A Large Prospective North American Epidemiologic Study of Hospital-Associated *C. Difficile* Colonization & Infection

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Abstract

BACKGROUND: *Clostridium difficile* infection (CDI) is the most common cause of infectious diarrhea occurring in hospitalized patients in developed countries. Increases in the incidence and severity of CDI in some centers have been linked to epidemic virulent CD strains, an aging population, and increased use of certain antibiotics. Although CD is considered an emerging pathogen, there are little data on the natural history of CD acquisition, colonization and infection in the healthcare setting.

METHODS: A multi-site, hospital-based prospective study is being conducted in the U.S. and Canada. Patients admitted to general medical and surgical units, on antibiotics, with no CDI diagnosis in the past 6 months, and over 60 years of age are eligible for enrollment. Patients who are negative for CD colonization at enrollment are followed prospectively to examine the timing of CD acquisition, and the rates of asymptomatic carriage and symptomatic CDI. Patients are followed for 30 days post discharge or 60 days in the hospital, whichever comes first. Stool specimens or rectal swabs are collected every 3 days from enrollment to discharge. Stool specimens are also tested for CD toxins A and B if patients develop diarrhea. CDI cases are defined as patients with no CDI diagnosis and culture-negative for CD at the time of enrollment who later develop a diagnosis of CDI. Asymptomatic carriers are those patients with no CDI diagnosis and culture-negative for CD at the time of enrollment who later develop a positive stool culture for CD, but do not develop CDI during follow-up. *Hin*dIII restriction endonuclease analysis (REA) typing was performed on all cultured CD isolates.

RESULTS: As of April 2010, 570 patients were enrolled in the study; 57 (10%) of those patients were colonized with CD at enrollment. In the 513 patients who were negative for CD at enrollment, 11 asymptomatic carriers (2.14%) and 6 CDI cases (1.17%) were identified. The average age of CDI cases was 79.2 years versus 74.8 years for asymptomatic carriers (p=0.28). Four of the 6 (67%) CD isolates from CDI cases were REA group BI, compared to 1 of the 11 isolates (9%) from the carriers (p=.09). From the time of admission, the mean time to colonization was 9.8 days (range 3-31; cases: 10.3 days and asymptomatic carriers: 9.5 days).

CONCLUSION: Data from this large epidemiologic CDI study will help further our understanding of the timing of healthcare-associated CD acquisition and symptomatic infection, as well as assist in the planning of future clinical trials designed to evaluate candidate preventive and therapeutic CDI agents.

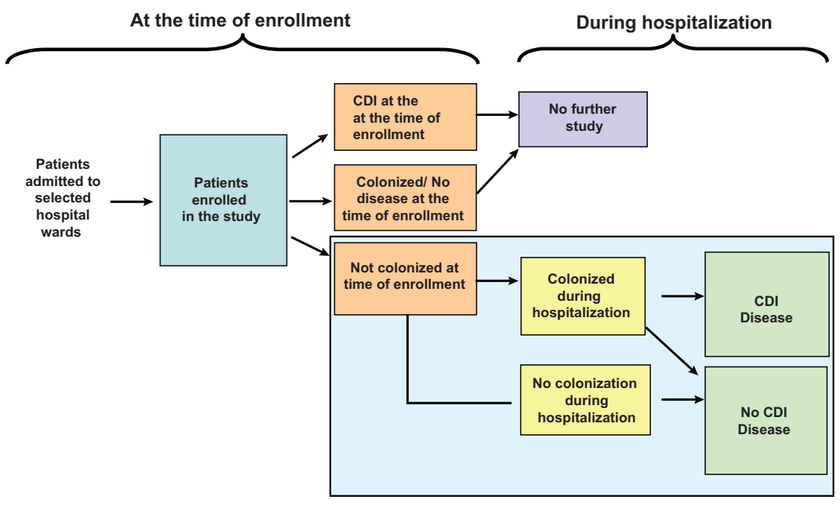
Background

- *Clostridium difficile* infection (CDI) is the most common cause of infectious diarrhea occurring in hospitalized patients in developed countries.
- Exposure to CD in the healthcare setting may lead to asymptomatic colonization or symptomatic CDI (from mild diarrhea to life-threatening colitis).
- Increases in the incidence and severity of CDI in some centers have been linked to epidemic virulent CD strains, an aging population, inadequate infection control, and increased use of certain antibiotics.
- Although CD is considered an emerging pathogen, there are little data on the natural history of CD acquisition, colonization and infection in the healthcare setting.
- A study was designed to describe CD acquisition, colonization and infection in the hospital setting.

Methods

- Study Design
  - A multi-site, hospital-based prospective cohort study being conducted in the U.S. and Canada.
- Study Population
  - Patients admitted to general medical and surgical units, on antibiotics, and over 60 years of age are enrolled in the study.
  - Patients negative for CD colonization at enrollment are followed prospectively to determine the timing of possible CD acquisition, and the rates of CD colonization and symptomatic CDI.
  - All patients provided informed consent.
  - Definitions
    - **CDI case definition:** CDI cases are defined as patients without a CDI diagnosis and culture-negative for CD at the time of enrollment who later develop a diagnosis of CDI.
    - **Asymptomatic carrier definition:** Asymptomatic carriers are those patients without a CDI diagnosis and culture-negative for CD at the time of enrollment who later develop a positive stool culture for CD while hospitalized, but do not develop CDI during follow-up.
- Sample Size
  - Targeted study enrollment: ~1250 patients in order to accrue 53 CDI cases and 53 asymptomatic carriers
- Patient Follow-up
  - Patients are being followed until 60 days post enrollment or 30 days post-hospital discharge, whichever comes first.
  - Patient enrollment started February 2009 and will continue until expected number of cases and asymptomatic carriers are accrued
- Specimen Collection and Testing
  - Stool specimens or rectal swabs are collected every 3 days from enrollment to hospital discharge
  - Stool specimens are tested for CD toxin if patients develop diarrhea. Anaerobic stool culture tests for CD on selective TCCFA (cycloserine-cefoxitin-fructose agar with added taurocholate) media is being used to determine if colonization occurs in the study population and to confirm local CDI diagnoses at hospitals
  - *Hin*dIII restriction endonuclease analysis (REA) typing is performed on all cultured CD isolates.
- Data Analysis
  - Descriptive statistics are provided for demographic characteristics, medical history, hospital ward at enrollment, reason for admission, and time to colonization/disease
  - P-values are calculated to assess statistical differences between CDI cases and asymptomatic carriers
    - Fishers Exact test is used for categorical variables
    - T-test or Kruskal Wallis test is used for normally and non-normally distributed continuous variables, respectively

Figure 1. *C. Difficile* Related Outcomes for Patients Enrolled in the Study



Results

Table 1. Baseline Demographic Characteristics of Patients Enrolled as of April 2010 (n=589)

Characteristic		All Patients (n=589)	CDI Cases (n=6)	Asymptomatic Carriers (n=11)	Non-Colonized (n=572)	P-value*
Age	Mean (SD)	73.5 (8.0)	79.2 (8.6)	74.8 (7.2)	73.4 (8.0)	p= 0.28
Age Category	< 65	67 (11.4)	0	0	67 (11.7)	p= 0.72
	65-69	147 (25.0)	1 (16.7)	3 (27.3)	143 (25.0)	
	70-74	119 (20.2)	1 (16.7)	3 (27.3)	115 (20.1)	
	75-79	111 (18.9)	2 (33.3)	2 (18.2)	107 (18.7)	
	80-84	86 (14.6)	0	2 (18.2)	84 (14.7)	
	>=85	59 (10.0)	2 (33.3)	1 (9.1)	56 (9.8)	
Sex	Male	322 (54.7)	4 (66.7)	5 (45.5)	313 (54.7)	p = 0.62
Ethnicity	Hispanic or Latino	42 (7.1)	0	0	42 (7.3)	p= NA
	Non Hispanic or Latino	547 (92.9)	6 (100)	11 (100)	530 (92.7)	
Race	White	491 (83.4)	5 (83.3)	11 (100)	475 (83.0)	P=0.35
	Black	81 (13.8)	1 (16.7)	0	80 (14.0)	
	Asian	9 (1.5)	0	0	9 (1.6)	
	American Indian or Alaska Native	1 (0.2)	0	0	0 (0.2)	
	Other	7 (1.2)	0	0	7 (1.2)	

* P-values are measuring statistical differences between CDI cases and asymptomatic carriers

Table 2. Baseline Medical History of Patients Enrolled as of April 2010 (n=589)

Characteristic		All Patients (n=589)	CDI Cases (n=6)	Asymptomatic Carriers (n=11)	Non-Colonized (n=572)	P-value*
Albumin (g/gL)	Mean (SD)	3.4 (0.6)	3.3 (0.5)	3.2 (0.7)	3.4 (0.6)	p=0.77
	Missing, n (%)	76 (12.9)	0	1 (9.0)	75 (13.1)	
WBC (10^9/L)	Median	9.2 (0.1- 87.0)	13.1 (0.1-31.1)	7.7 (6.0-25.9)	9.2 (0.2-87.0)	p=0.27
	Missing, n (%)	2 (0.4)	0	0	2 (0.3)	
History of CDI in the past year	Yes	0	0	0		NA
	No	586 (99.4)	6 (100.0)	11 (100.0%)	569 (99.5)	
	Missing	3 (0.6)	0	0	3 (0.5)	
Modified Horn's Index	Level 1 – Low	221 (37.7)	2 (33.3)	0	219 (38.5)	p=0.12
	Level 2 – Moderate	235 (40.1)	3 (50.0)	7 (63.6)	225 (39.5)	
	Level 3 – Major	119 (20.3)	1 (16.7)	4 (36.4)	114 (20.0)	
	Level 4 – Extreme	10 (1.7)	0	0	10 (1.8)	
	Missing, n (%)	1 (0.2)	0	0	1 (0.2)	
Charlson Comorbidity Index	Median (range)	1.0 (0-19.0)	0.5 (0-4.0)	3.0 (0-7.0)	1.0 (0-19.0)	p=0.07
	Missing, n (%)	2 (0.4)	0	0	2 (0.3)	

* P-values are measuring statistical differences between CDI cases and asymptomatic carriers

Table 3. Hospital Ward and Primary Reason for Admission at Baseline Visit for CDI cases and Asymptomatic Carriers

	CDI Patients (n=6)	Asymptomatic Carriers (n=11)
Hospital Ward	**n (%)**	**n (%)**
Cardiology	0 (0.0)	2 (18.2)
General Medical	1 (16.7)	7 (63.6)
Pulmonary	2 (33.3)	2 (18.2)
Oncology/Hematology	1 (16.7)	0 (0.0)
Orthopedic	1 (16.7)	0 (0.0)
Emergency	1 (16.7)	0 (0.0)
Primary Reason for Admission	**n (%)**	**n (%)**
Cellulitis	0 (0.0)	4 (36.4)
Chest Pain	0 (0.0)	1 (9.1)
OA Right Knee	0 (0.0)	1 (9.1)
Shortness of Breath/COPD	1 (16.7)	1 (9.1)
Weakness	0 (0.0)	1 (9.1)
Bacterial Pneumopathy	0 (0.0)	1 (9.1)
Pneumonia	1 (16.7)	2 (18.2)
Altered Mental State	1 (16.7)	0 (0.0)
Fever	1 (16.7)	0 (0.0)
OA Right Hip	1 (16.7)	0 (0.0)
Sepsis	1 (16.7)	0 (0.0)

OA=Osteoarthritis
COPD=Chronic Obstructive Pulmonary Disease

Table 4. Cumulative Incidence of CDI and Asymptomatic Colonization and Time to Colonization/Disease

	CDI Patients (n=6)	Asymptomatic Carriers (n=11)	P-value
Cumulative Incidence	6/589 = 1.0%	11/589 = 1.9%	
Mean (Median) Time in Days to Colonization	10.3 (11.0)	9.5 (8.0)	0.82
Mean (Median) Time in Days to Disease	14.7 (11.5)	—	
Mean Hospitalization Time in Days	26.2	21.8	0.69

Table 5. REA Group for CDI Cases and Asymptomatic Carriers

	CDI Patients (n=6)	Asymptomatic Carriers* (n=11)	P-value**
REA Group			
BI	4 (66.7)	1 (9.1)	0.09
Y	1 (16.7)	3 (27.3)	
DH1	0 (0.0)	2 (18.2)	
Non-Specific	1 (16.7)	9 (81.8)	

* 1 asymptomatic carrier had both Group Y and BI strains detected; 2 asymptomatic carriers had Group Y and a non-specific REA group detected; and 1 asymptomatic carrier had 1 DH1 and a non-specific REA group detected
**Comparison is for BI versus non BI REA group for CDI cases and asymptomatic carriers

Discussion

- Preliminary data indicate that patients with CDI are more likely to have a higher WBC count and are more likely to have BI strains compared with asymptomatic carriers. However, due to small samples sizes, these comparisons did not reach statistical significance.
- Data from this large epidemiologic study on the natural history of CDI will help further our understanding of the timing of hospital-associated CD acquisition and symptomatic infection.
- They will also assist in the planning of future clinical trials designed to evaluate candidate preventive and therapeutic CDI agents by providing cumulative CDI incidence rates, a better understanding of underlying disease conditions in CDI cases, and elucidating risk factors for CDI and asymptomatic colonization.

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