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Risk Factors for the Development of *Clostridioides difficile* Infection in Patients Colonized with *Clostridioides difficile*

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ABSTRACT

BACKGROUND
Asymptomatic patients colonized with *Clostridioides difficile* are at risk of progressing to *C. difficile* infection (CDI), but the risk factors associated with progression are poorly defined.

OBJECTIVE
The objectives of this study were to identify the prevalence and risk factors to progression of hospital-onset CDI (HO-CDI) among colonized patients.

METHODS
This was a retrospective cohort study conducted at a large academic medical center. Patients were included if they were ≥ 18 years of age and colonized with *C. difficile*, detected via polymerase chain reaction (PCR) on a rectal swab collected on admission from 2017 to 2020. Patients were excluded if they had prior CDI, CDI symptoms on admission, neutropenia, prior rectal surgery, or were hospitalized for less than 24 hours. CDI toxin positive patients were matched 1:3 to CDI negative patients using PCR colonization test date. The primary endpoints were the prevalence of HO-CDI and the risk factors for progression to HO-CDI. Descriptive analyses were used to describe the population and univariate analysis was used to determine risk factors associated with HO-CDI.

RESULTS
A total of 2,150 patients were colonized with *C. difficile*; 109 CDI toxin positive patients were matched to 327 CDI toxin negative patients. 321 patients were included and 3.2% (69/2150) developed HO-CDI. The mean age was 64 (± 16.1) and 177 patients (55.1%) were male. Intensive care unit (ICU) admission (OR 4.75, 95% CI: 2.37 – 9.52; *P* = < 0.0001), hospitalization within six months (OR 2.72, 95% CI: 1.11 – 6.69; *P* = 0.03), diabetes mellitus (OR 2.10, 95% CI: 1.09 – 4.1; *P* = 0.03), cirrhosis (OR 3.16, 95% CI: 1.19 – 8.43; *P* = 0.0214), immunosuppressant use (OR 3.73, 95% CI: 1.42 – 9.83; *P* = 0.008), and increasing number of antibiotic classes at risk for CDI (OR 1.53, 95% CI: 1.07 – 2.2; *P* = 0.02) were associated with HO-CDI via preliminary multivariate analysis.

CONCLUSIONS
Progression to HO-CDI was uncommon among colonized patients at our institution. This data suggests that among hospitalized patients colonized with *C. difficile*, ICU admission, hospitalization within six months, diabetes mellitus, cirrhosis, receipt of immunosuppressants, and receipt of increasing number of antibiotic classes at risk for CDI are associated with HO-CDI.

OBJECTIVES

PRIMARY OBJECTIVE
To identify the prevalence of hospital-onset CDI among patients colonized with *C. difficile*.

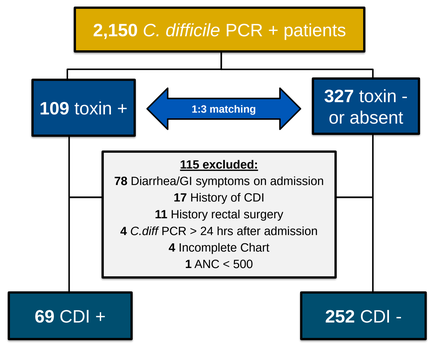
SECONDARY OBJECTIVE
To identify risk factors associated with progression to hospital-onset CDI among patients colonized with *C. difficile*.

METHODS

- Single center, retrospective cohort study of patients admitted with a positive *C. difficile* PCR rectal swab on admission from November 2017 to December 2020
- *C. difficile* toxin positive patients were matched to toxin absent or negative patients in a 1:3 ratio based on PCR rectal swab test date
- **Inclusion criteria**: Age ≥ 18 years of age, Positive *C. difficile* PCR rectal swab collected on admission
- **Exclusion Criteria**: History of CDI, diarrhea or other severe gastrointestinal symptoms on admission, hospitalized < 24 hours, *C. difficile* PCR screen completed > 24 hours after admission, neutropenia (ANC < 500) on admission, history of rectal surgery, pregnancy
- Univariate analysis to determine risk factors associated with HO-CDI; *P*-value < 0.05 statistically significant
- Associations between outcomes and explanatory variables measured by odds ratios (OR) with a 95% Confidence Interval

RESULTS

FIGURE 1: FLOW DIAGRAM OF PATIENT SELECTION



RESULTS

TABLE 1: BASELINE CHARACTERISTICS

Characteristic – no. (%)	CDI (n = 69)	No CDI (n = 252)	*P*-value
Male Sex	36 (52.2)	141 (56)	0.5875
Age, years, (SD)	66.2 (± 14.1)	63.4 (± 16.5)	0.1992
BMI – kg/m^2, (SD)	25.9 (± 5.6)	27.5 (± 8.8)	0.1410
Hospital LOS – days, (SD)	22.7 (± 34.7)	8.9 (± 13.3)	**< 0.0001**
Hospital LOS Pre-CDI – days, (SD)	7.4 (± 11.7)	8.9 (± 13.3)	0.3827
Hospital LOS Post-CDI – days, (SD)	15.3 (± 30)	8.9 (± 13.3)	**0.0097**
Admission Disposition			
Home	41 (59.4)	184 (73)	**0.0373**
Other health-care institution (SNF + OSH)	28 (40.6)	68 (27)	**0.0377**
Ethnicity			
Not Hispanic or Latino	59 (85.5)	217 (86.1)	1
Caucasian	1 (1.5)	4 (1.6)	1
Hispanic or Latino	9 (13)	31 (12.3)	0.8389
ICU Admission	48 (69.6)	79 (31.3)	**< 0.0001**
ICU LOS – days, (SD)	9.9 (± 10.6]	7.6 (± 16.2)	0.2656
Recent Hospitalization within 6 Months	61 (88.4)	137 (54.4)	**< 0.0001**

SD: Standard Deviation; **SNF**: Skilled Nursing Facility; **OSH**: Outside Hospital; **ICU**: Intensive Care Unit; **LOS**: Length of Stay

TABLE 2: UNIVARIATE ANALYSIS OF DEMOGRAPHIC AND CLINICAL RISK FACTORS

Characteristic – no. (%)	CDI (n = 69)	No CDI (n = 252)	OR [95% CI]	*P*-value
Male Sex	36 (52.2)	141 (56)	0.86 [0.50 – 1.50]	0.5762
Age, years, (SD)	66.2 (± 14.1)	63.4 (± 16.5)	1.01 [0.99 – 1.04]	0.2908
Admission Disposition				
Home	41 (59.4)	184 (73)	0.54 [0.31 – 0.94]	**0.03**
Other health-care institution (SNF + OSH)	28 (40.6)	68 (27)	1.85 [1.06 – 3.22]	**0.03**
ICU Admission	48 (69.6)	79 (31.3)	5 [2.81 – 8.92]	**< 0.0001**
Recent Hospitalization within 6 Months	61 (88.4)	137 (54.4)	6.4 [2.94 – 13.93]	**< 0.0001**
Malignancy	20 (29)	37 (14.7)	2.37 [1.27 – 4.44]	**0.0069**
Diabetes Mellitus	35 (50.7)	76 (30.2)	2.38 [1.38 – 4.10]	**0.002**
Cirrhosis	12 (17.4)	18 (7.1)	2.74 [1.25 – 6.00]	**0.01**
Asthma	1 (1.5)	20 (7.9)	0.17 [0.02 – 1.30]	0.09
COPD	14 (20.3)	42 (16.7)	1.27 [0.71 – 2.26]	0.42
ESRD on HD	53 (76.8)	108 (42.9)	1.53 [0.77 – 3.03]	0.23
CKD Stage III+	14 (20.3)	36 (14.3)	1.34 [0.78 – 2.32]	0.29
Congestive Heart Failure	28 (40.6)	85 (33.7)	1.27 [0.71 – 2.26]	0.47
Hypertension	22 (31.9)	68 (27)	1.28 [0.68 – 2.40]	0.44
HIV	2 (2.9)	5 (2)	1.47 [0.28 – 7.77]	0.65
Inflammatory Bowel Disease	42 (60.9)	60 (23.8)	2.52 [0.69 – 9.21]	0.1611
Prior Gastrointestinal Surgery	17 (24.6)	52 (20.6)	1.26 [0.67 – 2.35]	0.4739

TABLE 3: UNIVARIATE ANALYSIS OF MEDICATION REALTED RISK FACTORS

Medication Related Variable – no. (%)	CDI (n = 69)	No CDI (n = 252)	OR [95% CI]	*P*-value
Immunosuppressant Use	15 (21.7)	20 (7.9)	3.22 [1.55 – 6.70]	**0.002**
PPI During Admission	44 (63.8)	124 (49.2)	1.82 [1.05 – 3.15]	**0.03**
PPI Prior to admission	31 (44.9)	80 (31.7)	1.75 [1.02 – 3.02]	**0.043**
Composite PPI Use	48 (69.6)	138 (54.8)	1.89 [1.07 – 3.34]	**0.0287**
Opioid Use During Admission	54 (78.2)	175 (69.4)	1.58 [0.84 – 2.98]	0.15
Chronic Steroid Use	10 (14.5)	22 (8.7)	1.77 [0.80 – 3.95]	0.16
Composite Antibiotic Use*	65 (94.2)	220 (87.3)	2.36 [0.81 – 6.93]	0.117
Antibiotic Use Within 3 Months	53 (76.8)	108 (42.9)	4.42 [2.39 – 8.15]	**< 0.0001**
Antibiotic Use During Admission	59 (85.5)	194 (77)	1.76 [0.85 – 3.67]	0.1284
Number of Antibiotic Classes at Risk for CDI†				
0	4 (5.8)	40 (15.9)	*Ref*	*Ref*
1	11 (15.9)	83 (32.9)	1.33 [0.40 – 4.42]	0.6469
2	12 (17.4)	69 (27.4)	1.74 [0.53 – 5.76]	0.3648
3 or more	42 (60.9)	60 (23.8)	7.00 [2.33 – 21.05]	**0.0005**

*Composite of antibiotic use within 3 months and during inpatient admission; **PPI**: Proton-pump inhibitor; †: penicillins, β-Lactam/β-Lactamase inhibitor, cephalosporins, carbapenems, fluoroquinolones, aminoglycosides, macrolides, trimethoprim-sulfamethoxazole, & clindamycin

FIGURE 2: FOREST PLOT OF ANTIBIOTIC USE AS RISK FACTORS

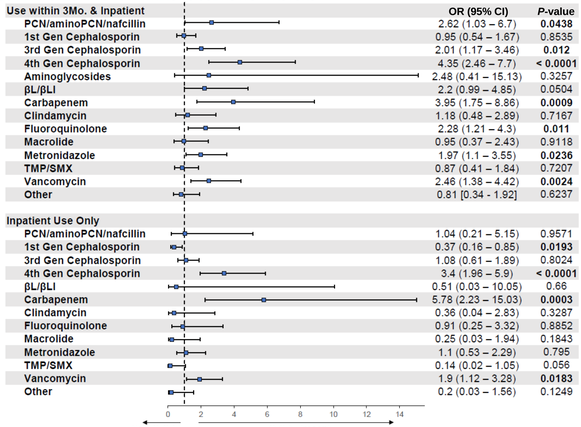


TABLE 4: PRELIMINARY MULTIVARIATE ANALYSIS OF RISK FACTORS

Characteristic	Risk of CDI	
	Adj. OR [95% CI]	*P*-value
Age	1.01 [0.99 – 1.04]	0.2908
Admission from Home	0.79 [0.29 – 2.15]	0.6469
Admission from SNF/OSH	2.28 [0.97 – 5.37]	0.0602
ICU Admission	4.75 [2.37 – 9.52]	**< 0.0001**
Recent Hospitalization within 6 Months	2.72 [1.11 – 6.69]	**0.029**
Malignancy	2.06 [0.88 – 4.83]	0.0965
Diabetes Mellitus	2.10 [1.09 – 4.10]	**0.0273**
Cirrhosis	3.16 [1.19 – 8.43]	**0.0214**
Medication Related Risk Factors		
Immunosuppressant Use	3.73 [1.42 – 9.83]	**0.0076**
PPI prior to admission	1.64 [0.84 – 3.19]	0.1466
Opioid Use During Admission	1.22 [0.55 – 2.68]	0.63
No. of Abx Classes at Risk for CDI*	1.53 [1.07 – 2.20]	**0.0199**
Composite Antibiotic Use	1.17 [0.34 – 4.01]	0.8025

*Per 1 class increase on a scale of 0 to ≥ 3

CONCLUSIONS

- 3.21% of *C. difficile* colonized patients progressed to HO-CDI.
- ICU admission, hospitalization with 6 months, diabetes mellitus, cirrhosis, immunosuppressant use, and receipt of increasing number of antibiotic classes at risk for CDI were associated with progression to HO-CDI among patients colonized with *C. difficile*.
- These finding identify variables stewardship programs can target to potentially decrease the risk of progression to HO-CDI.

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