Antimicrobials for the Management of *Clostridium difficile*

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Disclosures

- No financial relationships or affiliations
- Discussion of agents for off-label indications

Objectives

- Review the SHEA/IDSA Treatment Guidelines for Management of *Clostridium difficile*
- Discuss current treatment options, including new drug therapy, for *Clostridium difficile*
  - Metronidazole
  - Vancomycin
  - Rifaximin
  - Fidaxomicin

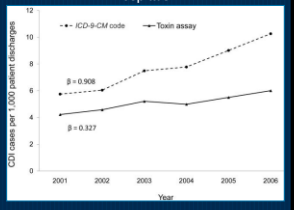
Clostridium difficile

- Anaerobic, Gram-positive, spore-forming bacilli
- Most common type of antibiotic associated-diarrhea

Epidemiology

- Overall incidence increasing
- Outbreaks of severe disease in North America and Canada
- Estimated costs $3.2 billion per year
- 15,000-20,000 deaths in US annually

Annual Incidence of CDI at 5 Academic Hospitals



Dubberke ER, et al. Inf Contr Hosp Epi 2010;31:262-8.
Burbut F, et al. Curr Opion Inf Dis 2011;24:370-6.

NAP1/BI/027 Strain

- North American Pulsed Field type 1 (NAP1), restriction endonuclease analysis group BI and PCR ribotype 027
- Implicated in outbreaks in the US and Canada
  - Up-regulation of transcription of toxins A and B
    - Mutation of the tcdC regulatory gene
  - Binary toxins
  - Associated with increase fluoroquinolone exposure

Kelly CP, et al. NEJM 2006;350(18):1932-40/

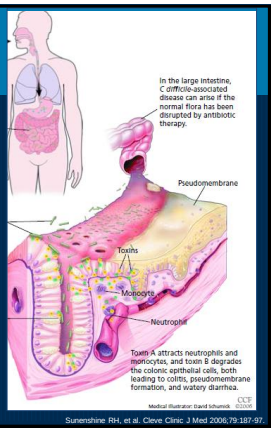
Definitions

- HO-HCFA = healthcare facility-onset, healthcare facility-associated
- CO-HCFA = community onset, healthcare facility-associated
- CA = community-associated

Cohen SH, et al. Infect Control Hosp Epidemiol 2010;31(5): 431-55.

Pathophysiology

- Fecal-oral route
- Spores
- Germinate into vegetative form
- Protein exotoxins
  - Toxin A
  - Toxin B
- Pseudomembranes



Sunenshine RH, et al. Cleve Clinic J Med 2006;79:187-97.

Risk Factors

- Antibiotic Use
- Duration of hospitalization
- Severe underlying illness
- Nasogastric intubation
- Acid suppressing medications
- Chemotherapy
- Age greater than 65 years

Sunenshine RH, et al. Cleve Clinic J Med 2006;79:187-97.

Risk Factors: Antibiotics

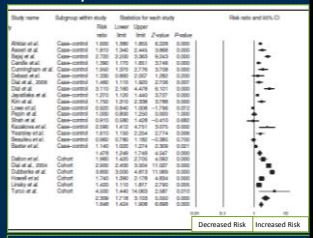
Low Risk	Medium Risk	High Risk
• Aminoglycosides	• Penicillins	• Clindamycin
• Vancomycin	• 1st gen Cephalosporins	• Carbapenems
• Daptomycin	• Macrolides	• Cephalosporins
• Nitrofurantoin	• Aztreonam	• Quinolones
• Linezolid		
• SMX/TMP		
• Tetracyclines		

Mullane KM, et al. CID 2011;53(5):440-7.

Proton Pump Inhibitors and CDI

- Acid suppression →
  - Inadequate sterilization
  - Colonization
  - Disruption of bowel flora
- PPIs > H_2RA
- Conflicting evidence
- Association vs. causality?

Meta-Analysis: Association between PPI and CDI

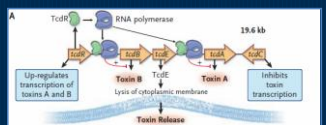


Relative risk of CDI among PPI use 1.69 (95% CI 1.40-1.97)

Janarthanan S, et al. Am J Gastroenterol 2012;107:1001-10.
Kwok CS, et al. Am J Gastroenterol 2012;107:1011-9.

Diagnosis

	Enzyme Immunoassay (EIA)	PCR
	Toxin A	Toxin genes tcdA and tcdB
Sensitivity	60-95%	94-100%
Specificity	92-98%	95-97%
Time	2-8 hours	1-4 hours



Peterson LR. CID 2007;46:1152-60.
Kelly CP, et al. NEJM 2008;359:1932-40.

Impact of PCR Testing at Cleveland Clinic

- Historically testing performed by EIA
- PCR testing implemented October 2010
- 3 month before/after study

	EIA	PCR	P value
Number of Specimens	2579	2534	
CDI Positive, n(%)	167 (6.5)	382 (15.1)	<0.001
CDI Rates, per 10,000 pt-days	4.9	10.3	<0.001

Fong KS, et al. Infect Control Hosp Epidemiol 2011;32(9):932.

SHEA-IDSA GUIDELINE

Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA)

Severity	Definitions	Treatment Recommendation
Mild or Moderate	WBC < 15 cells/L AND SCr < 1.5x baseline	Metronidazole 500 mg po TID x 10-14d
Severe	WBC > 15 cells/L OR SCr > 1.5x baseline	Vancomycin 125 mg po QID x 10-14d
Severe, Complicated	Hypotension or shock, ileus, or megacolon	Vancomycin 500 mg po QID PLUS Metronidazole 500 mg IV Q8 hrs If ileus, consider vancomycin enemas

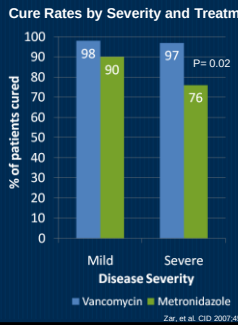
Cohen SH, et al. Infect Control Hosp Epidemiol 2010;31(5): 431-55.

Metronidazole

- Mainstay of therapy for 25 years
- Dosing: 500 mg TID oral or intravenous
- Pharmacokinetics
  - 95% bioavailability
  - Hepatobiliary elimination
  - 6-15% excreted in stool; lower concentrations in formed stools
- Adverse effects
  - Metallic taste, nausea/vomiting
  - Peripheral neuropathy with long-term exposure

Metronidazole vs. Vancomycin

- Prospective, randomized, single-center trial
- Intervention
  - Vancomycin 125 mg QID
  - Metronidazole 250 mg QID
- Stratified by disease severity
- Cure = resolution of diarrhea and (-) toxin at day 6
- In severe disease, higher cure rates with vancomycin



Zar, et al. CID 2007;45:302-7.

Vancomycin

- FDA approved for *C. difficile*
- Dosing: 125 mg po QID
  - Ileus 500 mg po QID
- Pharmacokinetics
  - Poor oral absorption
- Formulation
  - Capsules vs. oral liquid

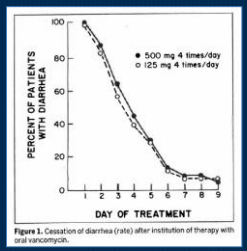


Figure 1. Cessation of diarrhea (rate) after institution of therapy with oral vancomycin.

Fekety R, et al. Am J Med 1989;86:15-19.

Comparison of CDI Outcomes with Oral Capsules vs. Solution

- Retrospective chart review
- Inclusion
  - July 2006 to July 2011
  - Severe CDI disease
- Exclusion
  - Recurrent disease
  - Co-morbidities affecting stool output
- Primary Outcome
  - Time to clinical cure (resolution of diarrhea without complication)

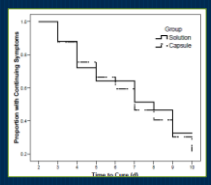
Neuner EA, et al. Presented at IDWeek 2012.

Comparison of CDI Outcomes with Oral Capsules vs. Solution

- Demographics
  - Charlson co-morbidity score balanced between groups
  - Lactate was higher in solution (1.5 vs. 0.6 mmol/L, p <0.001)
- Treatment

	Solution N=25	Capsules N=51	P
Dose, mg/day	1000 (721-1737)	888 (500-1000)	0.006
Duration	10 (8.5-10)	10 (9-10)	0.307
Combination	16 (64%)	26 (51%)	0.332

- Results
  - No difference in time to cure (8 vs. 7 days)
  - No difference in cure at day 10 (64% vs. 59%)
  - Time to clinical cure



Neuner EA, et al. Presented at IDWeek 2012.

Recurrence

- 6-25% of patients experience at least 1 additional episode
  - Risk increases with each recurrence
- Reinfection or relapse
- Risk factors
  - Antimicrobial administration
  - Defective immune response
- First recurrence: metronidazole or vancomycin
- Additional recurrences: vancomycin

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

Treatment of Recurrent *C. difficile*

- Goal: restoration of normal gut flora while suppressing *C. difficile*
- Options:
  - Vancomycin taper or pulse
  - Rifaximin
  - Stool transplant
  - ?Fidaxomicin

Vancomycin Taper or Pulse Dosing

- Rationale:
  - Decrease load of vegetative *C. difficile*
  - Decrease burden of toxins
  - Gradual weeding out of spores
  - Allowance of normal flora to recolonize

Example of Vancomycin Taper
125 mg po QID x 14 days
125 mg po TID x 7 days
125 mg po BID x 7 days
125 mg po Qday x 7 days
Additional Pulse Doses
125 mg po every 2 days x 8 days
125 mg po every 3 days x 15 days

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

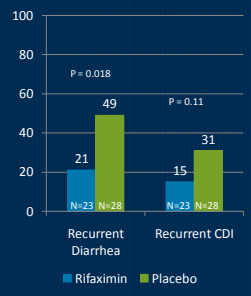
Rifaximin

- Non-absorbable rifamycin
- High colonic concentrations (8000 mg/g)
- Recurrent or refractory disease
  - "Chaser" 400 mg po TID x 10 days
- Resistance
- Limited data
  - Larger, prospective, randomized trials needed

Basu PP, et al. Ther Adv Gastroenterol 2010;3(4):221-5.
Garey KW, et al. J Clin Gastroenterol 2009;43(1):91-3.
Garey KW, et al. J Anitmicrob Chemother 2011;66:2850-5.

Rifaximin: Clinical Efficacy

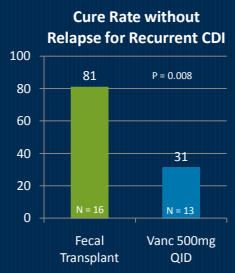
- Pilot study
- All patients received standard CDI therapy
- Randomized
  - Rifaximin 400 mg TID x 10 days
  - Placebo
- Primary outcome
  - Recurrent diarrhea within 90 days



Garey KW, et al. J Anitmicrob Chemother 2011;66:2850-5.

Fecal Transplant

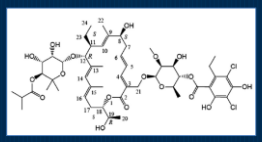
- Donor feces
- Administered via naso-gastric/duodenal tube or enema
- Challenges
  - Aesthetically unappealing
  - Logistically challenging
  - ? Translocation in immunosuppressed
  - Limited efficacy data



van Nood E, et al. NEJM 2013;368(5):407-15.

Fidaxomicin (Dificid®)

- Macrocyclic antibiotic
- Mechanism of action
  - Inhibits protein synthesis via sigma-dependent transcription of bacterial RNA polymerase
  - Prolonged post-antibiotic effect
  - Bactericidal



Venugopal AA, et al. CID 2012;54:568-74

Fidaxomicin: Spectrum of Activity

- *C. difficile*
  - MIC_{90} 0.25 mcg/ml
  - Active against NAP-1 strains
- Gram positive anaerobes
- Gram positive aerobes
- Not active against Gram negative organisms
- Resistance development in preclinical trials was low

Venugopal AA, et al. CID 2012;54:568-74

Effect on Microbiome

Organism / Treatment Day	Mean log10 CFU ± SD: Healthy Controls	Fidaxomicin	Vancomycin	P value
Bacteroides				
Day 0	9.66	8.52 ± 1.53	7.61 ± 2.21	
Day 10		9.33 ± 1.30	5.26 ±0.91	0.0001
Day 21		9.30 ± 1.44	5.95 ± 2.30	0.03
Enterobacteriaceae				
Day 0	5.53	7.94 ± 0.70	7.50 ± 1.70	N/A
Day 10		7.84 ±1.18	8.84 ± 0.57	
Day 21		7.06 ± 0.92	7.62 ± 1.03	
Enterococci				
Day 0	5.30	5.48 ± 1.35	6.17 ± 0.51	N/A
Day 10		5.93 ± 0.95	5.43 ± 0.36	
Day 21		6.12 ± 0.90	6.15 ± 0.67	
Lactobacillus				
Day 0	7.59	7.62 ± 0.54	7.55 ± 0.62	N/A
Day 10		7.64 ± 0.65	7.91 ± 0.70	
Day 21		7.34 ± 0.93	7.69 ± 0.48	

Louie TJ, et al. CID 2012;55(S2):S132-42.

Fidaxomicin: Pharmacokinetics

- Absorption
  - Minimal absorption
  - Administer with or without food
- Distribution
  - Mean fecal concentrations 5000 times average MIC_{90}
- Metabolism
  - Hydrolysis to an active metabolite OP-1118
- Elimination
  - Half-life: fidaxomicin 11.7 hrs, OP-1118 11.2 hrs
  - Undetectable in urine

Venugopal AA, et al. CID 2012;54:568-74

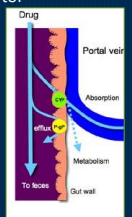
Adverse Events & Drug Interactions

Adverse Effects

- Similar to vancomycin in phase III studies
- Leukopenia
  - 2.5% fidaxomicin vs 1% vancomycin (p=0.06)
- GI hemorrhage
  - 4.1% fidaxomicin vs 3.1% vancomycin (p=0.37)

Drug Interactions

- P-glycoprotein substrate & inhibitor



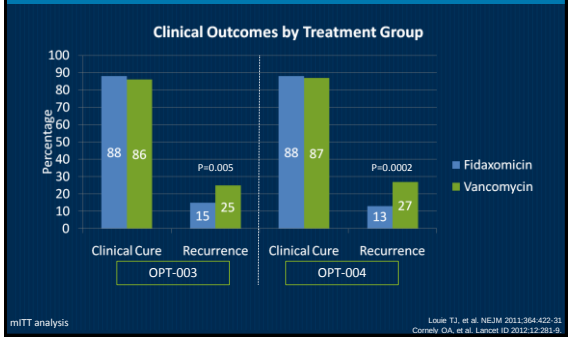
Weiss K, et al. CID 2012;55(S2):S110-15.

Fidaxomicin: Clinical Efficacy

- Two prospective, randomized, double-blind clinical trials
  - OPT-003 in US and Canada
  - OPT-004 in Europe, US and Canada
- Fidaxomicin 200 mg BID vs. Vancomycin 125 mg QID
- Outcomes
  - Clinical cure = resolution of diarrhea and absence of further treatment
  - Recurrence = diarrhea plus positive toxin within 4 weeks
- Baseline characteristics
  - 60-68% were inpatients
  - Severe disease in 39% OPT-003 and 25% OPT-004
  - BI/NAP1/027 strain 33-38%
  - Prior episode of CDI 15-17%

Louie TJ, et al. NEJM 2011;364:422-31
Cornely OA, et al. Lancet ID 2012;12:281-9.

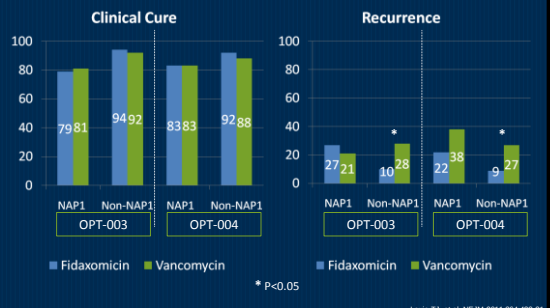
Primary & Secondary Endpoints



mITT analysis

Louie TJ, et al. NEJM 2011;364:422-31
Cornely OA, et al. Lancet ID 2012;12:281-9.

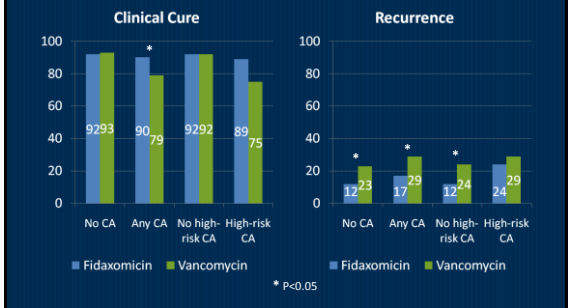
NAP1/BI/027



* P<0.05

Louie TJ, et al. NEJM 2011;364:422-31
Cornely OA, et al. Lancet ID 2012;12:281-9.

Concomitant Antibiotics

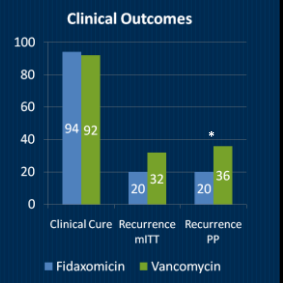


* P<0.05

Mullane KM, et al. CID 2011;53(5):440-7.

First Recurrence

- Single prior CDI episode in prior 3 months
- Characteristics
  - Therapy for prior CDI
    - None 15% vs 19%
    - Metro 62% vs 40%
    - Vancomycin 15% vs 21%
  - NAP1 strain 35% vs 26%
  - Inpatients 53%
  - Severe 18% vs 26%



N= 159 mITT, 128 for PP analysis

Cornely OA, et al. CID 2012;55(S2):S154-61.

Fidaxomicin Summary

- Fidaxomicin is non-inferior to vancomcyin for the treatment of CDI
- Fidaxomicin prevents more recurrences than vancomycin in certain subgroups
  - Non-NAP1/BI/027 strains
  - Non-high risk concomitant antimicrobials
- Unanswered questions
  - Severe disease?
  - Multiple recurrences?
  - Pharmacoeconomic analysis?

Cost Comparison

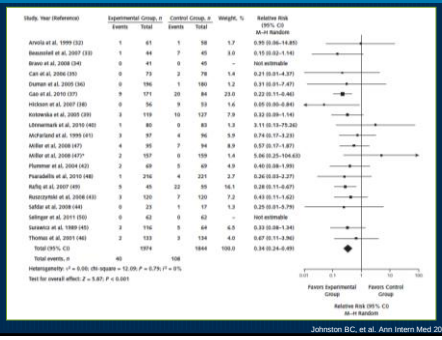
Drug	Dose	Cost/day	Cost/10 day course
Metronidazole	500 mg po Q8 hr	$0.15	$1.50
Vancomycin capsules (Vancocin®)	125 mg po Q6 hr	$60	$600
	250 mg po Q6 hr	$120	$1200
	500 mg po Q6 hr	$240	$2400
Vancomycin oral liquid	125 mg po Q6 hr	$7	$70
Fidaxomicin (Dificid®)	200 mg po Q12 hr	$210	$2100
Rifaximin	400 mg po Q8 hr	$70	$700

Probiotics for Prevention of CDI

- Live microorganism which when administered in adequate amounts confer a health benefit
  - *Saccharomyces boulardii*
  - *Lactobacillus* species
- Challenges
  - Lack of standardization
  - Variations in bacterial count
  - Concern for fungemia or bacteremia
  - Limited evidence
- IDSA/SHEA Guidelines do NOT recommend probiotics to prevent primary CDI (C-III)
- Controversy exists

Cohen SH, et al. Infect Control Hosp Epidemiol 2010;31(5): 431-55.

Meta-Analysis Probiotics for Prevention of CDI

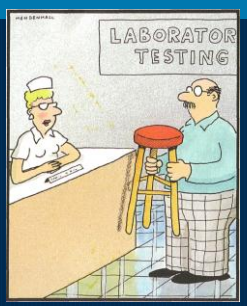


Johnston BC, et al. Ann Intern Med 2012;157:878-888.

Conclusions

- *C. difficile* is a toxin-producing, Gram-positive bacillus that is the most common type of antibiotic-associated diarrhea
- IDSA/SHEA Guidelines recommend
  - Mild-moderate: Metronidazole 500 mg po TID
  - Severe: Vancomycin 125 mg po QID
  - Complicated: Vancomycin 500 mg po QID + Metronidazole 500 mg IV Q8hr ± Vancomycin PR
- Recurrent CDI continues to be challenging
- Fidaxomicin is a new agent for treatment

Questions



"That's not quite the stool sample we had in mind."