residence in a nursing home – 3 points
    - Chronic hemodialysis – 2 points
    - Critical illness – 1 point
    - Score of ≥4 = high risk
- **PREDICTORS: Aliberti S, et al (*CID*. 2012;54:470)**
    - Hospitalization in the preceding 90 days (odds ratio [OR] 4.87; 95% CI 1.90–12.4)
    - Residency in a nursing home (OR 3.55; 95% CI 1.12–11.24)
- **ALERT: Micek S, et al (*Crit Care Med*. 2014;42:1832)**
    - Prior use of broad-spectrum ABX
    - Prior + culture for MDRO
- **Strongest Risk Factor: Prior Antibiotics**

National Action Plan for Combating Antibiotic-Resistant Bacteria

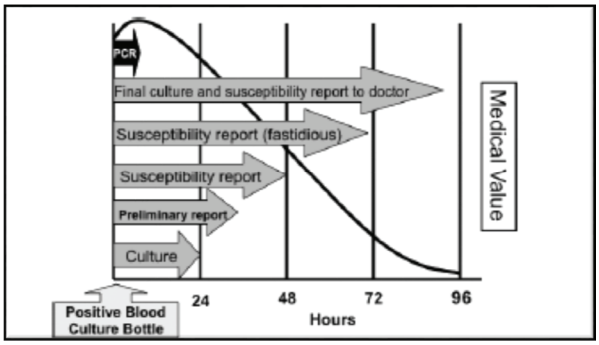
GOALS

- Slow the emergence of resistant bacteria and prevent the spread of resistant infections
- Strengthen national one-health surveillance efforts to combat resistance
- Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria
- Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines
- Improve international collaboration and capacities for antibiotic-resistance prevention, surveillance, control and antibiotic research and development

National Action Plan for Combating Antibiotic-Resistant Bacteria. March 2015. Available: https://www.whitehouse.gov/sites/default/files/docs/national_action_plan_for_combating_antibotic-resistant_bacteria.pdf. Accessed April 13, 2016.

Diagnostic Testing: Time to ID

- Rapid diagnostic tests
  - PNA FISH, PCR, MALDI-TOF



Goff DA, et al. *Pharmacother.* 2012;32:677-88.

Resistant Infections: Treatment Options

- **Optimize PK/PD**
  - Extended infusion; continuous infusion; higher doses for beta-lactams (e.g., cefepime, ampicillin/sulbactam)[1-4]
- **Use of old drugs: colistin IV**
- **New drugs**
  - Ceftolozane/tazobactam
  - Ceftazidime/avibactam
- **Combination therapy**
  - Variable combinations (colistin, carbapenems, tigecycline, rifampin…)
- **Alternative administration**
  - e.g., aerosolized drugs for VAP (aminoglycosides, colistin)

1. Courter JD, et al. *Pediatr Blood Cancer.* 2009;53:379-385.
2. Lodise TP Jr, et al. *Clin Infect Dis.* 2007;44:357-363.
3. Chastre J, et al. *Crit Care Med.* 2008;36:1089-1096;
4. Betrosian AP, et al. *Scand J Infect Dis.* 2007;39(1):38-43.

Audience Question

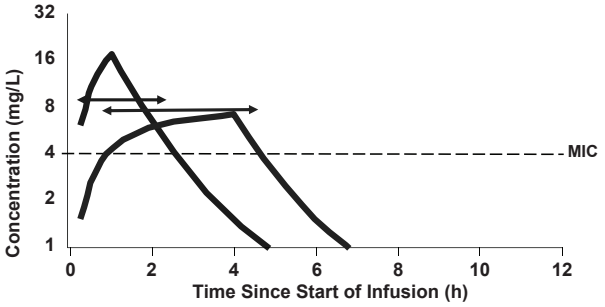
Do you routinely use prolonged infusion of broad-spectrum beta-lactams?

1. Yes
2. No

Optimizing Beta-lactam Therapy: Maximizing %T>MIC

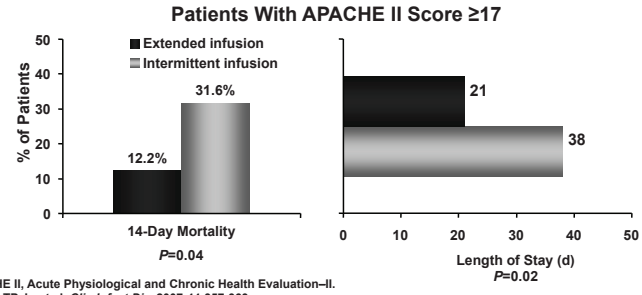
Increased duration of infusion

- Prolonged infusion
  - Same dose and dosing interval, 100–250 mL, however, change duration of infusion (0.5 hr → 3–4hr)



Prolonged Infusion Dosing Strategy: Piperacillin/ Tazobactam for *P. aeruginosa* Infection

- Retrospective cohort study
- Extended (4 h) vs. intermittent (30 min) infusion
- Infusion schedule not associated with differences in mortality or length of stay for patients with APACHE II score <17



APACHE II, Acute Physiological and Chronic Health Evaluation–II.
Lodise TP Jr, et al. *Clin Infect Dis.* 2007;44:357-363.

Need for Optimal Antibiotic Dosing

A prospective, multinational pharmacokinetic point-prevalence study (n=361) from 68 hospitals

- Positive clinical outcome associated with increasing target attainment
  - 50% f $T_{>MIC}$ and 100% f $T_{>MIC}$ ratios (odds ratios: 1.02 and 1.56, respectively, p<0.03)
- Targets achieved more frequently with prolonged infusions
  - 20% intermittent bolus did not achieve 50% f $T_{>MIC}$ vs 7% for prolonged infusions

50% f $T_{>MIC}$, 100% f $T_{>MIC}$= free antibiotic concentrations above the MIC of the pathogen at 50% and 100% of the dosing interval, respectively

Roberts JA, et al. *Clin Infect Dis.* 2014;58(8):1072-1083.

Efficacy, Safety of Pharmacodynamic Dose Optimization of Beta-Lactam Antibiotics

Variable	PDOP Group (N=41) n (%)	Non-PDOP group (N=38) n (%)	P Value
In-hospital mortality	5 (14%)	15 (39%)	0.025
30-day All-cause mortality	5 (14%)	16 (42%)	0.013
Avg. time on Ventilation	11.7	15.0	0.171
Avg. ICU LOS (days)	14.4	19.7	0.87

PDOP, pharmacodynamics dose optimization
Panno NJ, et al. Poster 1635. Presented at IDWeek 2012. San Diego. CA.

Agents Being Developed to Treat Resistant Gram-Negative Bacteria

Agent	Related-Class	Developer
Ceftolozane-Tazobactam	BLBLI	Merck
Ceftazidime-Avibactam	BLBLI	Allergan
Meropenem-RPX7009	BLBLI	The Medicines Company
Imipenem-Relebactam	BLBLI	Merck
Aztreonam-Avibactam	BLBLI	AstraZeneca
S-649266	Cephalosporin	Shionogi
Eravacycline	Tetracycline	Tetraphase
Plazomicin	Aminoglycoside	Achaogen
POL7080	Macrocycle LptD Inhibitor	Roche / Polyphor

BLBLI, Beta-lactam/beta-lactamase inhibitor combinations

Beta-lactamase Inhibitor Revival: New Hope for Old Antibiotics

- Tazobactam
  - 2:1 ratio ceftolozane:tazobactam (FDA approval)
- Avibactam (NXL-104) and Relebactam (MK-7655)
  - Novel diazabicyclooctane class
  - 4:1 ratio ceftazidime:avibactam (FDA approval)
  - 2:1 and 4:1 imipenem:relebactam
- RPX7009
  - Boron-containing serine beta-lactamase inhibitor
  - 1:1 ratio meropenem:RPX7009

Garber K. *Nature Rev Drug Discovery.* 2015;14:445-447.
Drawz SM, et al. *Antimicrob Agents Chemother.* 2014;58:1835-1846.
Olsen I. *Eur J Clin Microbiol Infect Dis.* 2015;34:1303-1308 .

Audience Question

Which of the following is most accurate?

1. Ceftolozane/tazobactam provides greater activity against MDR *Pseudomonas* spp. than piperacillin/tazobactam.
2. All KPCs are resistant to both ceftolozane/tazobactam and ceftazidime/avibactam.
3. Both ceftazidime/avibactam and ceftolozane/tazobactam provide activity against most metallo-beta-lactamases.
4. In clinical trials, a lower creatinine clearance was associated with higher response rates with both ceftolozane/tazobactam and ceftazidime/avibactam.

Ceftolozane-Tazobactam

- **Antipseudomonal cephalosporin plus beta-lactamase inhibitor**
- **FDA approval in December 2014**
  - **Complicated Urinary Tract Infections, including Pyelonephritis**
  - **Complicated Intraabdominal Infections (plus metronidazole)**
  - **IV dose: 1.5 g (1 g ceftolozane; 0.5 g tazobactam) q8h (1-h infusion)**
- **Dosage adjustment in patients with renal impairment (CrCl ≤50 mL/min) or ESRD on hemodialysis**
- **Most common adverse reactions are nausea, diarrhea, headache, and pyrexia**
- **Ongoing Phase 3 Trial: Ventilated nosocomial pneumonia; *increased dose*: 3.0 g (2 g ceftolozane; 1 g tazobactam) q8h**
  - **For 8 days; however 14 days for *Pseudomonas aeruginosa***
- **Plasma-to-epithelial lining fluid penetration ~50%**

Zhanel GG, et al. *Drugs.* 2014;74:31-51. Liscio JL, et al. *Int J Antimicrob Agents.* 2015;46:266-271.
Chandorkar G, et al. *J Antimicrob Chemother.* 2012;67:2463-2469. ClinicalTrials.gov: NCT0207075.

Ceftolozane/Tazobactam

- Broad-spectrum activity against Gram-negative bacilli, including *P. aeruginosa* and most ESBL-producing Enterobacteriaceae
- Similar outcomes to levofloxacin for cUTI and cIAI (with metronidazole)
- Efficacy may be attenuated in patients with renal impairment (est CrCl <50 mL/min)

Activity of Ceftolozane-Tazobactam vs. *Pseudomonas aeruginosa* (n=2435)

Agent	All Isolates $MIC_{50/90}$	MDR (158) $MIC_{50/90}$
Ceftazidime	4/32	>32/>32
Ceftolozane/tazobactam	**0.5/1**	**2/16**
Ciprofloxacin	0.25/4	4/>16
Colistin	1/2	1/2
Meropenem	0.5/8	8/>32
Piperacillin/ Tazobactam	4/32	128/512
Tobramycin	≤0.5/2	4/64

- **95% ceftazidime-R = ≤8 mg/mL ceftolozane/tazobactam**
- **89% of MDR strains inhibited by ≤8 µg/mL ceftolozane/tazobactam**

CrCl, creatinine clearance; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; ESBL, extended-spectrum beta-lactamase; MDR, multidrug resistant; MIC, minimum inhibitory concentration

Walkty A, et al. *Antimicrob Agents Chemother.* 2013;57(11):5707-5709.

Ceftolozane-tazobactam (+metronidazole) vs. Meropenem for Complicated Intraabdominal Infections

	Ceftolozane/ tazobactam plus metronidazole No. (%)	Meropenem No. (%)	Percentage difference (95% CI)
MITT population	n = 389	n = 417	
Cure	323 (83.0)	364 (87.3)	–4.2 (–8.91 to .54)
Failure	32 (8.2)	34 (8.2)	
Indeterminate	34 (8.7)	19 (4.6)	
ME population	n = 275	n = 321	
Cure	259 (94.2)	304 (94.7)	–1.0 (–4.52 to 2.59)
Failure	16 (5.8)	17 (5.3)	

Solomkin J, et al. *Clin Infect Dis.* 2015;60:1462-71.

Ceftazidime-Avibactam

- Antipseudomonal cephalosporin plus beta-lactamase inhibitor
- FDA approval in February 2015 (based on Phase 2 data)
  - **Complicated Urinary Tract Infections, including Pyelonephritis**
  - **Complicated Intraabdominal Infections (plus metronidazole)**
  - **IV dose: 2.5 g (2 g ceftazidime; 0.5 g avibactam) q8h (2-h infusion)**
  - **For patients with limited or no alternative treatment options**
- Dosage adjustment in patients with CrCl ≤50 mL/min
- Most common adverse reactions are vomiting, nausea, constipation, and anxiety

- Clinical trials: Nosocomial pneumonia - Dose of 2.5 g q8h
- Plasma-to-epithelial lining fluid penetration ~30%

Zhanel GG, et al. *Drugs.* 2013;73:159-177. Liscio JL, et al. *Int J Antimicrob Agents.* 2015;46:266-271.
Nicolau D, et al. *J Antimicrob Chemother.* 2015;70:2862-2869. ClinicalTrials.gov: NCT01808092.

Ceftazidime-avibactam (+ metronidazole) vs. Meropenem for Complicated Intraabdominal Infections

Clinical cure rate at test of cure by baseline renal function – mITT population*

	Ceftazidime/avibactam + metronidazole % (n/N)	Meropenem % (n/N)
Normal function / mild impairment (CrCl >50 mL/min)	**85% (322/379)**	**86% (321/373)**
Moderate impairment (CrCl 30 to ≤50 mL/min)	**45% (14/31)**	**74% (26/35)**

*mITT, microbiological modified intent-to-treat population included patients who had at least one bacterial pathogen at baseline and received at least one dose of study drug.
Avycaz™ (ceftazidime and avibactam) for injection Prescribing Information. Forest Pharmaceuticals, LLC. Cincinnati, OH, September 2015.

Ceftazidime/Avibactam

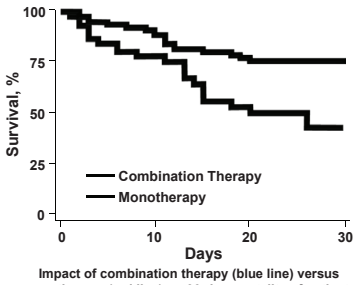
- 3rd-generation antipseudomonal cephalosporin, non-beta-lactam beta-lactamase inhibitor[1]
  - Inhibits Ambler class A, C and some D beta-lactamases (ESBL, AmpC, KPC)
  - Extends spectrum to include most Enterobacteriaceae including AmpC, ESBL, KPC and OXA-type carbapenemases; *P aeruginosa* with high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

Genotype[2]	Ceftazidime $MIC_{50/90}$	Ceftazidime/ Avibactam $MIC_{50/90}$ (fold >)
ESBL *E coli* (n = 161)	16/64	0.12/0.25 (256)
ESBL *K pneumoniae* (n = 29)	64/>64	0.5/1 (>64)
AmpC *E coli* (n = 94)	16/64	0.12/0.5 (128)
ESBL and AmpC *E coli* (n = 8)	32/>64	0.12/0.12 (>512)

1. Actavis plc. 9/5/14. http://www.actavis.com/news/news/thomson-reuters/actavis-announces-fda-acceptance-of-the-nda-filing. Accessed April 13, 2016.
2. Lagace-Wiens PR et al. *Antimicrob Agents Chemother.* 2011;55(5):2434-2437.

Resistant Infections: Treatment Options

- Variable combinations[1,2]
  - Colistin
  - Carbapenems (for CRE MIC ≤8)
  - Tigecycline
  - Rifampin
  - Fosfomycin
  - Aminoglycosides
- Aerosolized drugs (aminoglycosides, colistin)
  - 18 of 21 with MDR *A. baumannii* or *P. aeruginosa* responded favorably[3]
  - 4 of 5 with MDR *A. baumannii* or *P. aeruginosa* "cured"[4]



Impact of combination therapy (blue line) versus monotherapy (red line) on 30-day mortality of patients with KPC-producing *K. pneumoniae* bloodstream infection (*P*=.002)[5]

CRE, carbapenem-resistant *Enterobacteriaceae*; MIC, minimum inhibitory concentration

1. Gilad J, et al. *Drugs.* 2008;68(2):165-189. 2. Rahal JJ. *Clin Infect Dis.* 2006;43(suppl 2):S95-S99. 3. Kwa AL, et al. *Clin Infect Dis.* 2005;41(5):754-757. 5. Tumbarello M et al. *Clin Infect Dis.* 2012;55(7):943-950, figure used by permission of Oxford University Press.

De-escalation Strategies

- **What:**
  - Moving from broad-spectrum to narrow-spectrum therapy
  - Decreasing number of agents used
  - Reducing duration of therapy
  - Discontinuing empiric therapy based on clinical criteria, culture results
  - All depends on timely identification of pathogen, clinical response, biomarkers
- **Why:**
  - More effective targeting of causative pathogen
  - Decreased antimicrobial exposure, risk of driving resistance
  - Cost savings

1. Dellit TH, et al. *Clin Infect Dis.* 2007;44:159-177.
2. Khasawneh FA, et al. *Infect Drug Resist.* 2014;7:177-182.

Strategy for Optimization: De-escalation

- **De-escalation in ICU[1]**
  - 20 ICUs; 398 pts with VAP (MRSA, *Pseudomonas* most frequent pathogens)
  - Mortality
    - No de-escalation (62%): 24%
    - Escalation: 43%
    - DE-ESCALATION: 17% (*P*=0.001)
- **De-escalation for VAP in Surgical ICU[2]**
  - Retrospective evaluation
  - 138 of 1596 patients (8.7%) developed VAP
  - Mortality
    - De-escalation: 35.1%
    - No de-escalation: 42.1% (*P*=0.324)

1. Kollef MH, et al. *Chest*. 2006;129:1210-1218.
2. Eachempati SR, et al. *J Trauma*. 2009;66:1343-1348.

Duration of Antimicrobial Therapy

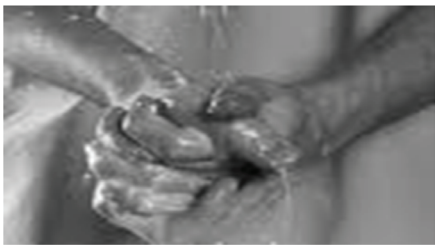
- Advantages of SHORT(ER) antimicrobial therapy
  - Lower Cost
  - Less toxicity
  - Better adherence
  - Reduced antimicrobial resistance
- Short-course therapy based on PK/PD principles
  - Concentration-dependent effect
  - Time-dependent effect
- Concept: "Hit hard and fast … then leave ASAP."*
  - Consider PK/PD parameters
- Available data indicates short-course therapy effective
  - VAP (Chastre J, et al. *JAMA*. 2003;290:2588-98.)
  - CAP (IDSA/ATS Guidelines. *CID*. 2007;44:S27-72.)
  - Intra-Abd Infections (Sawyer RG, et al. *NEJM*. 2015;372:1996-2005.)

*File TM Jr. *Clin Infect Dis*. 2004 39 (Suppl 3): S159-164.

Key Points

- Many factors drive choice of initial therapy for Gram-negative healthcare-acquired infections – keys are knowing the agents available and the susceptibilities of the pathogens you are combating
- Hope of newer diagnostics
- Need to optimize prevention and therapy
  - Stewardship
    - Avoid unnecessary use (colonization)
    - De-escalation
    - Shorter course therapy
  - Newer approaches
    - PK/PD principles
    - Newer agents (ceftolozane/tazobactam; ceftazidime/avibactam)

MDR Infections: Prevention



Overview

- Epidemiological trends for CDI*
- Risk factors for infection, severe disease, and recurrence
- Evidence-based strategies for the management of CDI
- Role of newer therapeutic approaches to manage CDI

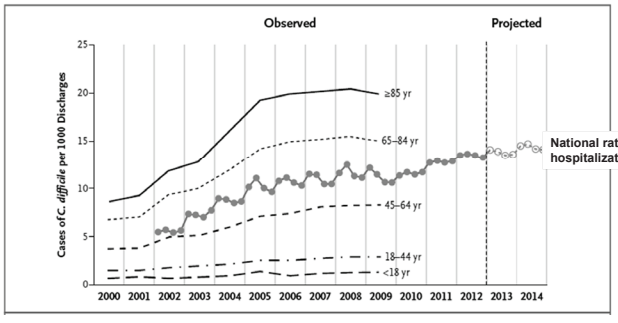
*CDI, *Clostridium difficile* infection

CDI is a Top Priority

- **CDC:** urgent threat, EIP surveillance
- **NIH:** requests for applications for novel therapeutics
- **CMS**: publically reported, may impact hospital reimbursement

CDC, Centers for Disease Control and Prevention; CMS, Centers for Medicare & Medicaid Services; EIP, Emerging Infections Program; NIH, National Institutes of Health

The Rate of *C. difficile* Infection is Predicted to Remain High

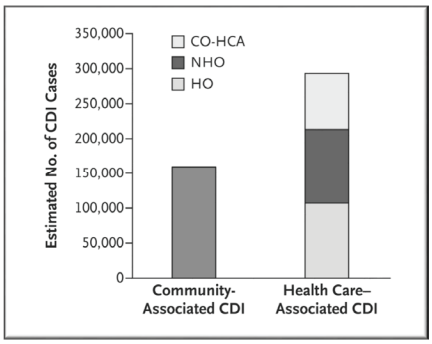


Steiner C et al. HCUP projections report #2014-01. Rockville MD: Agency for Healthcare Research and Quality 2014. [http://hcup-us.ahrq.gov/reports/projections/2014-01.pdf.]
Lessa FC, et al. *Clin Infect Dis.* 2012;55(Suppl 2):S65-S70.
Leffler DA, Lamont TJ. *N Engl J Med.* 2015;372:1539-48.

Estimated U.S. burden of CDI:

~ a half million cases per year!

Number of cases according to the location of stool collection and inpatient healthcare exposure, 2011



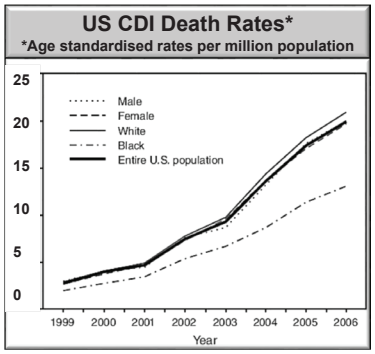
HCA CDI: 293,000
- ***CO-HCA***: 81,300
- ***NHO***: 104,400
- ***HO***: 107,600

CA CDI: 159,700
- 82% had outpatient health care exposure

2/3 were HCA, but only 1/4 had onset during hospitalization

CA, community-associated; HCA, healthcare-associated; CO, community-onset; HO, hospital-onset; NHO, non-hospital-onset
Lessa FC, et al. *N Engl J Med.* 2015;372:825-34.

C. difficile Infection & Mortality



29,000 CDI-related deaths

Lessa FC, et al. *N Engl J Med.* 2015;372(9):825-34.

Two Major Challenges in Treating CDI

- Severe CDI
  - Decrease morbidity and mortality
- Recurrent CDI
  - Decrease recurrences

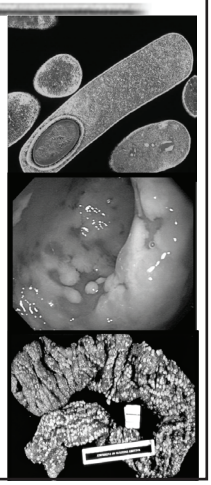
Recurrent CDI

- Recurrence is common
  - ~25% after a 1st CDI episode
  - ~35% after a 2nd CDI episode
  - ~50% after a 3rd or subsequent CDI episode
- 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.

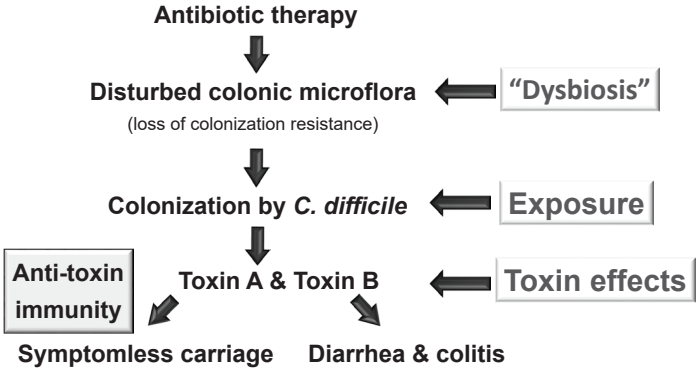
Risk Factors for Recurrent CDI

- Antibiotic treatment for antibiotic-induced CDI perpetuates dysbiosis and predisposes to recurrence.
- Host immune responses (anti-toxin antibody production) can protect against recurrent CDI.
- Factors that predict a higher risk for recurrence include:
  - Prior recurrences
  - Additional (concomitant) antibiotic use
  - Older age
  - Severe underlying disease



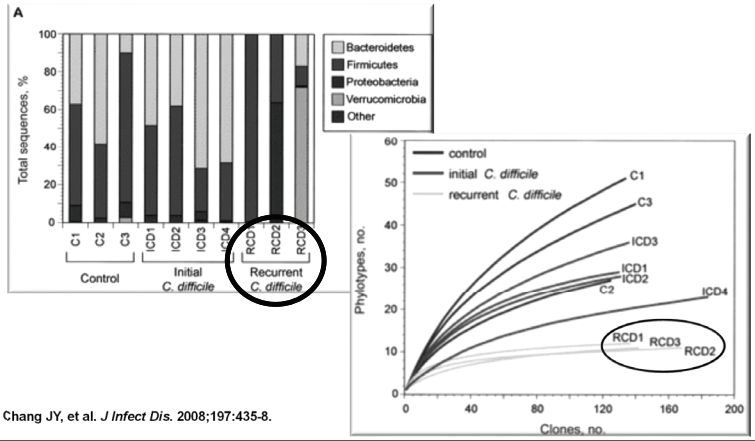
Olsen MA, et al. *Am J Infect Control.* 2015;43:318-22.
Olsen MA, et al. *Clin Microbiol Infect.* 2015;21:164-70.
Dubberke ER, et al. *Infect Control Hosp Epidemiol.* 2014;35:1400-7.

Pathogenesis of *C. difficile* infection



Kelly CP, LaMont JT. *N Engl J Med.* 2008;359:1932-40.
Kyne L, et al. *Lancet.* 2001;357:189-93.

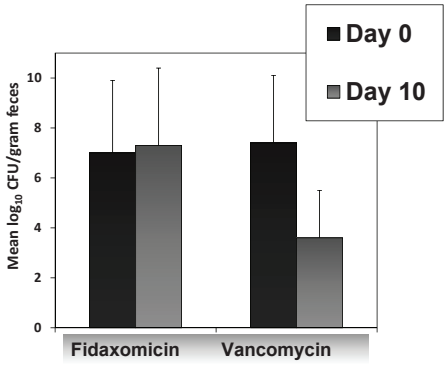
Decreased Diversity of Fecal Microbiome in CDI



Chang JY, et al. *J Infect Dis.* 2008;197:435-8.

Intestinal Dysbiosis: Not All Antibiotics are Equal

***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.

CDI: Case Presentation

- 87-year-old man undergoes hip replacement surgery following fractured femur
- Medical history: diabetes mellitus, COPD & severe CAD with congestive heart failure
- POD #6: diarrhea. Stool test positive for toxigenic *C. difficile*
- WBC 18,200 cells/μL, creatinine 1.9 mg/dL (baseline 1.2 mg/dL)
- Treated with oral vancomycin 125 mg q6h
- 36 hours later, he develops nausea, abdominal distension and hypotension.
- His WBC is now 34,700 cells/μL and creatinine is 2.7 mg/dL

Audience Question

How would you change his management at this time?

1. Increase oral vancomycin dose to 500 mg q6h
2. Increase oral vancomycin dose to 500 mg q6h and add IV metronidazole 500 mg q8h
3. Increase oral vancomycin dose to 500 mg q6h, add IV metronidazole 500 mg q8h AND request a surgery consultation
4. Switch to oral fidaxomicin 200 mg bid
5. Switch to oral fidaxomicin 200 mg bid AND request a surgery consultation

C. difficile Infection: Basic Principles of Management

- Suspect on clinical grounds
- **Discontinue non-essential antibiotics**
- Confirm presence of toxin-producing *C. difficile* by stool testing (usually PCR or EIA)
- Empiric treatment best avoided UNLESS:
  - Very high clinical index of suspicion
  - OR very severe illness

Treatment Guidelines for CDI in Adults: SHEA/IDSA 2010

- Metronidazole is the drug of choice for the initial episode of mild-to-moderate CDI (500 mg orally TID) for 10–14 days
- Vancomycin is the drug of choice for an initial episode of severe CDI. The dose is 125 mg orally QID for 10–14 days
- Vancomycin orally (and per rectum if ileus is present) with or without metronidazole IV … for severe, complicated CDI. Vancomycin is dosed at 500 mg.
- Consider colectomy in severely ill patients…(ideally before) serum lactate rises to 5 mmol/L and WBC 50,000 per mL.

Cohen SH, et al. *Infect Cont Hosp Epidemiol.* 2010;31:431-55.

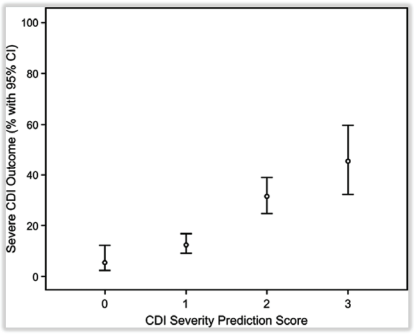
Clinical Prediction Rule for Severe CDI

Derivation & validation from a cohort of 638 patients at 3 centers

1 point for each:
- -age ≥65 years
- -peak creatinine ≥2 mg/dL
- -peak WBC ≥20k cells/μL

Severe CDI:
- -colectomy
- -admission to ICU or
- -death from CDI or with CDI as a contributor

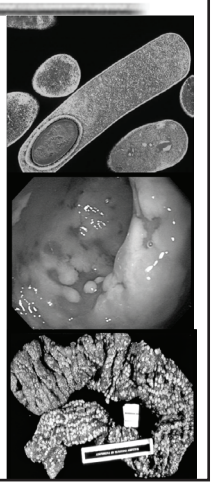
Current IDSA/SHEA guidelines definition of severity:
WBC >15,000/mm^3 or,
Cr >1.5x baseline



Na X, et al. *PLoS One.* 2015;10(4):e0123405.

Refractory and Fulminant (CDI)

- Severe complicated (fulminant) CDI can result in SIRS (systemic inflammatory response syndrome), hypotension, organ failure and toxic megacolon.
- Vancomycin therapy is indicated in severe CDI – metronidazole is not an appropriate sole therapy.
- In refractory CDI, timely surgical intervention can be lifesaving.



Colectomy vs. Temporary Loop Ileostomy in Severe Complicated or Fulminant CDI

- Subtotal colectomy can be life-saving in severe complicated CDI, but should be performed before lactate reaches 5 mg/dL or WBC is >50,000/mm^3 to avoid mortality, which is high even with colectomy.
- Diverting loop ileostomy followed by intraoperative lavage of 8 L of warmed polyethylene glycol and 500 mg vancomycin q8h was performed in 42 patients (35 laparoscopically) and compared to the previous 42 historical colectomy patients.
  - **Mortality was 19% vs. 50%; odds ratio, 0.24; p=0.006.**
  - Preservation of the colon was achieved in 39 of 42 patients (93%).

Neal MD, et al. *Ann Surg.* 2011;254:423-7.

Treatment Guidelines for CDI in Adults: SHEA/IDSA 2010 – *Recurrent CDI*

- Treatment of the first recurrence is usually with the same regimen as for the initial episode but should be stratified by disease severity.
- Do not use metronidazole beyond first recurrence or for long-term chronic therapy
- Treatment of the second or later recurrence with vancomycin using a taper and/or pulse regimen is the preferred next strategy
- No recommendations can be made regarding prevention of recurrent CDI in patients requiring continued antimicrobial therapy

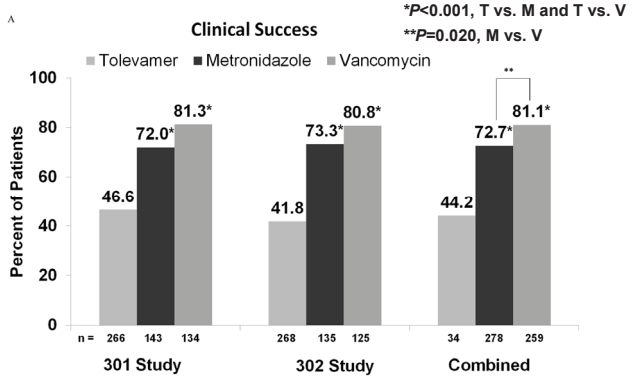
Cohen SH, et al. *Infect Cont Hosp Epidemiol.* 2010;31:431-55.

New Data on CDI Treatment Since Publication of the IDSA/SHEA Guidelines

- Fidaxomicin phase 3 trials, including a randomized sub-study of patients with first CDI recurrence
- Randomized trial of FMT
- Findings from the largest and most rigorous randomized comparison of metronidazole and vancomycin (phase 3 trials of tolevamer)
- New data on the use of immune-based therapy (monoclonal antibodies) to prevent CDI recurrence

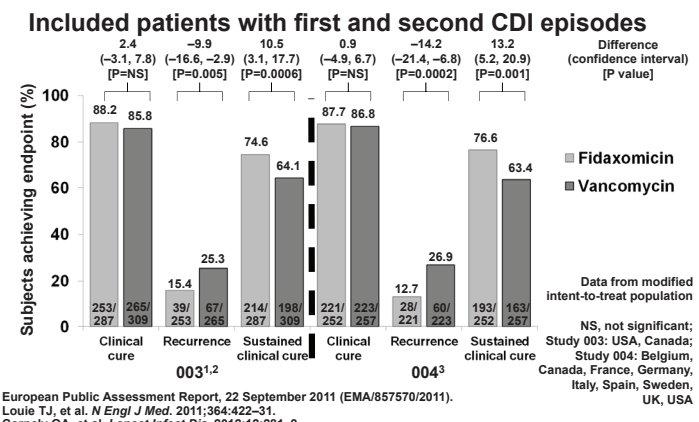
Phase 3 Trials of Tolevamer for CDI

Comparison of a non-antibiotic, toxin-binder to treatment with vancomycin and metronidazole



Johnson S, et al. *Clin Infect Dis.* 2014; 59:345-54.

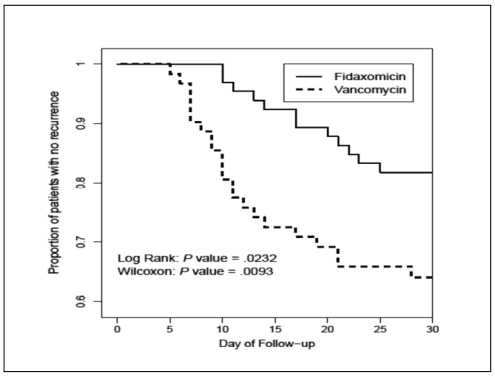
Phase 3 Trial Results of Fidaxomicin vs. Vancomycin for CDI



1. European Public Assessment Report, 22 September 2011 (EMA/857570/2011).
2. Louie TJ, et al. *N Engl J Med.* 2011;364:422–31.
3. Cornely OA, et al. *Lancet Infect Dis.* 2012;12:281–9.

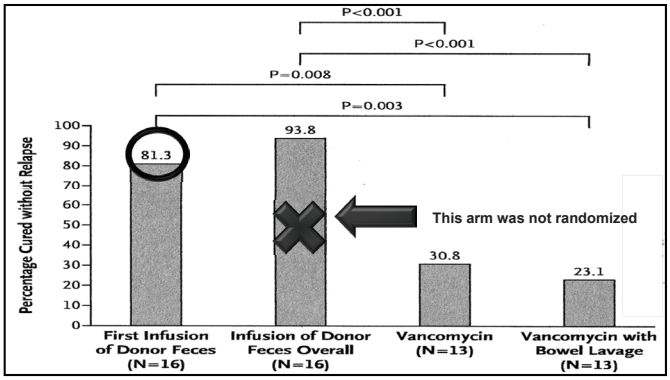
Rate of Recurrent CDI in Patients Treated for 1st Recurrence of CDI

Randomized Substudy of Phase 3 Fidaxomicin Trials



Cornely OA, et al. *Clin Infect Dis.* 2012;55(Suppl 2):S154-61.

Randomized Trial of Fecal Microbiota Transplantation (FMT)



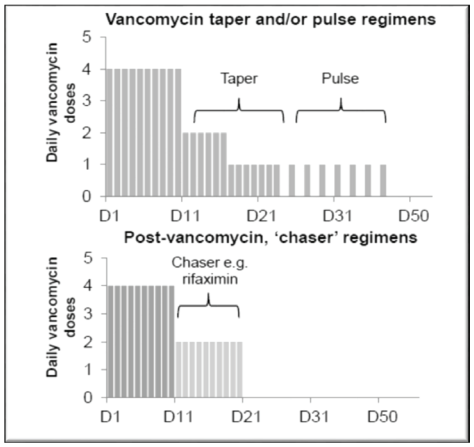
van Nood E, et al. *N Engl J Med.* 2013;368:407-15.
Kelly CP. *N Engl J Med.* 2013;368:474-5.

Alternative Approaches to Therapy for Patients with Recurrent CDI

- Switch treatment agent (fidaxomicin is more effective than vancomycin for sustained response in primary CDI and in first recurrences, but is not predictably effective in patients with multiple recurrences*)
- Tapering/pulsed treatment regimens (vancomycin, fidaxomicin)
- Post-vancomycin chaser regimens (rifaximin, fidaxomicin)
- Host microbiota replacement (various means to deliver FMT)
- Immune approach (only anecdotal support for IVIG, but mAb will likely be available in the near future)

*Orenstein R. *Clin Infect Dis.* 2012;55:613-4.

Alternative Dosing Strategies for Treatment of Recurrent CDI



Alternative Fidaxomicin Dosing Regimens for Patients with Multiple CDI Recurrences

Symptom-free intervals (SFI) & subsequent recurrence rates

n	Age, mean±SD	Sex (F)	No. of CDI episodes, mean±SD	Longest SFI* prior to FDX regimen, median (IQR)	SFI* post FDX regimen median (IQR)	Subsequent recurrence rate
Fidaxomicin Chaser *(200 mg bid x 10d)*						
8	66.9±19	75%	5.5±2	57 (48)	278 (649)	38%
Fidaxomicin Taper *(200 mg daily x 7d, then q every other day x 26d)*						
12	63.6±16	58%	5.1±2	25 (30)	257 (280)**	18%

82% Sustained response

**SFI: Symptom-free interval, days*
***p=0.003, compared with non-fidaxomicin taper SFI, Mann-Whitney U test*
Treatments prior to the fidaxomicin regimens included:
metronidazole, vancomycin, rifaximin chaser, IVIG, fecal transplant, and vancomycin taper (all patients had at least 1 vancomycin taper [mean no.= 2.3])

Soriano MM. *Open Forum Infect Dis.* 2014;1(2): doi: 10.1093/ofid/ofu069.

Emerging Approaches in Treating CDI and Reducing the Risk of Recurrence

- **Narrow-spectrum antibiotics**
  - Several new antibacterial agents under study (e.g., cadazolid, ridinilazole**)**
- **Microbial approaches**
  - FMT (pre-screened donors, capsules)
  - Biotherapeutics (e.g., non-toxigenic *C. difficile [NTCD]*)
- **Toxin binders**
  - Tolevamer or similar agent as adjunctive therapy?
- **Immune approaches**
  - Monoclonal antibody to toxin B (bezlotoxumab*)*

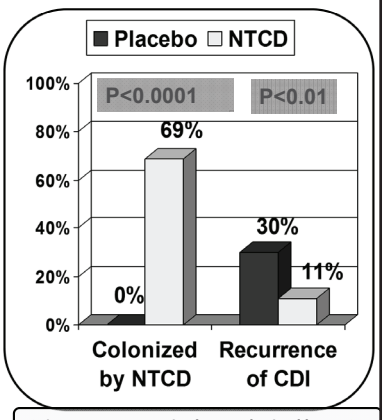
Non-toxigenic *C. difficile* Spores
Nature's Tailor-made Probiotic?

- **NTCD (Non-toxigenic *C. difficile)***
  - Spores of strain VP20621
- **Protects hamsters** against colonization by toxigenic *C. difficile* and against CDI

Phase II trial:

Pts with CDI on standard treatment (vanco or metro) randomized to:

- **Placebo (n=43)**
- ***or* NTCD (Total n=125)**
  - 10^4 x 7 days (n=41)
  - 10^7 x 7 days (n=43)
  - 10^7 x 14 days (n=41)



2% Recurrence rate in those colonized by NTCD

Gerding DN, et al. *JAMA*. 2015;313:1719-27.

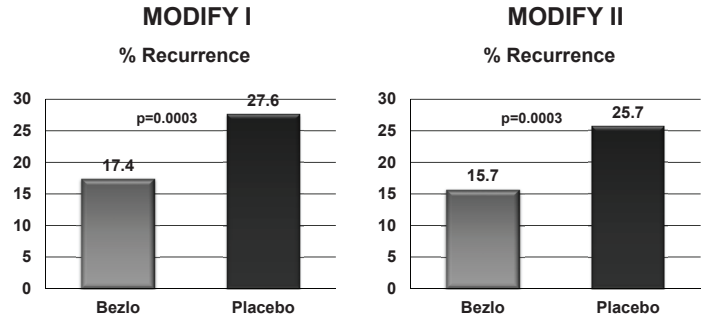
Phase 3 Trials of Bezlotoxumab as Adjunctive Therapy for CDI

Bezlotoxumab: a fully human monoclonal antibody designed to neutralize *C. difficile* toxin B

- MODIFY I and MODIFY II enrolled over 2600 patients with recurrent CDI
- Patients received standard of care antibiotics and randomly assigned to one IV infusion of
  - ACT+BEZ 10 mg/kg each
  - ACT 10 mg/kg alone *(Modify I)*
  - BEZ 10 mg/kg alone
  - Placebo
- Primary endpoint: recurrent CDI at 12 weeks

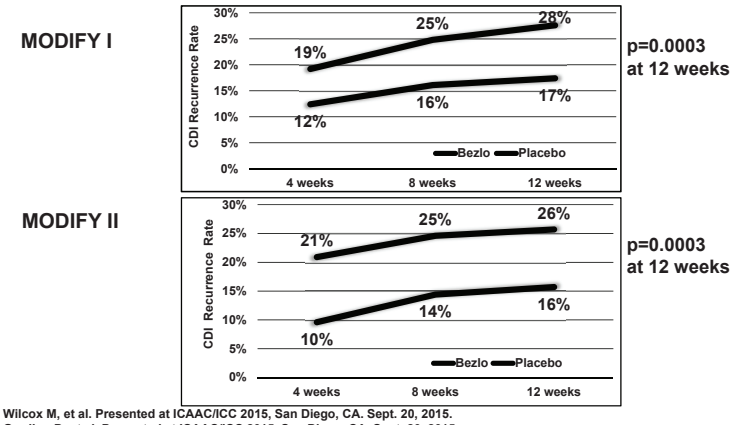
ACT, actoxumab (toxin A antibody); BEZ, bezlotoxumab (toxin B antibody)
Wilcox M, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.
Gerding D, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.

Recurrent CDI Rates at 12 Weeks: Bezlotoxumab vs. Placebo



Wilcox M, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.
Gerding D, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.

CDI Recurrence by Timepoint: Efficacy Sustained Over 12 weeks



Wilcox M, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.
Gerding D, et al. Presented at ICAAC/ICC 2015, San Diego, CA. Sept. 20, 2015.

Bezlotoxumab for Prevention of CDI Recurrence?

Findings from MODIFY I and MODIFY II:

- Recurrence rates with bezlotoxumab were lower than placebo for various high-risk groups:
  - Prior CDI episode within past 6 months
  - Infected with BI/NAP1/027 strain
  - Severe CDI (Zar score ≥2)
  - Patients ≥65 years
  - Patients with compromised immunity
- Treatment with combination actoxumab/ bezlotoxumab did not provide added efficacy compared to bezlotoxumab alone

Gerding DN, et al. Poster presented at ECCMID 2016, Amsterdam, The Netherlands, April 9-12, 2016.

Bezlotoxumab for Prevention of CDI Recurrence?

Based on data from MODIFY I and MODIFY II:

- Granted priority review by FDA for biologics license application
  - FDA action date in July 2016
- Possible first-ever indication for prevention of CDI recurrence

Questions to be determined:

- First recurrence or later?
- Use with metronidazole, vancomycin, or fidaxomicin?
- Mild/moderate vs. severe cases?
- As adjunctive therapy for fulminant CDI?

Summary

- Accumulating data indicate that metronidazole is inferior to vancomycin in the treatment of CDI
- Vancomycin and fidaxomicin are similarly effective for primary CDI and fidaxomicin is superior for sustained response
- Most patients with recurrent CDI can be managed with currently available anti-infectives (e.g., vancomycin and fidaxomicin) but novel regimens need to be used (e.g., taper, post-vancomycin chaser regimens) and patients need careful follow-up
- Potential new treatments for CDI include additional narrow-spectrum antibiotics, biotherapeutics (NTCD), and immune-based therapy (mAb)