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## A Propensity Score-Matched Analysis Evaluating Oral Fidaxomicin versus Oral Vancomycin for Treatment of Severe *Clostridium difficile* Infection

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IRB Approved

## Disclosure

- Phuong Khanh Nguyen
- Potential conflicts of interest: none
- Sponsorship: none
- Proprietary information or results of ongoing research may be subject to different interpretations
- Speaker's presentation is educational in nature and indicates agreement to abide by the non-commercialism guidelines provided






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## Learning Objectives

- Describe *Clostridium difficile*'s bacteriology
- Discuss current treatment standards for *Clostridium difficile* infection (CDI)



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## Pre-Test Self-Assessment #1

Which characteristics best describe *Clostridium difficile*?

- Gram-positive, aerobic
- Gram-positive, anaerobic
- Gram-negative, anaerobic
- Atypical, anaerobic



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## Pre-Test Self-Assessment #2

Which antibiotic is currently recommended for the initial treatment of severe *Clostridium difficile* infection per the 2017 IDSA *Clostridium difficile* Infection guidelines?

- Oral vancomycin
- Metronidazole
- Fidaxomicin
- A & C






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## Veterans Health Administration

- Largest integrated health care system in the United States
- 1,240 health care facilities
  - 170 VA Medical Centers
  - 1,061 outpatient sites
- Over 9 million Veterans enrolled in the VA health care program
- Services
  - Surgery, critical care, mental health, orthopedics, pharmacy, radiology, and physical therapy (traditional hospital-based services)
  - Audiology, speech pathology, dermatology, dental, geriatrics, neurology, oncology, podiatry, prosthetics, urology, and vision care
  - Organ transplants and plastic surgery (advanced services)

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## Background

- *Clostridium difficile* is an anaerobic, spore-forming, toxin-producing, ubiquitous, Gram-positive bacillus
- Acute diarrhea and colitis often preceded by antimicrobial use
- Most common cause of infectious diarrhea in healthcare setting
- Accounts for ~12% of hospital-acquired infections
- Direct cost of admissions for CDI ~\$4 billion annually
- Recurrence rates ~25% to 30%

## The Burden of Severe CDI

- IDSA/SHEA 2017 CDI Guideline definition:
  - White blood cell count  $\geq 15,000$  cells/mL OR
  - Serum creatinine  $>1.5$  mg/dL
- More hospitalizations (often intensive care unit admission)
- ~10% mortality at 30 days
- Complications
  - Ileus, toxic megacolon, intestinal perforation, acute peritonitis
  - Shock
  - Colectomy (mortality rate  $>50\%$ )
  - Recurrence
- High-quality evidence for treatment of severe CDI lacking

## Treatment

IDSA/SHEA 2017 CDI Guidelines:

- Vancomycin 125mg orally four times daily OR
- Fidaxomicin 200mg orally twice daily
- Treatment for 10 days

## Fidaxomicin: Summary

- Two phase 3 randomized clinical trials
  - Fidaxomicin demonstrated non-inferiority to vancomycin for the treatment of CDI (e.g. clinical cure)
  - Fidaxomicin was associated with a significantly lower rate of recurrence compared to oral vancomycin
- What about Severe *Clostridium difficile* infection?
  - Less than half of CDI cases were severe episodes
  - Clinical cure rates similar between fidaxomicin and vancomycin in sub-group analyses by disease severity (e.g. severe disease)
  - Fidaxomicin had fewer recurrences compared to vancomycin

## Current Research

## Research Objectives

Primary aim: to evaluate fidaxomicin compared to oral vancomycin in the treatment of severe *Clostridium difficile* infection

- Primary study endpoint: recurrence rates
- Secondary study endpoint: mortality at 30, 90, and 180 days from index case

## Methods

- Study design
  - Retrospective, nationwide, propensity score-matched analysis
- Data source
  - Veterans Affairs Informatics and Computing Infrastructure (VINCI) database across the Veterans Health Administration
- Study population
  - Adult patients treated for severe *Clostridium difficile* infection from any Veterans Affairs Medical Center between June 1, 2011 through June 30, 2017

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## Study Inclusion

- ≥18 years of age
- Diagnosis of severe *Clostridium difficile* infection
  - Positive result for presence of *C. difficile* toxin (positive enzyme immunoassay, or positive polymerase chain reaction)
  - White blood cell count ≥15,000 cells/mL OR
  - Serum creatinine ≥1.5 times baseline
- Documented treatment within 72 hours of positive toxin result with an appropriate oral fidaxomicin or oral vancomycin course
- Concomitant oral or intravenous metronidazole within 72 hours of the intervention drugs was allowed
- If a patient has a series of severe CDI recurrences and meets all inclusion and no exclusion criteria, only the first episode treated with fidaxomicin or oral vancomycin was analyzed

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## Study Exclusion

- Treatment duration <7 days
- Fecal transplant therapy
- Discharge diagnosis, surgical report, or radiologic report consistent with toxic megacolon
- Conversion to alternative therapy within 72 hours of intervention initiation

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## Statistical Methods

- Determination of univariate variables associated with the selection of an oral fidaxomicin course
  - Nominal logistic multivariate analysis to determine independent variables associated with the selection of oral fidaxomicin using univariate variables with a P value of 0.1 or less
- Generation of formula to calculate a propensity score for each episode (0 to 1)
- Oral vancomycin regimens matched to oral fidaxomicin courses by propensity score match, next-nearest approach in 3:1 ratio
- Assuming a 35% combined clinical failure/recurrence rate for vancomycin, at least 134 patients would need to be analyzed in each arm to find a 20% combined clinical failure/recurrence rate for fidaxomicin to be statistically different, assuming  $\alpha=5\%$  and  $\beta=0.2$

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## Study Population Flow Chart\*

```

    graph TD
      A[10,343 severe Clostridium difficile episodes] --> B[223 fidaxomicin courses]
      A --> C[10,120 vancomycin courses]
      B --> D[221 fidaxomicin courses]
      C --> E[663 vancomycin courses]
      B -.-> F[2 episodes unmatched**]
      C -.-> G[56 episodes unmatched**]
      B --- H[Propensity Match] --- C
      D --- H --- E
    
```

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\*June 1, 2011 - June 30, 2017  
 \*\* unaffiliated data

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## Baseline Demographics I

Baseline Variable	Fidaxomicin (N=221)	Vancomycin (N=663)	P Value
Age > 65 years	147 (66.5)	439 (66.2)	.935
Male gender	209 (95.0)	632 (96.2)	---
Race			.310
Caucasian	154 (69.7)	479 (72.3)	
African American	41 (18.6)	107 (16.1)	
Hispanic	7 (3.17)	35 (5.28)	
Other	19 (8.60)	42 (6.33)	
Episode type			.894
Initial	42 (19.0)	129 (19.5)	
Recurrent	163 (73.8)	492 (74.2)	
Subsequent	16 (7.24)	42 (6.33)	

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## Baseline Demographics II

Baseline Variable	Fidaxomicin (N=221)	Vancomycin (N=663)	P Value
Inpatient status			1.00
Ward	114 (51.6)	342 (51.6)	
ICU admit	26 (11.8)	78 (11.8)	
No admit	20 (9.05)	60 (9.05)	
Nosocomial	61 (27.6)	183 (27.6)	

## Baseline Demographics III

Baseline Variable	Fidaxomicin (N=221)	Vancomycin (N=663)	P Value
Comorbidities			
Musculoskeletal	76 (34.4)	262 (39.5)	.172
Neurologic	95 (43.0)	299 (45.1)	.584
Metabolic	175 (79.2)	530 (79.9)	.810
Hematologic	113 (51.1)	350 (52.8)	.669
Immunologic	28 (12.7)	72 (10.9)	.467
Neoplastic	48 (21.7)	161 (24.3)	.434
Respiratory	111 (50.2)	309 (46.6)	.351
Renal	160 (72.4)	476 (71.8)	.863
Cardiovascular	192 (86.9)	573 (86.4)	.864
Gastrointestinal	107 (48.4)	338 (51.0)	.509
Hepatic	47 (21.3)	117 (17.7)	.236

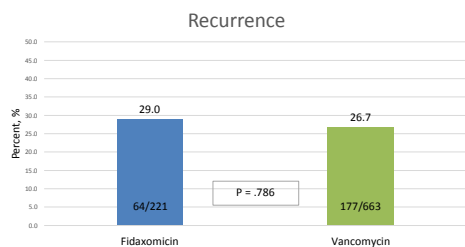
## Baseline Demographics IV

Baseline Variable	Fidaxomicin (N=221)	Vancomycin (N=663)	P Value
Hyponatremia	90 (40.7)	274 (41.3)	.875
Hypernatremia	1 (.450)	8 (1.21)	.293
Hypokalemia	92 (41.6)	340 (51.3)	.013
Hyperkalemia	18 (8.14)	52 (7.84)	.886
Hypochloremia	48 (21.7)	156 (23.5)	.578
Hyperchloremia	78 (35.3)	230 (34.7)	.871
Low carbon dioxide	122 (55.2)	370 (55.8)	.876
Elevated carbon dioxide	1 (.450)	31 (4.68)	.0005
Hypoglycemia	13 (5.88)	36 (5.43)	.800
Hyperglycemia	142 (64.3)	437 (65.9)	.654

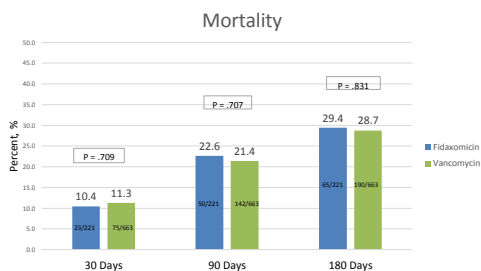
## Baseline Demographics V

Baseline Variable	Fidaxomicin (N=221)	Vancomycin (N=663)	P Value
Anemia	193 (87.3)	604 (91.1)	.112
Thrombocytopenia	52 (23.5)	186 (28.1)	.185
Leukocytosis	168 (76.0)	553 (83.4)	.016
Leukocytosis >30	21 (9.50)	76 (11.5)	.413
Scr ≥1.5x baseline	58 (26.2)	184 (27.8)	.662
Neutropenia	2 (.900)	17 (2.56)	.108
SBP <90 mmHg	55 (24.9)	131 (19.8)	.110
DBP <60 mmHg	130 (58.8)	338 (51.0)	.043
Pulse >100 bpm	103 (46.6)	257 (38.8)	.041
RR >20	83 (37.6)	227 (34.2)	.372
Abnormal temperature	55 (24.9)	157 (23.7)	.717

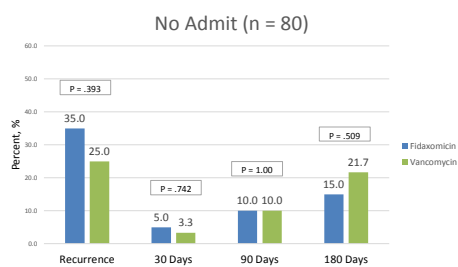
## Primary Outcome



## Secondary Outcomes



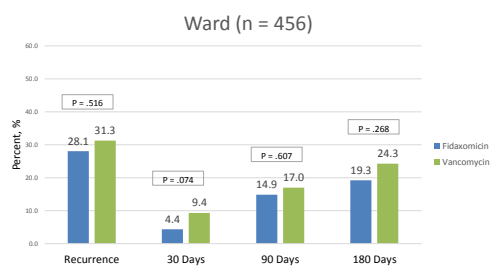
## Subgroup Analysis



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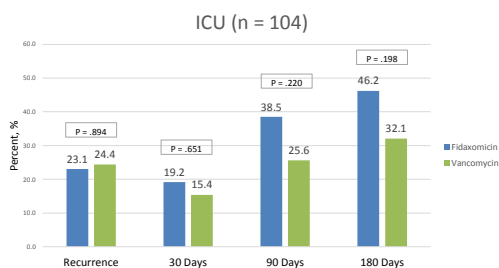
## Subgroup Analysis



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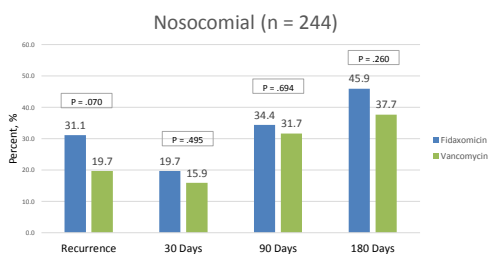
## Subgroup Analysis



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## Subgroup Analysis



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## Discussion

- Present study is the first to focus specifically on severe episodes of *Clostridium difficile* infection
- No difference in recurrence or mortality at 30, 90, and 180 days from severe index case
- No difference in outcomes when stratified by admit status



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## Conclusion

- Findings consistent with current IDSA recommendations for treatment of severe CDI
- Large, randomized controlled trials are still needed to substantiate the current recommendation for using either oral vancomycin or oral fidaxomicin for severe CDI



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## Post-Test Self-Assessment #1

Which characteristics best describe *Clostridium difficile*?

- A. Gram-positive, aerobic
- B. Gram-positive, anaerobic
- C. Gram-negative, anaerobic
- D. Atypical, anaerobic



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## Post-Test Self-Assessment #2

Which antibiotic is currently recommended for the initial treatment of severe *Clostridium difficile* infection per the 2017 IDSA *Clostridium difficile* Infection guidelines?

- A. Oral vancomycin
- B. Metronidazole
- C. Fidaxomicin
- D. A & C



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