Clostridium difficile Infection (CDI):

Discovering the need for new treatment algorithms and care pathways

APRIL 4, 2013

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OPTIMER PHARMACEUTICALS

Overview of Potential Treatment Options for CDI

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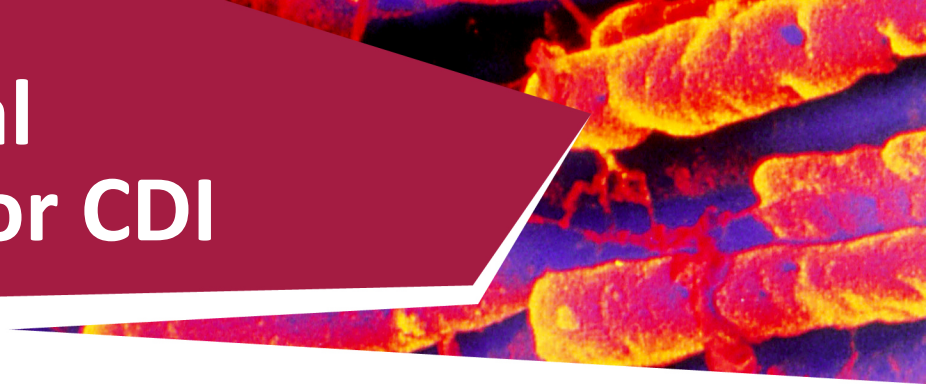

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UNIVERSITY OF MANITOBA

FACULTY OF MEDICINE

Overview of Potential Treatment Options for CDI

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AMMI Canada
CONFLICT OF INTEREST DISCLOSURE SLIDE

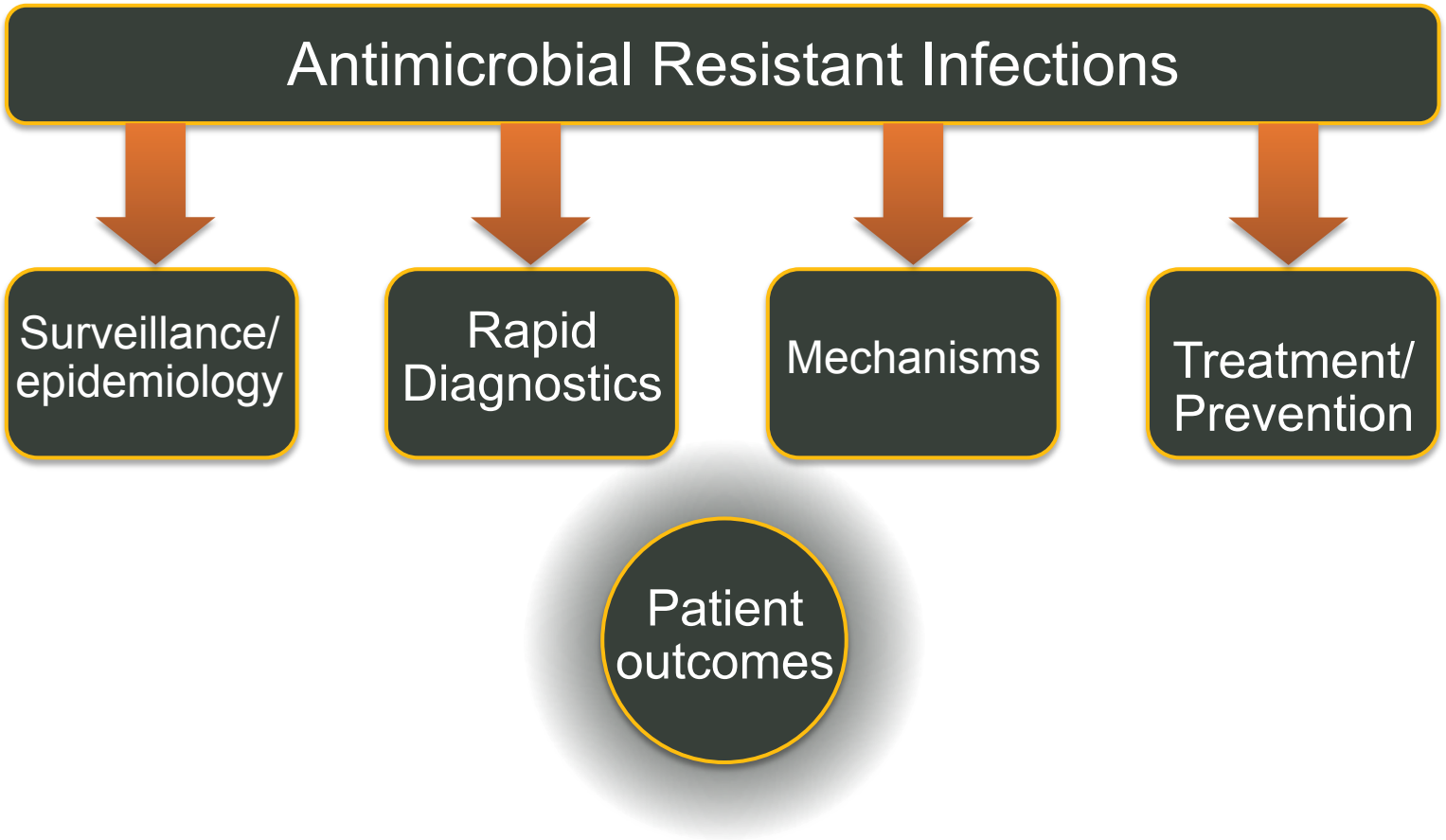
In the past 2 years I have been an employee of:	**University of Manitoba/Health Sciences Center**
In the past 2 years I have been a consultant of:	**NA**
In the past 2 years I have held investments in the following pharmaceutical organizations, medical devices companies or communications firms:	**NA**
In the past 2 years I have been a member of the Scientific advisory board of:	**NA**
In the past 2 years I have been a speaker for:	**Astellas, Cubist, Merck, Optimer, Pfizer**
In the past 2 years I have received research support (grants) from:	**Abbott, Achaogen, Affinium, Astellas, AstraZeneca, Bayer, Cerexa, Cubist, Forest, Merck, Optimer, Pfizer, Sunovion, The Medicines Company, Therevance, Triton, Trius**
In the past 2 years I have received honoraria from:	**Astellas, Cubist, Merck, Optimer, Pfizer**
I agree to disclose approved and non-approved indications for medications in this presentation:	**YES / NO…YES**
I agree to use generic names of medications in this presentation:	**YES / NO… YES**

There are no relationships to disclose ☐

Objectives

1. Compare the current treatment recommendations for CDI
2. Contrast vancomycin with fidaxomicin for the treatment of CDI
3. List the advantages and disadvantages of fidaxomicin in the treatment of CDI

Canadian Antimicrobial Resistance Alliance (CARA)




CANADIAN ANTIMICROBIAL RESISTANCE ALLIANCE
CARA
HOME
ABOUT US
ANTIBIOTIC SURVEILLANCE
ANTIBIOGRAM
ANTIMICROBIAL USAGE
SLIDE GALLERY
RECENT RESEARCH
MEDIA/PUBLIC
Welcome
About CAN-R
The Canadian Antimicrobial Resistance Alliance (CARA) launched a website in early 2007, CAN-R (www.can-r.ca). The site is an online research portal designed to aid and educate Canadian healthcare providers on the escalating issue of antimicrobial resistance in Canada. In 2010, the site was redesigned with a clean and simple layout, and a user-friendly interface.
Providing current and comprehensive information, the site includes a variety of features and tools on antimicrobial resistance in Canada including:
Surveillance of pathogens and infections
Antimicrobial usage data
Summary content from major conferences and meetings
Key publications from evidence-based medical literature
Areas of focus:
Emerging issues
New research
Investigational and new antimicrobials
Resistance surveillance
Who will benefit from CAN-R
CAN-R is a useful tool for researchers, medical care providers, and the media in understanding the rise of antimicrobial resistance in Canada and how it is being managed.
Intended audiences include:
Infectious disease specialists
Medical microbiologists
Clinical microbiologists
Clinical pharmacists
Researchers
Urologists
Respirologists
Intensivists
Surgeons
Residents and Fellows
Laboratory and Nursing staff
Media
Public
Please select an icon below to search the most recent antimicrobial resistance data.
09 CANWARD
09 ANTIBIOGRAMS
09 ANTIMICROBIAL USAGE
LINKS | SITE MAP | CONTACT US
AMMI Canada
APUA
BSAC
CACMID
CBSN Canadian Bacterial Surveillance Network
ICID International Centre for Infectious Diseases
University of Manitoba

www.can-r.ca

SHEA *Clostridium difficile* Guidelines 2010: IDSA

Clinical Definition	Clinical Data	Rec Treatment	Rec Strength
Initial episode (mild-mod)	Leukocytosis (WBC ≤15,000) Scr < 1.5x baseline	Metronidazole 500mg TID PO 10-14days	A-I
Initial episode (severe)	Leukocytosis (WBC ≥15,000) Scr ≥ 1.5x baseline	Vancomycin 125mg QID PO 10-14days	B-I

Cohen et al. ICHE 2010;31(5):431-455.

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SHEA *Clostridium difficile* Guidelines 2010: IDSA

Clinical Definition	Clinical Data	Rec Treatment	Rec Strength
Initial episode (severe, complicated)	Hypotension or shock, ileus, megacolon	Vancomycin 500mg QID PO/NG +/- Metronidazole 500mg Q8H IV	**C-III**
First recurrence		Same as initial episode (ie. metronidazole)	A-II
Second recurrence		Vancomycin taper or pulsed regimen	B-III

Cohen et al. ICHE 2010;31(5):431-455.

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Potential *Clostridium difficile* Treatments

Metronidazole

- effective in mild-mod CDI
- very low fecal concentrations
- reports of increased failure rates and slow response
- inferior to vancomycin in severe CDI

Cohen et al. ICHE 2010;31(5):431-455.
Venugopal and Johnson CID 2012;55 (Suppl 2):71-76.

Potential *Clostridium difficile* Treatments

Vancomycin

- the gold standard comparator in clinical trials
- for multiple recurrences used as taper/pulsed regimen
- many limitations (effects on flora, VRE selection, dosing etc)

Cohen et al. ICHE 2010;31(5):431-455.
Venugopal and Johnson CID 2012;55 (Suppl 2):71-76.

Potential *Clostridium difficile* Treatments

- Metronidazole
- Vancomycin

- Nitazoxanide (not approved for CDI, * special access)
- Rifaximin (not approved for CDI, * special access)
- Tigecycline (not approved for CDI)
- Bacitracin (not approved for CDI, use the IV)
- Fusidic acid (not approved for CDI, *special access)
- Teicoplanin (not approved for CDI, *special access)
- Probiotics
- Resins (not approved for CDI)
- IVIG (not approved for CDI)
- Fecal transplant
- Fidaxomicin

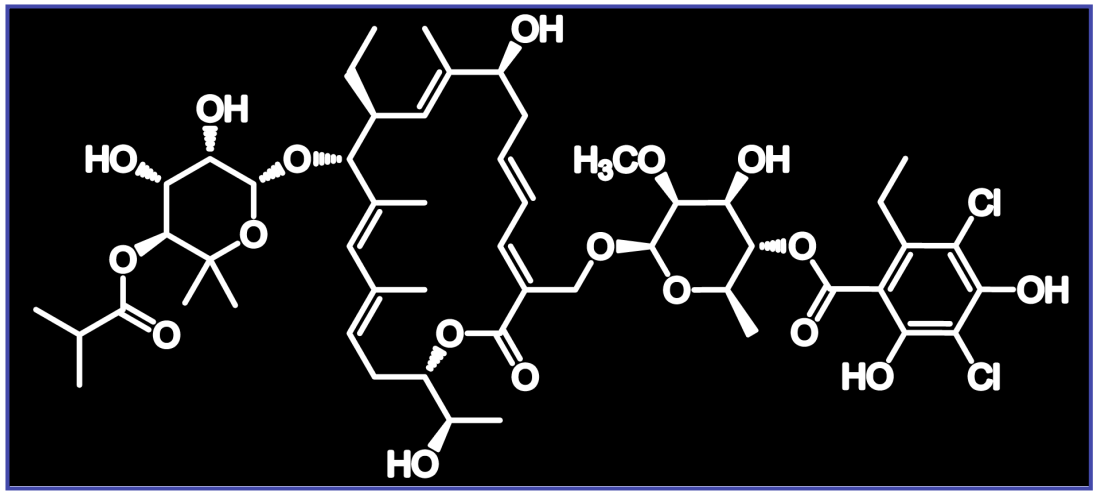
Cohen et al. ICHE 2010;31(5):431-455.
Venugopal and Johnson CID 2012;55 (Suppl 2):71-76.

Fidaxomicin Review

- **1. Review non-Clinical Trial and Clinical Trial data with fidaxomicin**
  - **Chemistry**
  - **Mechanism of action/resistance**
  - **Microbiology**
  - **PK/PD**
  - **Data on:**
    - **impact on normal flora**
    - **Inhibiting spore formation**
    - **Inhibiting toxin expression**
    - **selection of VRE and *Candida* spp.**
- **2. Clinical trial data**

Fidaxomicin: a new macrocyclic antibacterial

- First in a new class of antibiotics called “macrocycles”
  - Fermentation product of *Dactylosporangium aurantiacum*
  - 18 membered ring
- Health Canada approval
  June 07, 2012



Johnson and Wilcox. JAC 2012;67:2788-2792.

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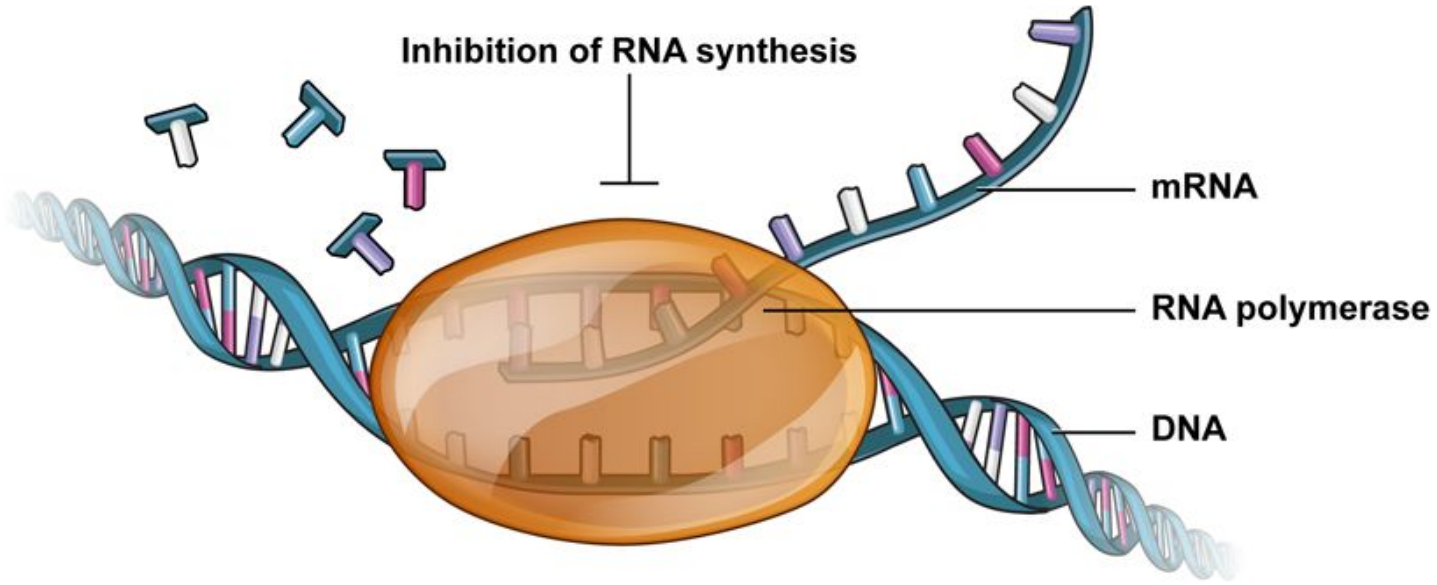
Fidaxomicin Mechanism of Action

- Inhibits transcription by bacterial RNA polymerase
- MOA distinct from rifamycins
- Not cross-resistant with rifamycins
- Rapid resistance should not occur



Artsimovitch et al. CID 2012;55(S2):127-131.

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Activity versus *Clostridium difficile* (MIC ug/ml, n= 208)

	≤ 0.06	0.12	0.25	0.5	1	2	4
Fidaxomicin	2	**73**	**65**	**51**	17		
Vancomycin				120	81	6	1
Metronidazole			25	102	67	13	1

Karlowsky and Zhanel. AAC 2008;52:4163-4165.

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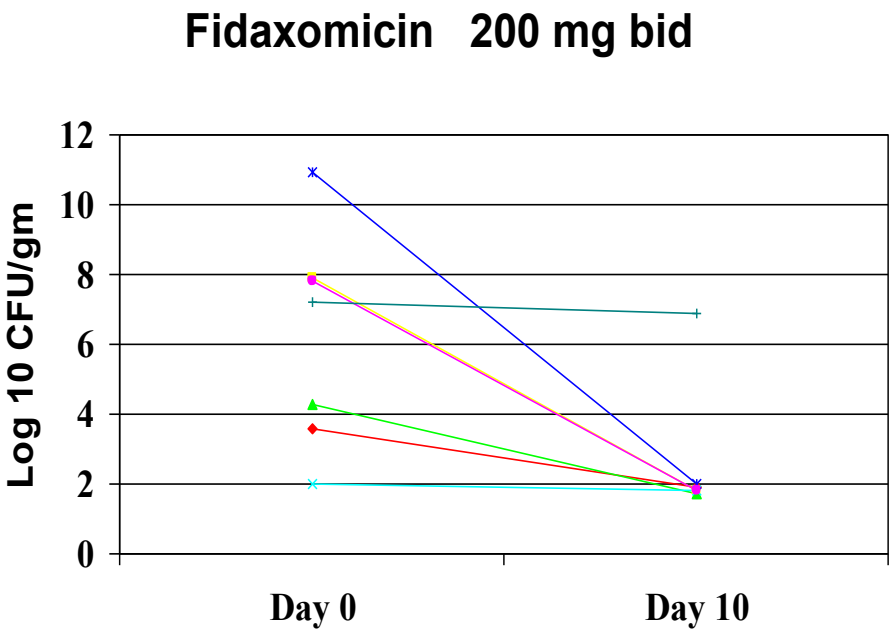
Fidaxomicin is Bactericidal in Vitro

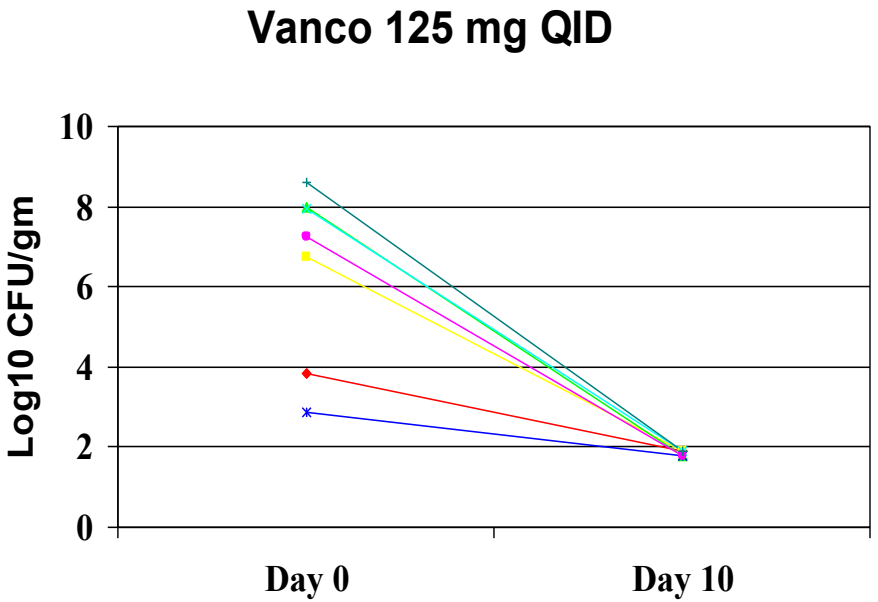
- Bactericidal against *C. difficile* in vitro
  - NAP1/027/BI (4x MIC ≥ 3 log $_{10}$ in 48hrs)
  - Killing > vancomycin
  - Bactericidal vs. lab generated mutant with reduced susceptibility
- Long post-antibiotic effect vs *C. difficile*

Babakhani et al. J Med Microbiol;2011:60:1213-1217.

Johnson and Wilcox. JAC 2012;67:2788-2792.

Fidaxomicin is Bactericidal in Vivo





Louie et al. AAC 2009;53:261-263.

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Fidaxomicin-Microbiology

- Very active versus most *Clostridia* spp (not *C. coccoides* or *C. leptum*), including *C. difficile*
- Active versus *Staphylococcus* spp., *Enterococcus* spp. *Peptostreptococcus* spp., Micrococcus spp.
- Poor activity (MIC > 64ug/ml) versus Gram-negative bacilli
  - aerobes/anaerobes
  - Enterobacteriaceae
  - *Bacteroides* spp., *Bifidobacterium* spp., *Prevotella* spp., *Veillonella* spp., *Fusobacterium* spp.)

Goldstein et al. CID 2012;55(S2):143-8.
Johnson and Wilcox. JAC 2012;67:2788-2792.

Fidaxomicin Pharmacokinetics and Pharmacodynamics

Pharmacokinetics:

- Minimal systemic absorption
  - 18.0-56.4 ng/mL plasma (36.2-108ng/ml OP-1118)
  - High fecal concentrations (~400-4000 ug/g range)
  - 92% of dose recovered in stool
  - <1% of dose recovered in urine as OP-1118

Pharmacodynamics:

- Acts locally in the GI tract on *C. difficile*
- Time dependent killing
- Fecal conc / MIC ~3000

Louie et al. AAC 2009;53:223-228.
Sears et al. CID 2012;55 (Suppl 2):116-120.

Pharmacokinetics of Fidaxomicin and OP-1118 (Patients with CDI)

Fidaxomicin Dosage (mg/day)	No. subjects	Mean Fecal Conc (ug/g) Fidaxomicin	OPT-118
100	11	256 +/- 136	393 +/- 260
200	9	442 +/- 238	430 +/- 263
400	13	1433 +/- 975	760 +/- 373

Louie et al. AAC 2009;53:223-228.

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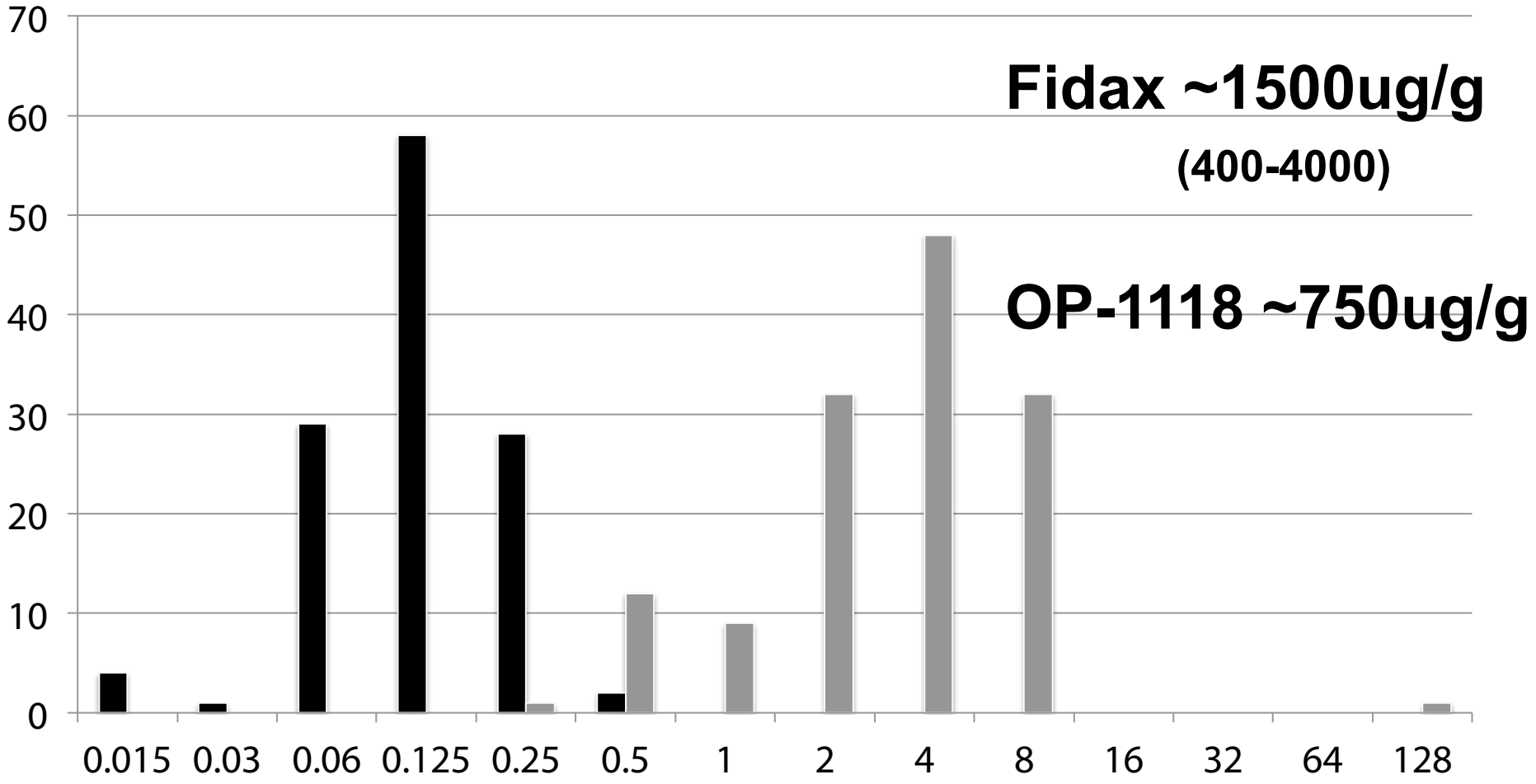
Fidaxomicin and OP-1118 Activity (MIC ug/ml) versus *Clostridium difficile* (n=135)



Goldstein et al. CID 2012;55(S2):143-8.

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Fidaxomicin Phase 2 Dose Response (200mg bid selected for Phase 3)

TABLE 3. Rates of clinical cure and recurrence in the population treated per protocol

Parameter of outcome	No. (%) of patients in the following treatment group showing clinical cure, failure, or recurrence:		
	100 mg of OPT-80/day	200 mg of OPT-80/day	400 mg of OPT-80/day
Total patients	14 (100)	15 (100)	16 (100)
Clinical cure			
Diarrhea resolution by day 10	10 (71)	12 (80)	15 (94)
Diarrhea resolves after day 10 with no additional treatment	2 (14)	1 (7)	1 (6)
Clinical failure (requiring change of therapy)	2 (14)	2 (13)	0 (0)
Clinical recurrence[a]	1 (8.3)	0 (0)	1 (6.3)

[a] Recurrence of toxin-positive diarrhea within 6 weeks after treatment, evaluated in patients who were clinical successes.

- Resolution of diarrhea by Day 10 was achieved in 71%, 80%, and 94% of patients in the 100 mg/day, 200 mg/day, and 400 mg/day dosing groups.
- There were no treatment failures in the 400 mg/day dosing group.
- Clinical recurrence within 6 weeks after treatment occurred in only 2 patients: 1 in the 100 mg/day group and 1 in the 400 mg/day group.

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Fidaxomicin Phase 3 Clinical Trials: (vs. Vancomycin for *C. difficile*)

TWO PHASE 3, RANDOMIZED, DOUBLE-BLIND, NON-INFERIORITY STUDIES OF DIFICID® (fidaxomicin) (N=542) VERSUS VANCOMYCIN (N=563)[1]

ENROLLED PATIENTS[1]
- C[I) defined by >3 unformed bowel movements (UBM) in the 24 hours before randomization and presence of either *C. difficile* toxin A or B in the stool within 48 hours of randomization
- Aged ≥18 years
- No more than 24 hours of pretreatment with vancomycin or metronidazole
- No prior C[I history or only one prior C[I) episode in the past 3 months

EXCLUDED PATIENTS[1]
- Subjects with life-threatening/fulminant infection, hypotension, septic shock, peritoneal signs, significant dehydration, or toxic megacolon

RANDOMIZATION

DIFICID 200 mg twice daily[1]

vancomycin 125 mg four times daily[1]

END OF TREATMENT

CLINICAL RESPONSE at the end of 10-day treatment
Primary endpoint; Non-Inferiority analysis

END OF FOLLOW-UP

SUSTAINED CLINICAL RESPONSE at 30 -day follow-up*
Secondary endpoint; Superiority analysis

- **16%** WERE PRESENTING WITH FIRST CDI RECURRENCE
- **33%** MODERATE CDI
- **37%** SEVERE CDI
- **50%** ≥65 YEARS
- **31%** ≥ 75 YEARS
- **48%** RENAL IMPAIRMENT
- **29%** CONCOMITANT SYSTEMIC ANTIBIOTIC THERAPY
- **36%** BI ISOLATES

Renal impairment was defined as estimated creatinine clearance of <79 ml/min.[19]
CDI severity was defined as: mild (4 to 5 UBM per day or white blood cell [WBC] < 12,000/mm^3), moderate (6 to 9 UBM per day or WBC of 12,001-15,000/mm^3), or severe (> 10 UBM per day or WBC > 15,001/mm^3)[18]

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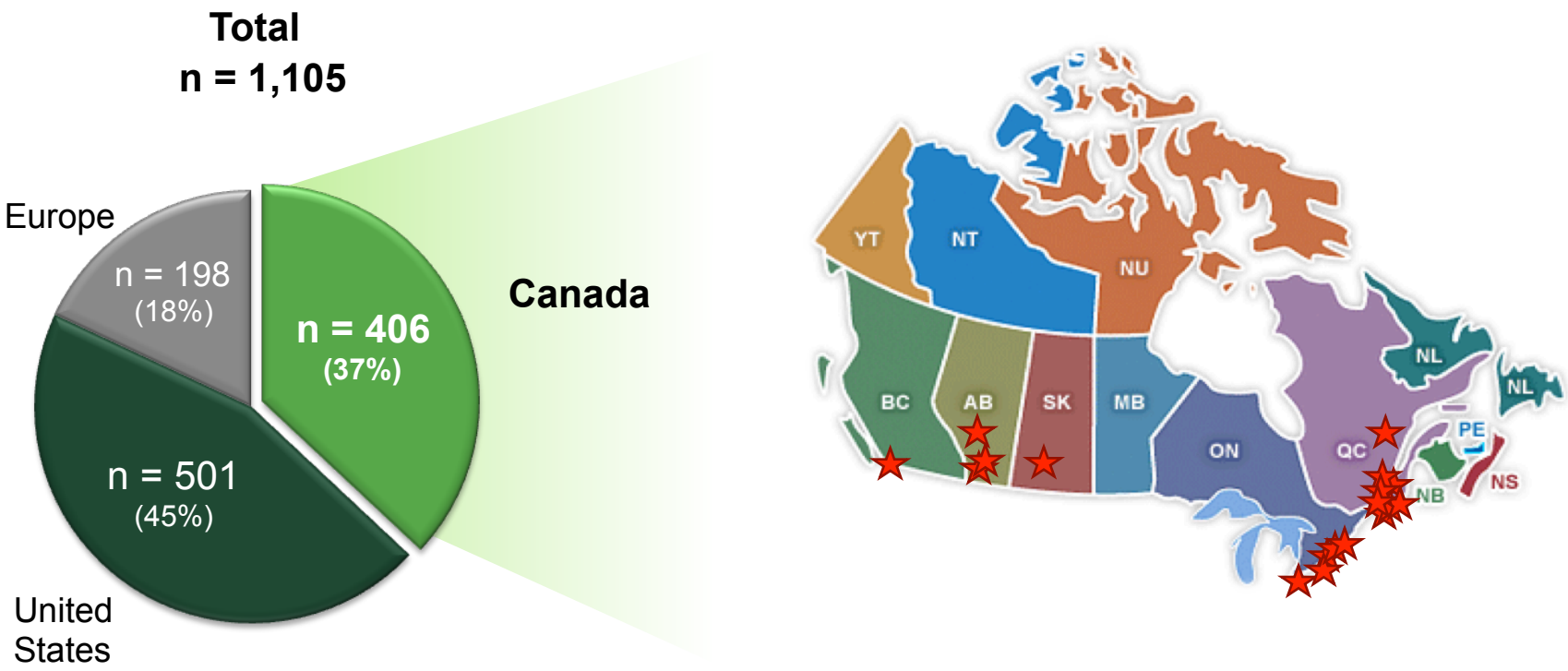
Significant Canadian participation in Fidaxomicin clinical trial program



- **406 Canadians enrolled in trial [54% QC]**
- **Canadian patients represented 37% of trial population**
- **20 unique Canadian sites [9 QC sites]**

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Landmark Clinical Trial Results Published in Top Notch International Journals

The NEW ENGLAND JOURNAL of MEDICINE

February 3, 2011

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection

Thomas J. Louie, M.D., Mark A. Miller, M.D., Kathleen M. Mullane, D.O., Karl Weiss, M.D., Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph.D., and Youe-Kong Shue, Ph.D., for the OPT-80-003 Clinical Study Group*

THE LANCET Infectious Diseases

8 February 2012

Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial

Prof Oliver A Cornely MD, Prof Derrick W Crook MD, Prof Roberto Esposito MD, André Poirier MD, Michael S Somero MD, Prof Karl Weiss MD, Pamela Sears PhD, Prof Sherwood Gorbach MD, for the OPT-80-004 Clinical Study Group

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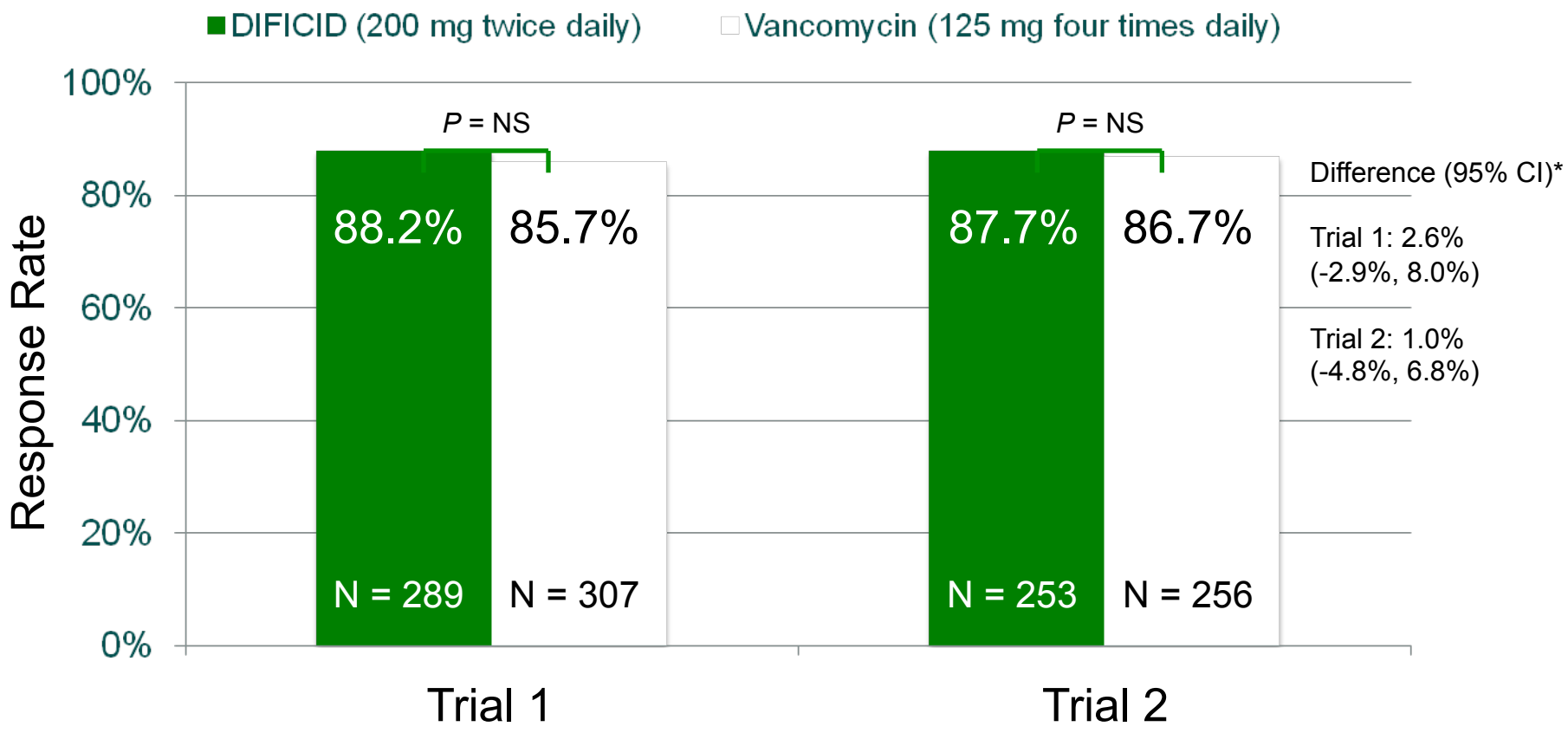
Fidaxomicin Achieved a Comparable Clinical Response Rate at the End of a 10-Day Treatment Versus Vancomycin



* Confidence interval was using a 2-sided method recommended by Agreseti and Caffo (2000) and p-value using Pearson's chi-square test.

DIFICID™ Product Monograph. Optimer Pharmaceuticals Canada, Inc. June 2012.

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Efficacy outcomes for clinical cure and recurrence rate endpoints in subpopulations at risk

Recurrence Risk Factor	% Clinical Cure			% Recurrence			Reference
	Vanco	Fidaxo		Vanco	Fidaxo		
Overall	90.1	91.9	NI	24.6	13.0	p<.05	Mullane DDW '11
Concomitant antibiotics	79.4	90.0	p<.05	29.0	17.0	p<.05	Mullane CID '11
Cancer	87.5	97.3	p=.06	30.0	14.1	p<.05	Cornely JCO '13
Renal failure (CrCl<30)	72.0	74.0	NI	33.0	15.0	p=.09	Mullane SHM '11
Prior CDI	92.0	94.0	NI	35.5	19.7	p<.05	Cornely CID '12
Age>65	93.0	94.0	NI	32.0	14.0	p<.05	Louie AGS '11

NI = Non-inferior

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Concomitant Antibiotics

CAs were categorized by risk of contributing to the incidence or progression of CDI.

High Risk	Medium Risk	Low Risk
Carbapenems 2nd generation cephalosporin 3rd generation cephalosporin 4th generation cephalosporin Fluoroquinolone Clindamycin) Penicillin (extended spectrum)	Penicillin (β-lactamase sensitive) Penicillin (β-lactamase resistant) Penicillin (extended spectrum, combination) 1st generation cephalosporin Macrolide Monobactam Streptogramin	Aminoglycosides Cell wall synthesis inhibitor Glycopeptide Imidazole Lipopeptides Nitrofuran Oxolidinone Polymyxin Rifamycin Antifolate and/or sulfonamide Tetracycline

Mullane K et al. *Clin Infect Dis*. 2011;53(5):440-7

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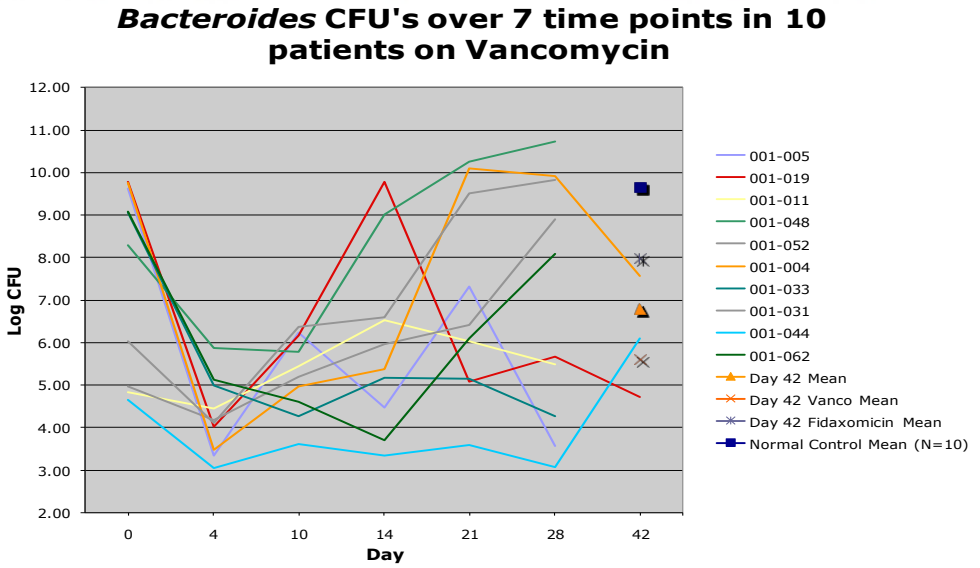
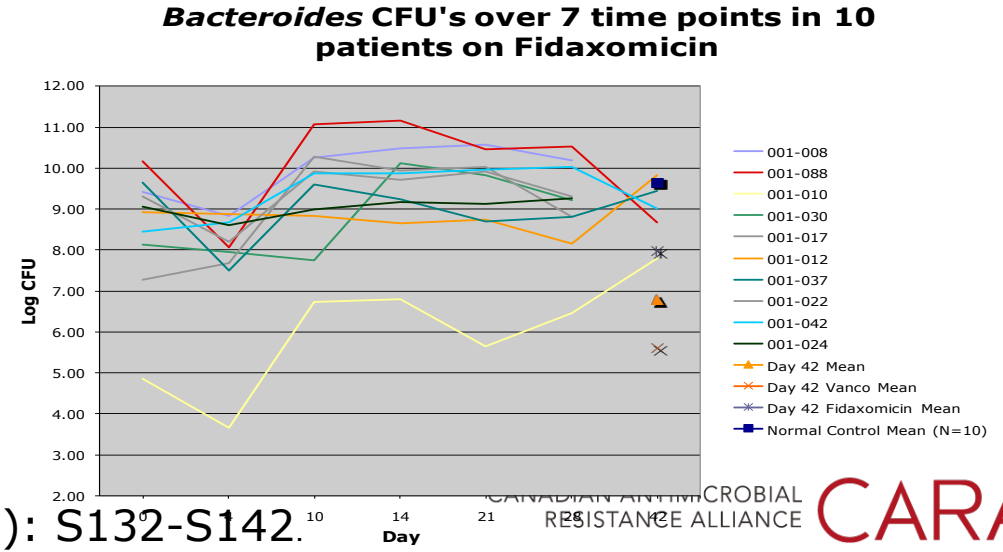
Vancomycin kills major components of the normal flora thought to prevent *C. difficile* disease

Vancomycin
125mg QID in 10 CDI pts



Fidaxomicin
200mg BID in 10 CDI pts



Louie et al (2012). CID: 55 (Supp 2): S132-S142.

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Fidaxomicin Inhibits Sporulation – Comparator Drugs Do Not

- Sporulation
  - Responsible for transmission of *C. difficile,* reinfection and relapse
  - suppression may play a role in preventing disease occurrence and recurrence
- Fidaxomicin, its metabolite OP-1118 and comparator drugs vancomycin and metronidazole assessed for impact on new spore formation

Babakhani et al (2012). CID: 55 (Supp 2): S162-S169.

Fidaxomicin Inhibits Sporulation

- Conclusion
  - Fidaxomicin and its metabolite strongly suppress spore formation
  - Fecal spore counts (CFU count/g) in patients who had received fidaxomicin were 2.3 $\log_{10}$ lower at 21 to 28 days post-therapy than in those patients who had received vancomycin
  - Inhibition of sporulation may provide, in part, a mechanism by which fidaxomicin improves sustained clinical response (prevents recurrence)

Babakhani et al (2012). CID: 55 (Supp 2): S162-S169.

Vancomycin vs. Fidaxomicin: Fecal *C. difficile* CFUs and [Toxin] in 89 pts

← Treatment Period →

		Day 0	Day 4	Day 10	Day 14	Day 21	Day 28	Day 42
Organism $\log_{10}$ CFU/g ± SD	VAN	6.2 ± 2.6	2.2 ± 0.9	2.0 ± 0.0	3.1 ± 2.2	4.4 ± 2.6	3.9 ± 2.2	4.5 ± 2.4
	FDX	5.8 ± 2.8	2.1 ± 0.9	2.6 ± 3.1	2.8 ± 3.1	4.4 ± 2.4	3.8 ±2.1	3.1 ±2.0
Toxin B titer ± SEM and (# pos/total)	VAN	2800 ± 1250	neg	neg	(7/30)	(15/30)	(3/22)	(1/12)
					28% (26/94) 1260 ± 350			
	FDX	2250 ± 600	neg	neg	(1/23)	(6/27)	(5/20)	(1/21)
					14% (13/91) 2400 ± 1400 [1 pt 16000]			

No difference in CFUs over time, but toxin expression reduced 50%

Louie et al (2012). CID: 55 (Supp 2): S132-S142.

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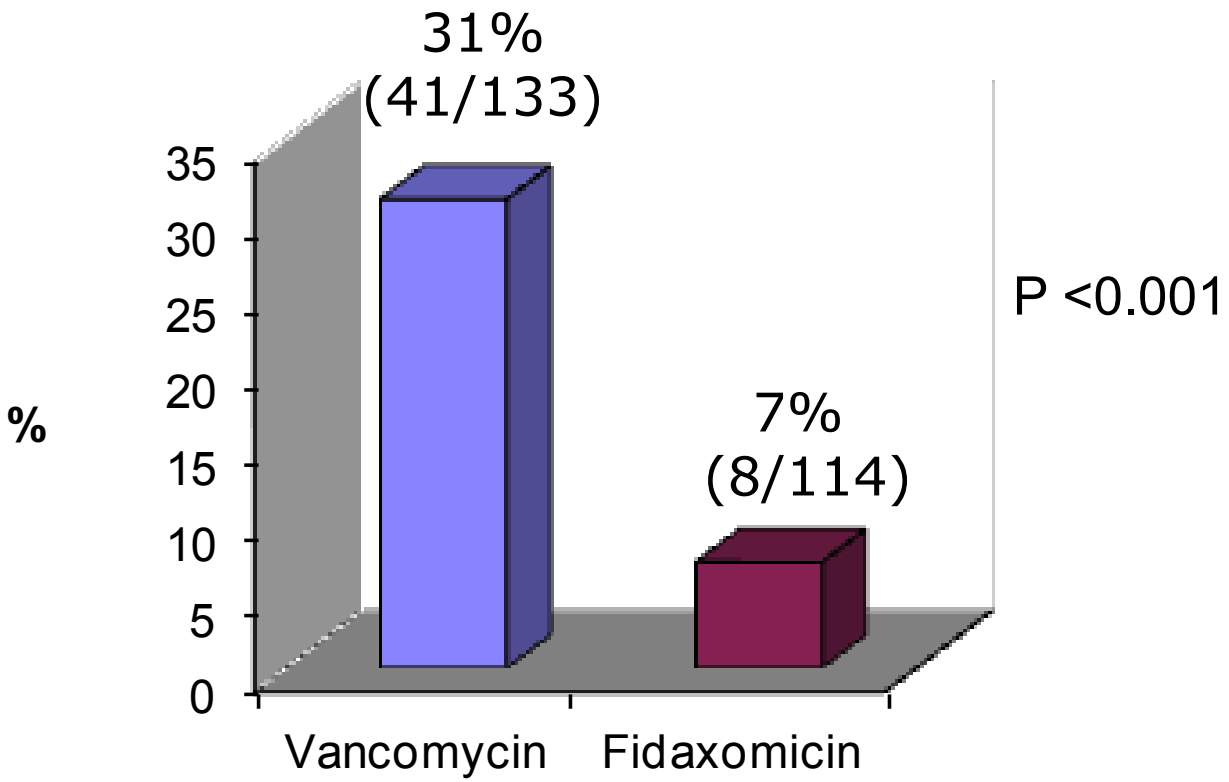
Acquisition of VRE or *Candida* spp. colonization during CDI treatment (Vanco versus Fidaxomicin)



Candida species: vancomycin 29% (40/136) vs. fidaxomicin 19% (12/116) (p=0.03).

Nerandzic et al (2012). CID: 55 (Supp 2): S121-S126.

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Conclusions - Fidaxomicin

- **Novel chemistry**
- **Inhibits RNA polymerase (unique site)**
- **Bactericidal vs. *C. difficile* (including resistant strains)**
- **Selective activity versus *C. difficile***
- **PK/PD: Very high fecal concentrations/MIC**
- **Versus vancomycin:**
  - **Minimal impact on normal flora**
  - **Inhibits spore formation**
  - **Inhibits toxin expression**
  - **Minimal selection of VRE and *Candida* spp.**
  - ***Better overall sustained response***

Cost ($CDN)

	Vancomycin IV Slurry		Vancomycin Oral Tablet		Fidaxomicin
	125mg QID 10 days	500mg QID 14 days	125 mg QID 10 days	500mg QID 14 days	200mg BID 10 days
BC	$ 30.00	$ 196.00	$ 368.60	$ 2,064.18	$ 2,200.00
ON	$ 30.00	$ 196.00	$ 351.96	$ 1,946.32	$ 2,200.00
QC	$ 30.00	$ 196.00	$ 207.20	$ 1,160.32	$ 2,200.00

Based on Vancocin PM, and IDSA Guidelines

Update in Mar 2013

Cost for Managing CDI ranges from $6176 to $15,397 per patient [1, 2, 3]

1. Kyne L, et al. *Clin Infect Dis*. 2002;34(3):346-353.
2. O'Brien JA, et al. *Infect Control Hosp Epidemiol.* 2007;28(11):1219-1227.
3. Dubberke ER, et al. *Clin Infect Dis.* 2008;46(4):497-504.

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