


Effect of time-to-treatment on 30-day mortality in patients presenting to the ED with severe *Clostridium difficile* infection

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Disclosure

- Dumitru Sirbu
- Potential conflicts of interest: none
- Sponsorship: none
- Proprietary information or results of ongoing research may be subject to different interpretations
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Objectives

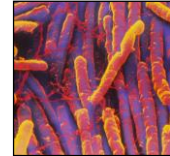
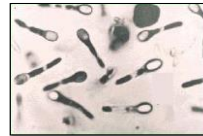
1. Differentiate between mild, moderate, and severe *Clostridium difficile* infections
2. Select a proper antimicrobial treatment regimen for severe *Clostridium difficile* infection

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Clostridium difficile

- Anaerobic, spore-forming, gram-positive bacillus
- Primarily transmitted via fecal-oral route
 - Hand washing!
- Ingestion of spores does not equal infection
 - Asymptomatic carriers



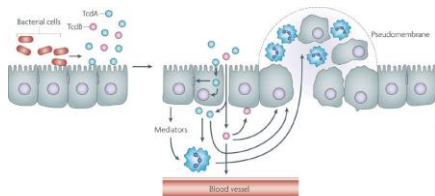
https://microbewiki.kenyon.edu/index.php/Clostridium_difficile-associated_disease

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Pathogenesis

- Ingestion of *C. difficile* spores
- Normal gut flora is altered
 - Antibiotics (clindamycin, fluoroquinolones, 3rd gen cephalosporins)



Source: Rupnik, M., *Clostridium difficile* infection: new developments in epidemiology and pathogenesis. *Nature Reviews Microbiology*.

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Epidemiology

- Majority of *Clostridium difficile* infections (CDI) are healthcare related
 - But, a growing proportion of CDI cases are community associated
- Estimated incidence of 9.3 cases per 10,000 patient-days
 - 336,600 individuals hospitalized in 2009 with a diagnosis of CDI
- Mortality rate of 9.1% in hospitalized patients
 - Nearly 90% of deaths occur in patients \geq 65 years old
- Recurrence rates range from 20% - 30%
- \$4.8 billion burden in excess costs to healthcare system
 - \$2,454 - \$29,000 per episode

Source: <https://www.cdc.gov/media/releases/2015/s0225-clostridium-difficile.html>

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Detection of *C. difficile*

Oklahoma City VA facility uses the following methods:

- Nucleic Acid Amplification Tests (NAATs) – i.e. Toxin A and B PCR
 - High sensitivity
 - Low/moderate specificity
 - Results in a couple of hours
- (Old) Glutamate dehydrogenase – i.e. *C. difficile* common antigen
 - High sensitivity
 - Low specificity

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Classification

- CDI is classified into four major categories by the IDSA
 - Non-severe
 - Severe
 - Fulminant
 - Previously termed “severe, complicated CDI”
 - Hypotension or shock, ileus, or megacolon
 - Recurrent

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Defining “Severe” CDI

| 2010 IDSA Guidelines | 2013 ACG Guidelines | 2017 IDSA Guidelines |
|--|--|---|
| <ul style="list-style-type: none"> • WBC $\geq 15,000$ cells/μL <u>or</u> • Serum creatinine ≥ 1.5x baseline level | <ul style="list-style-type: none"> • Serum albumin < 3 g/dL <u>plus</u> • WBC $\geq 15,000$ cells/μL <u>or</u> • Abdominal tenderness | <ul style="list-style-type: none"> • WBC $\geq 15,000$ cells/μL <u>or</u> • Serum creatinine > 1.5 mg/dL |

★ The criteria proposed for defining severe or fulminant CDI are based on expert opinion

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Treatment

- Recent IDSA guidelines update introduced some big changes

| Initial episode | Recommended treatment | |
|----------------------------|--|--|
| | 2010 IDSA Guidelines | 2017 IDSA Guidelines |
| Mild or moderate | Metro 500mg q8h x10-14 days | Van 125mg q6h <u>or</u> Fdx 200mg bid x10 days |
| Severe | Van 125mg q6h x10-14 days | Van 125mg q6h <u>or</u> Fdx 200mg bid x10 days |
| Severe, Complicated | Van 500mg q6h <u>plus</u> Metro 500mg q8h <u>and/or</u> Van PR | Van 500mg q6h <u>plus</u> Metro 500mg q8h <u>and/or</u> Van PR |


Metro = Metronidazole; Van = Vancomycin; Fdx = Fidaxomicin

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Risk Factors

- Risk factors for CDI-related mortality
 - Exposure to antibiotic therapy
 - Exposure to the healthcare system
 - Age
 - Comorbid conditions (inflammatory bowel disease, kidney disease)
 - Immunosuppression (disease or drug-induced)
 - Disruption of the GI system (feeding tubes, surgery, PPIs?)
 - **What about time to antibiotic initiation?**
 - Guidelines recommend to “start empiric antibiotic therapy if a substantial delay in laboratory confirmation is expected” or to “start antibiotic therapy after diagnosis”

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Effect of time-to-treatment on 30-day mortality in patients presenting to the ED with severe *Clostridium difficile* infection

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Study Design



- Aim of the study is to determine whether time to initiation of antibiotic treatment has an effect on mortality and recurrence rates in patients presenting to the ED with severe CDI
- Retrospective, observational chart review study conducted at the Oklahoma City VA Medical Center (VAMC)
- The VAMC is a 192-bed tertiary care facility that currently serves 48 Oklahoma counties, and two counties in North-central Texas, with a veteran population over 225,000

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Study Design continued

- Included patients admitted to the VAMC emergency department (ED) and diagnosed with severe CDI between June 1st, 2011 and October 26th, 2017
- Primary outcome
 - 30-day mortality
- Secondary outcomes
 - Rate of recurrence after 30 days
 - Previous history of *C. difficile* infection
- Powered to detect a 6% difference in mortality assuming $\alpha=0.05$ and $\beta=0.2$

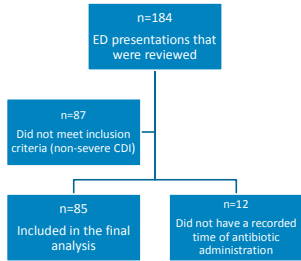
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Methods

| Inclusion Criteria | Exclusion Criteria |
|---|---|
| Males and females ≥ 18 years old presenting to the ED with diarrhea in the past 48 hours <u>plus</u> | Evidence of intent to perform fecal transplant |
| Severe CDI defined as WBC $\geq 15,000$ cells/mm <u>or</u> serum creatinine > 1.5 mg/dL <u>plus</u> | Discharge diagnosis of toxic megacolon based on surgical or radiological report |
| Positive test for presence of <i>C. difficile</i> toxin via ELISA <u>or</u> PCR | Pregnancy at time of presentation |

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Data Collection



```

    graph TD
      A[n=184  
ED presentations that were reviewed] --> B[n=87  
Did not meet inclusion criteria (non-severe CDI)]
      A --> C[n=85  
Included in the final analysis]
      A --> D[n=12  
Did not have a recorded time of antibiotic administration]
      C --- E[ ]
      D --- E
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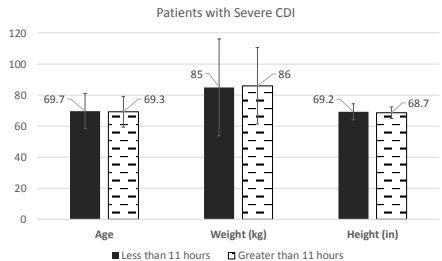
Results

| Parameter | Median | Mean \pm SD |
|--|--------|-------------------|
| Age | 66 | 64.23 \pm 14.19 |
| Weight (kg) | 82 | 87.13 \pm 24.5 |
| Height (in) | 69 | 69.14 \pm 3.96 |
| White Blood Cells (cells/mm) | 11.50 | 13.63 \pm 8.32 |
| Serum Creatinine (mg/dL) | 1.23 | 1.90 \pm 1.89 |
| Time-to-initiation of abx (Δ TI) | 10.95 | - |

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Results continued

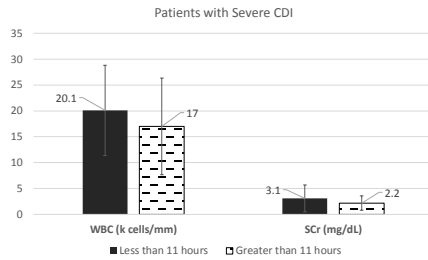
Patients with Severe CDI



| Parameter | Less than 11 hours | Greater than 11 hours |
|-------------|--------------------|-----------------------|
| Age | 69.7 | 69.3 |
| Weight (kg) | 85 | 86 |
| Height (in) | 69.2 | 68.7 |

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Results continued



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Results continued

| Outcome | Δ TTI <11 hrs | Δ TTI >11 hrs | p-value |
|----------------------|----------------------|----------------------|---------|
| Primary (#) | n=43 | n=42 | |
| 30-day mortality | 5 (11.6%) | 3 (7.1%) | 0.713 |
| Secondary (#) | | | |
| 30-day recurrence | 8 (18.6%) | 5 (11.9%) | 0.548 |
| History of CDI | 20 (46.5%) | 13 (30.1%) | 0.183 |

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Discussion

- Primary and secondary outcomes were not significant
- Study was underpowered to detect a significant 30-day mortality difference
 - Reviewed only 184 patients (needed 490)
- Mortality rates correlate well to published literature
 - ~5% overall mortality
 - ~9% mortality in severe CDI
- Study seems to trend towards the notion that sicker patients require earlier antibiotic intervention and might have increased rates of mortality and recurrence

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Assessment Question #1

Severe CDI is classified by presence of one or more of the following (choose all that apply):

- Leukocytosis (white blood cell count $\geq 15,000$ cells/mL)
- Fever (temperature $\geq 37^{\circ}$ C)
- Serum creatinine > 1.5 mg/dL
- Positive cultures

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Assessment Question #2

Which of the following antimicrobial regimens is appropriate for severe, non-fulminant CDI:

- Vancomycin 125mg PO four times daily
- Vancomycin 500mg PO four times daily
- Vancomycin 1g IV daily
- Metronidazole 500mg IV three times daily

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Thank You

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Questions?

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References

- Rupnik M, Wilcox MH and Gerding DN. *Clostridium difficile* infection: new developments in epidemiology and pathogenesis. *Nature Reviews Microbiology* 2009;7: 526–536
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