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Abstract 495

Predictors of *C. difficile* Infection and Impact of Primary Prophylaxis among Asymptomatic *C. difficile* Colonized Patients: A Cross Sectional Study

D. Poirier, MD, PhD[1,2]; P. Gervais, MD[1,2,3]; M. Fuchs PhD[4,5]; J.F. Roussy, MD[1,2,3]; B. Paquet-Bolduc, RN, MPA[3]; S. Trottier, MD[1,2,3]; J. Longtin, MD[1,2,6]; V.G. Loo, MD[7,8]; Y. Longtin, MD[7,9]

1) Laval University Faculty of Medicine, Quebec City, Canada; (2) Infectious Diseases Research Center, Centre Hospitalier Universitaire de Québec, Quebec City, Canada; (3) Quebec Heart and Lung Institute, Canada ; (4) Centre de recherche sur le cancer de l'Université Laval, Canada; (5) Centre de recherche du CHU de Québec-Université Laval, Canada; (6) Laboratoire de santé publique du Québec, Canada; (7) McGill University faculty of medicine, Canada; (8) McGill University Health Centre, Canada; (9) Jewish General Hospital, Montreal, Canada

Yves Longtin, MD, FRCPC. Email: Yves.Longtin@mcgill.ca

BACKGROUND

- *Clostridium difficile* infections (CDI) are the most common healthcare-associated infections in North America, causing 453,000 cases per year in the U.S. and 29,000 deaths
- Physiopathology is a 2-step process: (1) Colonization with toxigenic strain, followed by (2) progression to CDI.
- A systematic review evaluated the risk of CDI among *C. difficile* (CD) colonized patients at 22% (range, 4% to 71%)
- Few studies have investigated risk factors for CDI specifically among CD colonized patients
- Such study could help improve our understanding of the pathogenesis, and potentially identify strategies to prevent CDI among these patients
- Primary prophylaxis to prevent CDI among CD carriers has never been directly studied so far

OBJECTIVES

① Determine characteristics of CD colonized patients
② Quantify the risk of progression to CDI
③ Identify predictors of disease onset
④ Investigate the potential benefit of primary prophylaxis to prevent CDI

METHODS

- Retrospective cohort study, single center. Quebec Heart and Lung institute instituted a CD screening program on hospital admission in Nov. 2013
- All patients found to be colonized by CD between Nov 2013 and Jan 2017 were identified; Only first admission per patient; Patients with history of CDI were excluded
- CD colonization detected by amplification of the tcdB gene by commercial PCR on a rectal swab; CDI diagnosed based on clinical symptoms combined with single-step PCR
- Primary prophylaxis defined as reception of oral vancomycin or metronidazole in asymptomatic patients; Decision to start prophylaxis and choice of regimen left at the discretion of the treating physician
- Factors associated with hospital-onset CDI (HO-CDI) investigated by univariate and multivariate logistic regression (forced entry model)
- Secondary outcomes:
  - Complications (mortality, admission to ICU, colectomy)
  - Long-term evidence of CDI (i.e. post-discharge)
  - Impact of primary prophylaxis

RESULTS

- 19,112 patients screened; 960 (5%) CD colonized patients detected; 513 (53.4%) met inclusion criteria (45% female, ave. age 71)
- 63% received ATB during their hospital stay; median duration of therapy, 7 days
- 39/513 (7.6%) diagnosed with HO-CDI;
  - Median delay between admission and CDI: 4 days (range, 0-27 d)
  - 5/39 (12.8%) admitted to ICU
  - 1 toxic megacolon, no colectomy
  - 11 deaths within 30 days (case fatality, 28%)
  - Attributable mortality: 7/39 (18%)
- An additional 17 patients without HO-CDI had evidence of CDI following discharge, for an overall CDI risk of 10.9% (56/513)
- Characteristics of patients and univariate analysis in **Tables 1 and 2**
- Variables independently associated with HO-CDI on **Table 3**
  - Increasing length of stay, cirrhosis, exposure to multiple classes of antibiotics, reception of opioids and of probiotics associated with increased risk of HO-CDI (p<0.05 for each)
  - Use of laxatives associated with decreased risk of HO-CDI (p=0.04)
  - Age, use of PPI and primary prophylaxis NOT associated with risk of HO-CDI among CD colonized patients
- Clinical characteristics of patients who received a primary prophylaxis are described in **Table 4**

Table 1. Clinical Characteristics and Outcome of *C. difficile* colonized patients

Explanatory variable	Overall population n=513	No CDI n=474	CDI n=39	OR (95% CI)	P-value
Demographic characteristics					
Mean Age - years (SD)	71 (15.9)	70.9	71.4	1.002 (0.981-1.023)	0.84
Female Sex (%)	45.6	214 (45.1)	20 (51.3)	0.78 (0.41-1.50)	0.78
Mean length of stay, days (SD)	11.3 (13.3)	10.5	20.9	1.035 (1.018-1.053)	<0.001
Provenance					
Home (%)	437 (85.2)	408 (86.1)	29 (74.3)	Ref	Ref
Other healthcare institution (%)	76 (14.8)	66 (13.9)	10 (25.6)	2.13 (0.99-4.58)	0.052
Hospitalization QHLI within last year (%)	275 (53.6)	250 (52.7)	25 (64.1)	1.60 (0.81-3.15)	0.175
Comorbidities and past medical history					
Previous colectomy (%)	25 (4.9)	24 (5.1)	1 (2.6)	0.49 (0.07-3.74)	0.50
Previous gastrointestinal surgery (%)	72 (14.0)	68 (14.3)	4 (10.3)	0.68 (0.23-1.98)	0.48
Appendicectomy	12 (2.3)	12 (2.5%)	0 (0)	0	1.0
Biliary tract	18 (3.5)	16 (3.4)	2 (5.1)	1.55 (0.34-6.99)	0.57
Bariatric	7 (1.4)	7 (1.4)	0 (0)	0	1.0
Colon	29 (5.7)	28 (5.9)	1 (2.6)	0.42 (0.06-3.17)	0.40
Gastric	8 (1.6)	7 (1.5)	1 (2.6)	1.76 (0.21-14.64)	0.60
Other	9 (1.8)	9 (1.9)	0	0	1.0
Malignancy (%)	106 (20.7)	97 (20.5)	9 (23.1)	1.17 (0.54-2.54)	0.70
COPD (%)	188 (36.6)	175 (36.9)	13 (33.3)	0.85 (0.43-1.71)	0.66
Diabetes mellitus (%)	165 (32.2)	154 (32.5)	11 (28.2)	0.82 (0.39-1.68)	0.58
Renal insufficiency a (%)	172 (33.5)	159 (33.5)	13 (33.3)	0.99 (0.50-1.98)	0.98
Cirrhosis (%)	20 (3.9)	16 (3.4)	4 (10.3)	3.27 (1.04-10.31)	0.04
Heart failure[b] (%)	129 (25.1)	118 (24.9)	11 (28.2)	1.19 (0.57-2.45)	0.65
Coronary artery disease (%)	242 (47.2)	222 (46.8)	20 (51.3)	1.19 (0.62-2.30)	0.59
Immune suppressive disease (%)	31 (6.0)	30 (6.3)	1 (2.6)	0.39 (0.05-2.93)	0.36

NOTE. Data are no. of patients with characteristic/ no. of patients with information available (%), unless otherwise specified.
CDI: Clostridium difficile infection; IQR: Interquartile range; SD, standard deviation; QHLI, Quebec Heart and Lung Institute; PCR, detection of Toxin B gene tcdB by polymerase chain reaction; EIA/CCA, detection of glutamate dehydrogenase antigen and ToxA/B by enzyme immunoassay or cell culture cytotoxicity assay; OR, odds ratio; CI, confidence interval; COPD: chronic obstructive pulmonary disease; ICU, intensive care unit; WBC, white blood cell; log10 CFU/g: colony-forming unit per gram of stool (logarithmic scale); n/a: not available.
a Defined as glomerular filtration rate <30 mL/min/1.73m2
b Defined as an ejection fraction <50%

Table 2. Medication and Outcome of *C. difficile* colonized patients

Explanatory variable	Overall population n=513	No CDI n=474	CDI n=39	OR (95% CI)	P-value
Medication					
Antiperistaltics	13 (2.5)	13 (2.8)	0 (0)	0	1.0
Opioids	204 (39.8)	180 (38.0)	24 (61.5)	2.6 (1.33-5.11)	0.005
Laxatives	208 (40.5)	194 (40.9)	14 (35.9)	0.81 (0.41-1.59)	0.54
Proton pump inhibitors	313 (61.0)	285 (60.1)	28 (71.8)	1.55 (0.82-3.47)	0.16
Immunosuppressive drug use[c] (%)	191 (37.2)	176 (37.1)	15 (38.5)	1.06 (0.54-2.07)	0.87
Probiotics	46 (9.0)	38 (8.0)	8 (20.5)	2.95 (1.27-6.88)	0.01
Systemic antibiotics					
Systemic antibiotics within 3 months of admission	185 (36.1)	170 (35.9)	15 (38.5)	1.12 (0.57-2.19)	0.75
Systemic antibiotics during hospital stay	323 (63.0)	291 (61.4)	32 (82.1)	2.88 (1.24-6.65)	0.01
Median duration of antibiotic therapy, days (IQR)	7 (3-13)	7.0 (3-12)	10 (4-21)	1.02 (0.99-1.04)	0.06
Types of antibiotics					
Penicillins, aminopenicillins and cloxaxillin	20 (3.9)	18 (3.8)	2 (5.1)	1.37 (0.31-6.13)	0.68
B-lactams with B-lactamase inhibitors	126 (24.6)	106 (22.4)	20 (51.3)	3.65 (1.88-7.10)	<0.001
1st generation cephalosporins	62 (12.1)	53 (11.2)	9 (23.1)	2.38 (1.07-5.29)	0.03
2nd generation cephalosporins	1 (0.2)	1 (0.2)	0 (0)	0	1.0
3rd generation cephalosporins	68 (13.3)	61 (12.9)	7 (17.9)	1.48 (0.63-3.50)	0.37
Carbapenems	61 (11.9)	52 (11.0)	9 (23.1)	2.44 (1.10-5.41)	0.03
Quinolones	153 (29.8)	142 (30.0)	11 (28.2)	0.92 (0.45-1.90)	0.82
Aminoglycosides	20 (3.9)	19 (4.0)	1 (2.6)	0.63 (0.08-4.84)	0.66
Clindamycin	3 (0.6)	3 (06)	0 (0)	0	1.0
Macrolides	57 (11.1)	52 (11.0)	5 (12.8)	1.19 (0.45-3.19)	0.72
Vancomycin	39 (7.6)	35 (7.4)	4 (10.3)	1.43 (0.48-4.27)	0.52
Metronidazole	7 (1.4)	6 (1.3)	1 (2.6)	2.05 (0.24-17.49)	0.51
TMP-SMX	22 (4.3)	21 (4.4)	1 (2.6)	0.57 (0.07-4.33)	0.59
Linezolid	14 (2.7)	14 (3.0)	0 (0)	0	1.0
Daptomycin	2 (0.4)	1 (0.2)	1 (2.6)	12.45 (0.76-202.95)	0.08
Tigecycline	6 (1.2)	6 (1.3)	0 (0)	0	1.0
Others[d]	14 (2.7)	13 (2.7)	1 (2.6)	0.93 (0.12-7.32)	0.95
No. of ATB classes at-risk for CDI[e]					
0	192 (37.4)	185 (39.0)	7 (17.9)	0.34 (0.15-0.79)	0.01
1	150 (29.2)	138 (29.1)	12 (30.8)	1.08 (0.53-2.20)	0.83
2	91 (17.7)	82 (17.3)	9 (23.1)	1.43 (0.66-3.14)	0.37
3 or more	80 (15.6)	69 (14.6)	11 (28.2)	2.31 (1.10-4.85)	0.03
ATB with activity against *C. difficile*[f]	60 (11.7)	55 (11.6)	5 (12.8)	1.12 (0.42-2.99)	0.82
ATB prophylaxis against CDI	17 (3.3)	16 (3.4)	1 (2.6)	0.79 (0.1-5.84)	0.79
ATB prophylaxis or ATB active against C. difficile	77 (15.0)	70 (14.8)	7 (17.9)	1.26 (0.53-2.97)	0.59

c > 10mg of prednisone (or equivalent) for > 2 consecutive weeks
d Includes Doxycyclin, aztreonam. nitrofurantoin, and colistin
e Includes all penicillins, cephalosporins, carbapenems, quionolones, aminoglycosides, macrolides, TMP-SMX and clindamycin
f Includes vancomycin, metronidazole, daptomycin, linezolid and tigecycline

Table 3. Factors associated with CDI among *C. difficile* colonized patients (multivariate analysis)

Characteristic	Risk of CDI		
	Adjusted OR	95% CI	P value
Basic demographics			
Age	1.00	0.976-1.024	0.99
Inter-institutional transfer	1.91	0.82-4.43	0.13
Length of stay	1.03	1.01-1.06	0.006
Cirrhosis	5.49	1.56-19.30	0.008
Medication			
Probiotics	2.75	1.07-7.06	0.04
Proton pump inhibitors	1.68	0.76-3.71	0.20
Laxatives	0.36	0.16-0.80	0.01
Opioids	2.78	1.32-5.82	0.007
No. of classes of at-risk antibiotics	1.45	1.05-2.03	0.02
Duration antibiotic treatment	0.998	0.967-1.031	0.93
CDI prophylaxis	0.36	0.04-3.10	0.35

Note. CI, confidence interval; OR, odds ratio.

Table 4. Characteristics and outcome of *C. difficile* colonized patients who received primary prophylaxis

Characteristic	CD carriers with Prophylaxis N=17
Average duration, days (SD)	13.2 (9.9)
Type of prophylaxis[a]	
Vancomycin PO	12 (71%)
Metronidazole PO/IV	7 (41%)
Reasons for use (% or answers)[b]	
Severity of co-morbid conditions	5 (29%)
Use of systemic antibiotics	3 (18%)
Unexplained fever and/or leucocytosis without gastrointestinal symptoms	2 (12%)
Abdominal distension	2 (12%)
C. difficile colonization without other apparent reason	8 (47%)
Outcome	
CDI during prophylaxis	0 (0%)
HO-CDI after discontinuation of prophylaxis	1 (5.9%)
CDI within 8 weeks of prophylaxis discontinuation	2 (12%)

a Total is >100% because more than 1 prophylactic regimen could be used
b Total is >100% because more than one reason could be provided to start a prophylaxis for a single given patient

DISCUSSION / CONCLUSIONS

- This study identifies several variables that are specifically associated with the risk of CDI among C. difficile carriers and is the largest of its kind so far
- Whether modifying these risk factors could decrease the risk of CDI should be further explored (e.g. antibiotic stewardship, opioid stewardship)
- No apparent benefit of primary prophylaxis

LIMITATIONS

- Single-center retrospective study
- Immune status unknown
- Use of prophylaxis at the discretion of treating physician
- Diagnosis of CD colonization and CDI based on single-step PCR

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REFERENCES

1. Lin HJ, Hung YP, Liu HC, et al. Risk factors for Clostridium difficile-associated diarrhea among hospitalized adults with fecal toxigenic C. difficile colonization. J Microbiol Immunol Infect **2015**; 48(2): 183-9.
2. Starr JM, Martin H, McCoubrey J, Gibson G, Poxton IR. Risk factors for Clostridium difficile colonisation and toxin production. Age Ageing **2003**; 32: 657-60