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Global Practice Variation in the Management of *Clostridioides difficile* Infections: An International Cross-Sectional Survey of Clinicians

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Background. *Clostridioides difficile* infections (CDIs) are associated with significant morbidity, mortality, and economic burden globally. International guidelines conflict on various aspects of management, so we conducted a clinician survey to evaluate global practice variability on CDI diagnosis, treatment, and prophylaxis to inform future clinical trials.

Methods. An anonymous online survey through REDCap was distributed through multiple channels. Attending physicians, infectious disease pharmacists, and fellows in infectious diseases or medical microbiology who had managed ≥3 cases of CDI in the preceding year were eligible. Responses were compared across continents by chi-square test.

Results. Three hundred fifty-nine survey responses were collected from 31 countries and 6 continents (North America 80.5%, Europe 11.7%, other continents 7.8%). A 2-step CDI diagnostic algorithm was used by 75.8% of respondents with heterogeneity in assay type. Similarly, there was significant variability in first-line agents for the treatment of first episodes and first recurrences of uncomplicated CDI and a lack of consensus on treatments for fulminant CDI. Secondary CDI prophylaxis during antibiotic re-exposure was most commonly used in North America (84.1%), followed by other continents (50.0%) and Europe (31.0%; $P < .001$). Oral vancomycin was the most frequently used agent (96.3%), with significant variability in the dose (125–500 mg daily) and duration (1–28 days; $P < .01$).

Conclusions. Substantial global variability exists with respect to CDI diagnosis, treatment, and secondary prophylaxis, likely due to divergent guidelines and a paucity of robust evidence. These findings highlight critical knowledge gaps and areas of clinical equipoise and underscore the need for further randomized controlled trials to establish harmonized international best practices for CDI.

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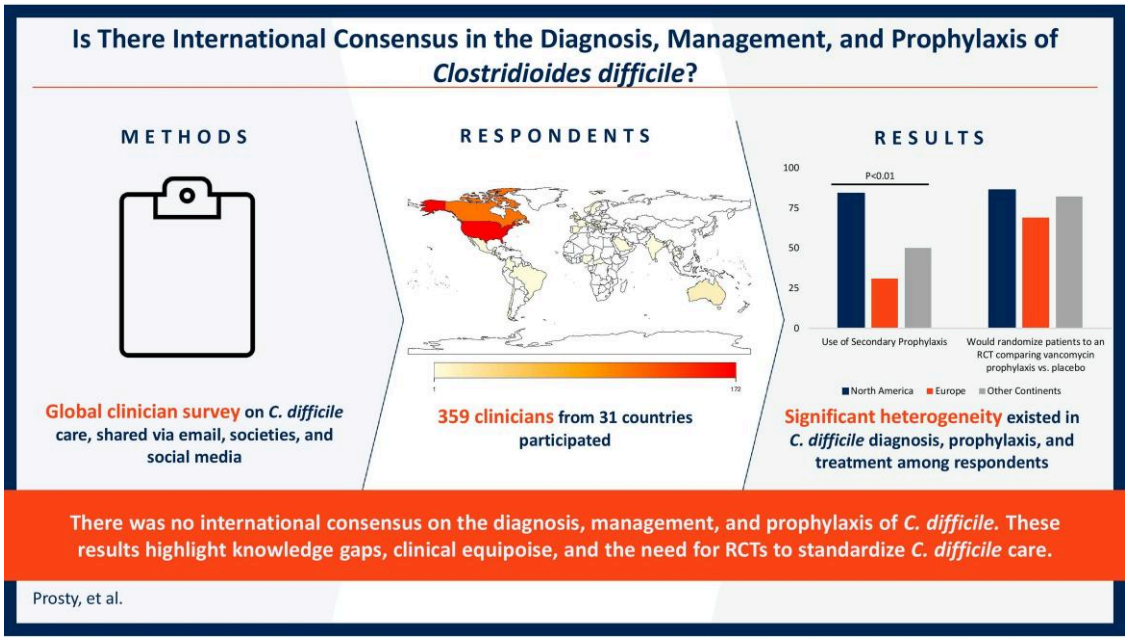
Graphical Abstract



Keywords. *Clostridioides difficile*; international; prophylaxis; survey; vancomycin.

Clostridioides difficile is a leading etiology of nosocomial infection, with an estimated global incidence of 49 cases/100 000 person-years, which corresponds to ~8 million cases total annually [1]. Up to 30% of cases of *Clostridioides difficile* infection (CDI) recur, and ~5% result in death [2]. The associated economic burden exceeds 6 billion dollars annually in the United States alone [3].

Multiple guidelines on the management of CDI exist, including those from the American College of Gastroenterology (ACG) [4], the Association of Medical Microbiology and Infectious Disease (AMMI) Canada [5], the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [6, 7], and the Infectious Diseases Society of America (IDSA) [8, 9]. While the guidelines are all based on similar evidence, recommendations are inconsistent across multiple aspects of CDI management including diagnostic testing, treatment of index episodes and recurrences, management of fulminant CDI, and the use of secondary CDI prophylaxis. (Supplementary Table 1). Conflicting recommendations across these fundamental components of CDI care imply a lack of international consensus and may identify potential knowledge gaps. However, it is unknown whether these variable recommendations translate to global differences in the management of CDI. A recent international survey identified wide practice variation in the treatment of *Staphylococcus aureus* bacteremia [10], and this helped inform the development of the *Staphylococcus aureus* Network Adaptive Platform (SNAP) trial [11]. In a similar manner, this cross-sectional survey aimed to assess various elements of clinician diagnosis and management of CDI globally, with the intent of identifying questions for a potential CDI platform trial. We hypothesize that there are significant geographic differences in CDI practice. Secondary CDI prophylaxis was the primary aim because there is a paucity of randomized controlled trials (RCTs) and only conflicting, low-quality observational data supporting this practice [12].

METHODS

Ethics and Consent

This cross-sectional survey was approved by the McGill University Health Centre research ethics board (2025-10917). Informed consent was implied by responding to the survey. Responses were entirely anonymous, voluntary, and without financial incentive.

Survey Design

This survey was administered through REDCap and adhered to the Consensus-Based Checklist for Reporting of Survey Studies (CROSS) reporting guidance [13]. The survey was designed to capture practices relating to (1) secondary CDI prophylaxis as the primary objective and (2) CDI diagnosis and management as the secondary objective. The survey was divided into 2 parts, 1 for each objective, disseminated through a single link, with an opt-out option for the second part to encourage more responses to the first. Anonymized demographic data were collected. Survey questions were conceived by identifying areas where

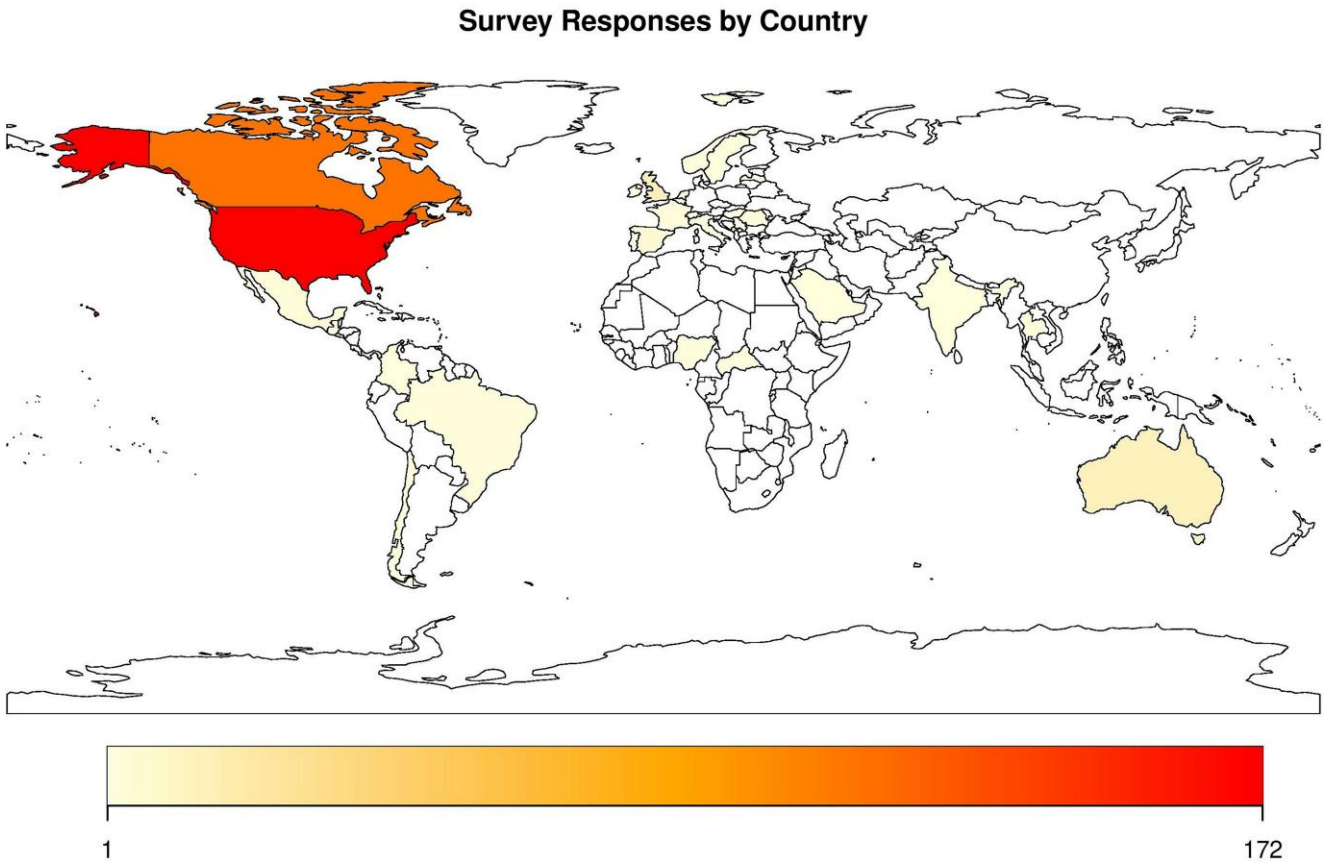


Figure 1. Geographic representation of survey respondents.

the ACG [4], AMMI [5], ESCMID [6], and IDSA [8, 9] CDI guidelines conflicted, where recommendations were based on weak evidence (Supplementary Table 1), or from personal observations of heterogeneous clinical practice. Drafts of survey questions circulated for 3 rounds of edits among the collaborators to optimize the survey's ease of use, pertinence, and readability. Participants were unable to abstain from answering questions but were able to answer "unsure" to opinion questions. A copy of the survey is available in Supplementary File 1.

Survey Eligibility

Physicians with an active unrestricted medical license (ie, attending physicians) in any specialty, infectious disease pharmacists, and fellows in infectious diseases and/or medical microbiology who had managed ≥3 adult cases of CDI in the preceding year were eligible to participate. The 3-case threshold was established to ensure a minimum level of experience, while still being inclusive of diverse perspectives. Trainees in other disciplines were ineligible.

Survey Distribution

The survey was available in both English and French. A publicly accessible link to the online REDCap survey was distributed through various channels including X (formerly Twitter), Bluesky, and infectious disease, gastroenterology, and internal medicine society websites, forums, and listservs. Participants were encouraged to share the link with colleagues. The survey remained open to responses from September 19, 2024, to December 1, 2024.

Statistical Analyses

Survey responses that did not enter their country of practice, were identical or ineligible, had incoherent responses to written questions, or straightlined (ie, selected the first option for all questions) were removed. Partially completed responses were retained as long as at least 1 nondemographics question was answered. Variables with missing data were omitted. Data were presented as proportions. Responses were grouped according to the respondent's continent and were compared by chi-square test. Because this was an exploratory analysis, we did not adjust for multiple hypothesis testing. All analyses were conducted in R (version 4.3.2; R Foundation for Statistical Computing, Vienna, Austria). A geographic representation of survey responses was rendered using *rworlmap* [14], and an alluvial plot of sequential treatment selection was generated using Raw Graphs 2.0 [15].

Table 1. Demographics of the Survey Participants

	North America n = 289, No. (%)	Europe n = 42, No. (%)	Other Continents n = 28, No. (%)	Total n = 359, No. (%)
Training				
Attending	241 (83.4)	28 (66.7)	25 (89.2)	294 (81.9)
Infectious disease/medical microbiology fellow	17 (5.8)	12 (28.6)	2 (7.1)	31 (8.6)
Infectious disease pharmacist	31 (10.7)	2 (4.8)	1 (3.6)	34 (9.5)
Cases of CDI managed in the last year				
3–10	114 (39.4)	23 (54.8)	16 (57.1)	153 (42.6)
>10	175 (60.5)	19 (45.2)	12 (42.9)	206 (57.4)
Medical specialty				
Infectious diseases	200 (77.5)	24 (60.0)	22 (81.5)	246 (75.7)
Medical microbiology	8 (3.1)	12 (30.0)	0 (0.0)	20 (6.2)
General internal Medicine	32 (12.4)	2 (5.0)	1 (3.7)	35 (10.7)
Other[a]	18 (7.0)	2 (5.0)	4 (14.8)	24 (7.4)
Years of practice as an attending				
<5	71 (29.5)	10 (35.7)	10 (40.0)	91 (31.0)
6–10	39 (16.2)	10 (35.7)	5 (20.0)	54 (18.4)
11–20	70 (29.0)	2 (7.1)	5 (20.0)	77 (26.2)
>20	61 (25.3)	6 (21.4)	5 (20.0)	72 (24.5)
Predominant practice setting				
Community hospital	121 (41.9)	9 (21.4)	5 (17.9)	135 (37.6)
University hospital	156 (54.0)	32 (76.2)	22 (78.6)	210 (58.5)
Outpatient clinics	8 (2.8)	1 (2.4)	1 (3.6)	10 (2.8)
Other[b]	4 (1.4)	0 (0.0)	0 (0.0)	4 (1.1)
Percentage of work hours allocated to research activities				
0	92 (31.8)	12 (28.6)	3 (10.7)	107 (29.8)
1–25	156 (54.0)	25 (59.5)	19 (67.9)	200 (55.7)
26–50	24 (8.3)	5 (11.9)	5 (17.9)	34 (9.5)
51–75	12 (4.2)	0 (0.0)	0 (0.0)	12 (3.3)
>75	5 (1.7)	0 (0.0)	1 (3.6)	6 (1.7)

Abbreviation: CDI, *Clostridioides difficile* infection.

[a]Includes emergency medicine, gastroenterology, intensive care, other internal medicine subspecialties, and other (family medicine, etc.).

[b]Defined according to the participant.

Table 2. CDI Diagnostics

Algorithm	North America n = 197, No. (%)	Europe n = 37, No. (%)	Other Continents n = 22, No. (%)	Total n = 256, No. (%)	*P* Value
No. of steps in the diagnostic algorithm					
1	49 (24.9)	6 (16.2)	7 (31.8)	62 (24.2)	.36
2	148 (75.1)	31 (83.8)	15 (68.1)	194 (75.8)	
First step[a]					
GDH	43 (21.8)	21 (56.8)	6 (27.3)	70 (27.3)	**<.001**
NAAT	126 (64.0)	16 (43.2)	11 (50.0)	153 (59.8)	**.040**
Toxin EIA	47 (23.9)	7 (18.9)	11 (50.0)	65 (25.4)	**.017**
TC/CCNA	0 (0.0)	1 (2.7)	0 (0.0)	1 (0.39)	.051
Unsure	15 (7.6)	1 (2.7)	0 (0.0)	16 (6.3)	NT
Second step[b]					
GDH	18 (9.1)	0 (0.0)	0 (0.0)	18 (7.0)	.055
NAAT	45 (22.8)	11 (29.7)	7 (31.8)	63 (24.6)	.48
Toxin EIA	86 (43.7)	20 (54.1)	8 (36.4)	114 (44.5)	.37
TC/CCNA	4 (2.0)	0 (0.0)	0 (0.0)	4 (1.6)	.54
Unsure	12 (6.1)	2 (5.4)	0 (0.0)	14 (5.5)	NT
Frequency of treating patients with NAAT+/toxin- results[c]					
Never	14 (7.7)	2 (5.6)	4 (18.2)	20 (8.3)	.11
1%–25%	49 (26.8)	11 (30.6)	5 (22.7)	65 (27.0)	
26%–50%	26 (14.2)	9 (25.0)	4 (18.2)	39 (16.2)	
51%–75%	24 (13.1)	0 (0.0)	3 (13.6)	27 (11.2)	
76%–99%	28 (15.3)	2 (5.6)	4 (18.2)	34 (14.1)	
100%	14 (7.7)	2 (5.6)	2 (9.1)	18 (7.5)	
Unsure	5 (2.7)	3 (8.3)	0 (0.0)	8 (3.3)	
NA	23 (12.6)	7 (19.4)	0 (0.0)	30 (12.4)	
Definition of recurrence for the purposes of treatment					
≤30 d	34 (17.3)	13 (35.1)	8 (36.4)	55 (21.5)	.30
≤56 d	36 (18.3)	5 (13.5)	3 (13.6)	44 (17.2)	
≤90 d	71 (36.0)	9 (24.3)	6 (27.3)	86 (33.6)	
≤120 d	6 (3.0)	1 (2.7)	0 (0.0)	7 (2.7)	
≤180 d	31 (15.7)	3 (8.1)	2 (9.1)	36 (14.1)	
Other[b]	4 (2.0)	1 (2.7)	0 (0.0)	5 (2.0)	
Unsure	15 (7.6)	5 (13.5)	3 (13.6)	23 (9.0)	

The bold values denote statistical significance.

Abbreviations: CCNA, cell cytotoxicity neutralization assay; EIA enzyme immunoassay; GDH, glutamate dehydrogenase; NA, not applicable (the testing algorithm does not include an NAAT and toxin EIA); NAAT, nucleic acid amplification test; NT, not tested; TC, toxigenic culture.

[a]Totals for the column may be greater than the total in the individual groups because certain algorithms used multiple tests in a single step.

[b]Defined according to the participant.

[c]Participants with institutions that use NAATs and Toxin EIAs.

RESULTS

Participant Demographics

Among a total of 450 responses, there were 359 eligible survey responses (79.8%). Of those excluded, 86 (19.1%) were because only demographics questions were answered, 3 (0.7%) had treated <3 cases of CDI in the preceding year, and 2 (0.4%) were ineligible practitioners. Responses spanned 31 countries (Supplementary Table 2) and 6 continents (North America 289 [80.5%], Europe 42 [11.7%], Australia 14 [3.9%], Asia 7 [1.9%], South America 4 [1.1%], Africa 3 [0.8%]) (Figure 1). For comparisons, Australia, Asia, South America, and Africa were grouped as other continents (28 [7.8%]). The majority of participants were attending physicians (81.9%) and had managed >10 cases of adult CDI within the preceding year (57.4%) (Table 1). Infectious disease specialists and/or medical microbiologists comprised the majority of physician respondents (81.8%), and university centers were the most common practice location (58.5%). Most participants were clinicians who allocated ≤25% of their working hours to research activities (85.5%). Two hundred fifty-six (71.3%) of the participants also responded to the second survey on diagnostics and treatments.

Diagnosis

A 2-step algorithm was most often (75.8%) used for the diagnosis of CDI (Table 2). The most common first tests included nucleic acid amplification tests (NAATs; 59.8%), glutamate dehydrogenase assays (27.3%), or directly performing a toxin enzyme immunoassay (EIA) (25.4%). The toxin EIA was the most common second step (44.5%) for those who started

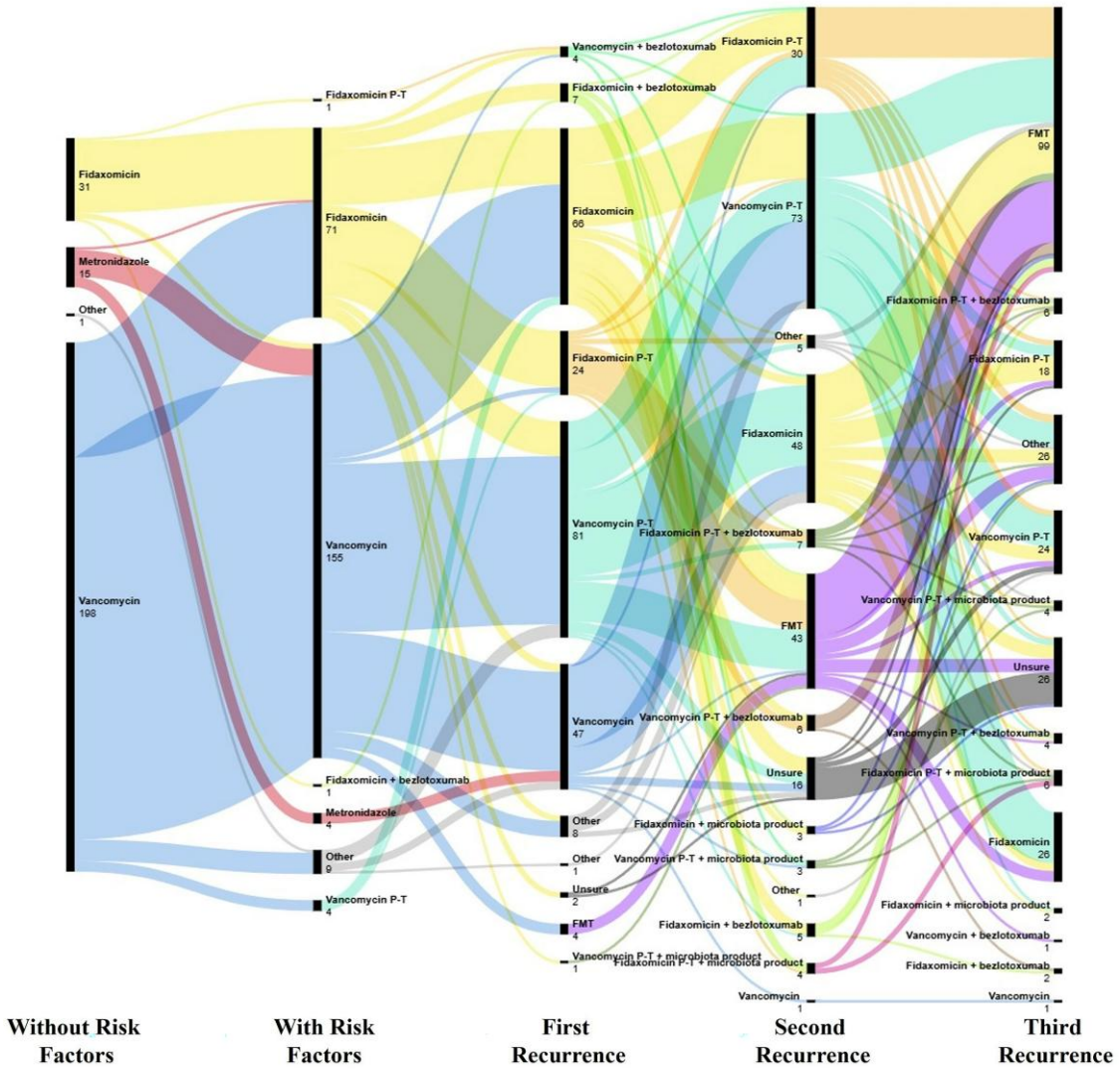


Figure 2. Alluvial diagram of the sequential treatment selection for CDI. Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplant; P-T, pulse and taper.

with NAAT and GDH. For patients with discordant NAAT and toxin EIA results (ie, NAAT+/toxin), 8.3% reported never giving treatment for CDI, 7.5% always treated for CDI, and the remainder administered CDI treatment some of the time.

Treatment of Uncomplicated CDI

When selecting a treatment regimen, 33.6% considered CDI within 90 days of a prior episode to be a recurrence, 21.5% ≤30 days, 17.2% ≤56 days, and the remainder used other cutoffs ($P = .30$).

An alluvial diagram depicting the relationship between the sequential treatment choices and episodes of uncomplicated CDI is presented in Figure 2. For an index episode of CDI, the majority preferred oral vancomycin both when risk factors for recurrence (as defined by the participant) were absent (80.8%) and when they were present (66.1%; $P < .001$ for both) (Table 3). For first recurrences, vancomycin pulse and taper (P-T; 34.3%), fidaxomicin (26.9%), and repeated vancomycin (20.4%) were the preferred regimens ($P < .01$). Vancomycin P-T remained the most frequently used agent (29.8%) for second recurrences, followed by fidaxomicin (19.6%) and fecal microbiota transplant (FMT; excluding commercial microbiota products [VOWST, REBYOTA etc.]; 17.6%; $P = .36$). For third recurrences, respondents most often used FMT (43.3%; $P = .11$).

For first and subsequent recurrences, most participants would consider randomizing their patients to vancomycin P-T vs fidaxomicin (68.2%) or fidaxomicin P-T (55.9%), and nearly half (49.4%) would consider randomizing their patients to fidaxomicin vs fidaxomicin P-T.

Treatment of Fulminant CDI

For fulminant CDI without ileus, vancomycin was the most frequently used agent (92.9%; $P < .001$), with the majority using

Table 3. Treatment of Uncomplicated CDI

Antibiotic	North America n = 188, No. (%)	Europe n = 36, No. (%)	Other Continents n = 21, No. (%)	Total n = 245, No. (%)	*P* Value
Uncomplicated CDI without risk factors for recurrence					
Metronidazole	5 (2.7)	3 (8.3)	7 (33.3)	15 (6.1)	**<.001**
Vancomycin	155 (82.4)	29 (80.6)	14 (66.7)	198 (80.8)	
Fidaxomicin	27 (14.4)	4 (11.1)	0 (0.0)	31 (12.7)	
Other[a]	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	
Uncomplicated CDI with risk factors for recurrence					
Metronidazole	0 (0.0)	1 (2.8)	3 (14.3)	4 (1.6)	**<.001**
Vancomycin	126 (67.0)	18 (50.0)	18 (85.7)	162 (66.1)	
Vancomycin P-T	3 (1.6)	1 (2.8)	0 (0.0)	4 (1.6)	
Fidaxomicin	56 (29.8)	15 (41.7)	0 (0.0)	71 (29.0)	
Fidaxomicin P-T	0 (0.0)	1 (2.8)	0 (0.0)	1 (0.4)	
Fidaxomicin + bezlotoxumab[b]	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	
Other[a]	2 (1.06)	0 (0.0)	0 (0.0)	2 (0.8)	
Uncomplicated first recurrence					
Vancomycin	34 (18.1)	7 (19.4)	9 (42.9)	50 (20.4)	**.0012**
Vancomycin P-T	68 (36.2)	8 (22.2)	8 (38.1)	84 (34.3)	
Vancomycin P-T + commercial microbiota product	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	
Vancomycin + bezlotoxumab	2 (1.1)	2 (5.6)	0 (0.0)	4 (1.6)	
Fidaxomicin	52 (27.7)	14 (38.9)	0 (0.0)	66 (26.9)	
Fidaxomicin P-T	19 (10.1)	4 (11.1)	1 (4.8)	24 (9.8)	
Fidaxomicin + bezlotoxumab	6 (3.2)	1 (2.8)	0 (0.0)	7 (2.9)	
FMT	1 (0.5)	0 (0.0)	3 (14.3)	4 (1.6)	
Other[a]	3 (1.6)	0 (0.0)	0 (0.0)	3 (1.2)	
Unsure	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.8)	
Uncomplicated second recurrence					
Vancomycin	0 (0.0)	0 (0.0)	1 (4.8)	1 (0.4)	.36
Vancomycin P-T	55 (29.3)	10 (27.8)	8 (38.1)	73 (29.8)	
Vancomycin P-T + commercial microbiota product	3 (1.6)	0 (0.0)	0 (0.0)	6 (2.4)	
Vancomycin P-T + bezlotoxumab	6 (3.2)	0 (0.0)	0 (0.0)	3 (1.2)	
Fidaxomicin	35 (18.6)	9 (25.0)	4 (19.0)	48 (19.6)	
Fidaxomicin + commercial microbiota product	3 (1.6)	0 (0.0)	0 (0.0)	3 (1.2)	
Fidaxomicin P-T	25 (13.3)	4 (11.1)	2 (9.5)	31 (12.7)	
Fidaxomicin P-T + bezlotoxumab	8 (4.3)	0 (0.0)	0 (0.0)	8 (3.3)	
Fidaxomicin P-T + commerical microbiota product	4 (2.1)	0 (0.0)	0 (0.0)	4 (1.6)	
Fidaxomicin + bezlotoxumab	5 (2.7)	1 (2.8)	0 (0.0)	6 (2.4)	
FMT	33 (17.6)	6 (16.7)	4 (19.0)	43 (17.6)	
Other[a]	1 (0.5)	2 (5.6)	0 (0.0)	3 (1.2)	
Unsure	10 (5.3)	4 (11.1)	2 (9.5)	16 (6.5)	
Uncomplicated third recurrence					
Vancomycin	0 (0.0)	0 (0.0)	1 (4.8)	1 (0.4)	.11
Vancomycin + bezlotoxumab	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	
Vancomycin P-T	16 (8.5)	2 (5.6)	6 (28.6)	24 (9.8)	
Vancomycin P-T + commercial microbiota product	4 (2.1)	0 (0.0)	0 (0.0)	4 (1.6)	
Vancomycin P-T + bezlotoxumab	6 (3.2)	0 (0.0)	0 (0.0)	6 (2.4)	
Fidaxomicin	19 (10.1)	3 (8.3)	4 (19.0)	26 (10.6)	
Fidaxomicin + commercial microbiota product	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.8)	
Fidaxomicin P-T	15 (8.0)	4 (11.1)	0 (0.0)	19 (7.8)	
Fidaxomicin P-T + bezlotoxumab	4 (2.1)	2 (5.6)	0 (0.0)	6 (2.4)	
Fidaxomicin P-T + commercial microbiota product	7 (3.7)	0 (0.0)	0 (0.0)	7 (2.9)	
Fidaxomicin + bezlotoxumab	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.8)	
FMT	80 (42.6)	18 (50.0)	8 (38.1)	106 (43.3)	
Other[a]	11 (5.9)	3 (8.3)	0 (0.0)	14 (5.7)	
Unsure	21 (11.2)	4 (11.1)	2 (9.5)	27 (11.0)	

Table 3. Continued

Antibiotic	North America n = 188, No. (%)	Europe n = 36, No. (%)	Other Continents n = 21, No. (%)	Total n = 245, No. (%)	*P* Value
Would consider randomizing to:					
Vancomycin P-T vs fidaxomicin for first and subsequent recurrences	135 (71.8)	19 (52.8)	13 (61.9)	167 (68.2)	NT
Vancomycin P-T vs fidaxomicin P-T for first and subsequent recurrences	120 (63.8)	9 (25.0)	8 (38.1)	137 (55.9)	NT
Fidaxomicin vs fidaxomicin P-T for first and subsequent recurrences	101 (53.7)	13 (36.1)	7 (33.3)	121 (49.4)	NT

The bold values denote statistical significance.

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation, commercial microbiota products (eg, VOWST, REBYOTA, etc.); NT, not tested; P-T, pulse and taper.

[a]Defined according to the participant.

[b]At the time the survey was conducted bezlotoxumab was still on the market. It has since been discontinued.

500 mg orally (PO) 4 times a day (QID; 66.5%; $P < .001$) (Table 4) and adjunctive intravenous metronidazole (75.5%; $P < .001$). Intrarectal vancomycin was used by a minority (17.4%). Results were similar when ileus was present; however, the majority administered intrarectal vancomycin in this circumstance (78.4%; $P < .05$).

Regardless of ileus, for fulminant CDI most respondents would randomize their patients to vancomycin 250–500 mg PO QID vs fidaxomicin (59.8%) or adjunctive intravenous tigecycline vs metronidazole (51.5%), and nearly half (47.7%) would randomize to vancomycin 125 mg vs 500 mg PO QID.

Secondary *C. difficile* Prophylaxis

Most participants had used secondary CDI prophylaxis during antibiotic re-exposure (75.2%), but use significantly varied geographically (North America 84.1%, Europe 31.0%, other continents 50.0%; $P < .001$) (Table 5). Among users of prophylaxis, it was considered by 56.7% after a single episode of CDI, 31.3% only after 2 episodes, and 4.9% only after 3 or more episodes. The time frame after an episode of CDI where secondary CDI prophylaxis was considered was <3 months in 23.5%, 3–6 months in 32.1%, 6–12 months in 31.7%, 1–5 years in 3.7%, and at any time in 4.9%. More than half of participants identified nitrofurantoin (63.7%), oral or intravenous metronidazole (63.0%), intravenous vancomycin (58.1%), and fosfomycin (53.3%) as systemic antibiotics not requiring prophylaxis (Supplementary Table 3). Only 11.5% of participants reported administering prophylaxis irrespective of the systemic antibiotic.

Vancomycin was used for secondary CDI prophylaxis by 96.3%. The dosages of oral vancomycin used were 125 mg BID (51.2%), 125 mg daily (38.0%), 125 mg QID (8.9%), a taper (0.4%), and other (1.2%; $P < .001$). Secondary CDI prophylaxis was most commonly dosed based on the duration of systemic antibiotics, with 28.0% matching the systemic antibiotic duration and 60.0% extending the duration by an additional week ($P < .001$). Similarly, when systemic antibiotics were required during the treatment of CDI, 16.8% extended CDI treatment for the duration of systemic antibiotics and 56.7% extended treatment by a week after cessation of systemic antibiotics ($P < .001$). Notwithstanding how common the use of secondary prophylaxis was overall, the majority (83.8%) of participants stated that they would enroll their patients in an RCT of secondary vancomycin prophylaxis vs placebo.

DISCUSSION

This comprehensive international survey on CDI practice patterns revealed multiple areas of heterogeneous practice in the diagnosis, treatment, and secondary prophylaxis of CDI both within and across geographical regions. Secondary vancomycin prophylaxis was more commonly used in North America, and there was no consensus on its dose, duration, or time frame of use. Although vancomycin was the most commonly used agent for first episodes and as a P-T for recurrences, there was heterogeneity.

There was significant variability in the diagnosis of CDI including 1- vs 2-step testing and which test or tests comprise each step. The results for this series of questions were naturally influenced by the availability of tests in a given center and local guidelines. Indeed, standalone NAATs were favored in North America [8, 9], whereas 2-step testing with a toxin EIA was favored in Europe [6]. There is no consensus on the optimal testing algorithm for CDI [4–6, 9]. Head-to-head studies comparing different algorithms or modalities and how they impact the decision to treat and subsequent clinical outcomes are lacking [16]. Further, the interpretation of NAAT+/toxin- results and assessment of those who require CDI treatment are controversial, which was also reflected in our findings [17, 18]. Consequently, this area can benefit from more research.

There are numerous treatments available for CDI including oral antibiotics (ie, vancomycin, fidaxomicin, metronidazole) that can be administered in various regimens (eg, 10–14 days, P-T regimen) and adjunctive microbiome agents (ie, VOWST, REBYOTA, and FMT). Head-to-head trials of several of these therapies are lacking, as well as trials combining these treatments, in addition to issues related to cost and access [19]. These knowledge gaps are reflected in our findings, where there was inconsistent treatment selection. Although the IDSA [9] and ESCMID [6] recommend fidaxomicin over vancomycin

Table 4. Treatment of Fulminant CDI

Antibiotic	North America n = 185, No. (%)	Europe n = 35, No. (%)	Other Continents n = 21, No. (%)	Total n = 241, No. (%)	*P* Value
Without concomitant ileus					
Oral CDI antibiotic					
Vancomycin	175 (94.6)	30 (85.7)	19 (90.5)	224 (92.9)	**.0026**
Fidaxomicin	4 (2.1)	5 (14.3)	2 (9.5)	11 (4.6)	
Other[a]	6 (3.2)	0 (0.0)	0 (0.0)	6 (2.5)	
Adjunctive treatment					
Metronidazole	148 (80.0)	20 (57.1)	14 (66.7)	182 (75.5)	**<.001**
Tigecycline	0 (0.0)	3 (8.6)	0 (0.0)	3 (1.2)	
Metronidazole + tigecycline	2 (1.1)	1 (2.9)	1 (4.8)	4 (1.7)	
Metronidazole + FMT	0 (0.0)	0 (0.0)	3 (14.3)	3 (1.2)	
FMT	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	
None	34 (18.4)	11 (31.4)	3 (14.3)	48 (19.9)	
Adjunctive intrarectal vancomycin					
Yes	30 (16.2)	9 (25.7)	3 (14.3)	42 (17.4)	.37
No	155 (83.8)	26 (74.3)	18 (85.7)	199 (82.6)	
Dose of oral vancomycin					
125 mg QID	29 (16.6)	10 (33.3)	6 (31.6)	45 (20.0)	**.0060**
250 mg QID	16 (9.1)	7 (23.3)	5 (26.3)	28 (12.5)	
500 mg QID	128 (73.1)	13 (43.3)	8 (42.1)	149 (66.5)	
Other[a]	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.9)	
With concomitant ileus					
Oral CDI antibiotic[b]					
Vancomycin	171 (92.4)	28 (80.0)	18 (85.7)	217 (90.0)	**.0043**
Fidaxomicin	4 (2.2)	6 (17.1)	3 (14.3)	13 (5.4)	
Vancomycin + fidaxomicin	3 (1.6)	1 (2.9)	0 (0.0)	4 (1.7)	
Other[a]	7 (3.8)	0 (0.0)	0 (0.0)	7 (2.9)	
Adjunctive treatment					
Metronidazole	163 (88.1)	23 (65.7)	15 (71.4)	201 (83.4)	**<.001**
Tigecycline	4 (2.1)	4 (11.4)	0 (0.0)	8 (3.3)	
Metronidazole + tigecycline	4 (2.1)	3 (8.6)	1 (4.8)	8 (3.3)	
Metronidazole + FMT	0 (0.0)	0 (0.0)	3 (14.3)	3 (1.2)	
FMT	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.8)	
Other[a]	0 (0.0)	1 (2.9)	0 (0.0)	1 (0.4)	
None	12 (6.5)	4 (11.4)	2 (9.5)	18 (7.5)	
Adjunctive intrarectal vancomycin					
Yes	151 (81.6)	22 (62.9)	16 (76.2)	189 (78.4)	**.045**
No	34 (18.4)	13 (37.1)	5 (23.8)	52 (21.6)	
Dose of oral vancomycin[c]					
125 mg QID	12 (8.6)	5 (29.4)	2 (16.7)	19 (11.2)	.14
250 mg QID	13 (9.3)	3 (17.6)	2 (16.7)	18 (10.7)	
500 mg QID	114 (81.4)	9 (52.9)	8 (66.7)	131 (77.5)	
Other[a]	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.6)	
Regardless of ileus					
Would consider randomizing to:					
Vancomycin 500 mg vs 125 mg PO QID	90 (48.6)	12 (34.3)	13 (61.9)	115 (47.7)	NT
Vancomycin 250–500 mg PO QID vs fidaxomicin	117 (63.2)	19 (54.3)	8 (38.1)	144 (59.8)	NT
Adjunctive intravenous tigecycline vs metronidazole	90 (48.6)	22 (63.9)	12 (57.1)	124 (51.5)	NT

The bold values denote statistical significance.

Abbreviations: CDI, *Clostridioides difficile* infection; FMT, fecal microbiota transplantation; NT, not tested; PO, oral; QID, 4 times daily.

[a]Defined according to the participants.

[b]Participants who did not specify an oral antibiotic for this question had their response from the preceding question on an oral antibiotic for fulminant CDI without ileus carried forward.

[c]48 participants who used vancomycin did not respond to this question.

as first-line for index episodes of CDI due to a reduced risk of recurrence [16], most respondents preferred vancomycin. This may be due to regional availability of fidaxomicin, as well as concerns regarding its cost [19]. Similarly, bezlotoxumab's uptake was low (<10%) despite strong guideline recommendations on its use for recurrences [4, 6, 9], which is possibly

Table 5. Use and Application of *C. difficile* Prophylaxis

	North America n = 289, No. (%)	Europe n = 42, No. (%)	Other Continents n = 28, No. (%)	Total n = 359, No. (%)	*P* Value
Use of *C. difficile* prophylaxis					
Yes	243 (84.1)	13 (31.0)	14 (50.0)	270 (75.2)	**<.001**
After how many prior episodes of CDI is secondary *C. difficile* prophylaxis used					
≥1	138 (57.3)	6 (46.1)	8 (57.1)	152 (56.7)	.56
≥2	75 (31.1)	6 (46.1)	3 (21.4)	84 (31.3)	
≥3	11 (4.6)	0 (0.0)	2 (14.3)	13 (4.9)	
Unsure	17 (7.1)	1 (7.7)	1 (7.1)	19 (7.1)	
Time frame after CDI that *C. difficile* prophylaxis is considered					
Any time	11 (4.6)	1 (7.7)	1 (7.1)	13 (4.9)	.50
<5 y	10 (4.1)	0 (0.0)	0 (0.0)	10 (3.7)	
<1 y	80 (33.2)	3 (23.1)	2 (14.3)	85 (31.7)	
<6 mo	74 (30.7)	7 (53.8)	5 (35.7)	86 (32.1)	
<3 mo	55 (22.8)	2 (15.4)	6 (42.9)	63 (23.5)	
Unsure	11 (4.6)	0 (0.0)	0 (0.0)	11 (4.1)	
Agent used for *C. difficile* prophylaxis					
Vancomycin	235 (97.5)	12 (92.3)	11 (78.6)	258 (96.3)	**<.001**
Metronidazole	3 (1.2)	0 (0.0)	2 (14.2)	5 (1.9)	
Fidaxomicin	0 (0.0)	1 (7.7)	1 (7.1)	2 (0.7)	
Unsure	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	
Other[a]	2 (0.8)	0 (0.0)	0 (0.0)	2 (0.7)	
Dose of vancomycin prophylaxis					
125 mg DIE	87 (37.0)	7 (58.3)	4 (36.4)	98 (38.0)	**<.001**
125 mg BID	129 (54.9)	2 (16.7)	1 (9.1)	132 (51.2)	
125 mg QID	14 (6.0)	3 (25.0)	6 (54.5)	23 (8.9)	
A taper (ie, decreasing doses over time)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	
Other[a]	3 (1.3)	0 (0.0)	0 (0.0)	3 (1.2)	
Unsure	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	
Frequency of CDI prophylaxis use					
~0%	9 (3.7)	0 (0.0)	0 (0.0)	9 (3.4)	.51
~25%	90 (37.3)	7 (53.8)	7 (50.0)	104 (38.8)	
~50%	44 (18.3)	1 (7.7)	5 (35.7)	50 (18.7)	
~75%	53 (22.0)	2 (15.4)	0 (0.0)	55 (20.5)	
~100%	31 (12.9)	2 (15.4)	1 (7.1)	34 (12.7)	
Unsure	14 (5.8)	1 (7.7)	1 (7.1)	16 (6.0)	
Duration of prophylaxis					
0–7 d fixed	3 (1.2)	0 (0.0)	0 (0.0)	3 (1.1)	**<.001**
8–14 d fixed	1 (0.4)	2 (15.4)	2 (14.3)	5 (1.9)	
15–28 d fixed	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	
Duration of systemic antibiotics	62 (25.7)	5 (38.5)	8 (57.1)	75 (28.0)	
Duration of systemic antibiotics + 1 wk	149 (61.8)	5 (38.5)	4 (28.6)	158 (60.0)	
Other[a]	24 (10.0)	1 (7.7)	0 (0.0)	25 (9.3)	
Unsure	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)	
Treatment prolongation when systemic antibiotics are required during CDI treatment					
Not prolonged	19 (7.9)	4 (30.8)	1 (7.1)	24 (9.0)	**.0019**
1–7 d fixed	11 (4.6)	0 (0.0)	0 (0.0)	11 (4.1)	
8–14 d fixed	5 (2.1)	0 (0.0)	0 (0.0)	5 (1.9)	
Duration of systemic antibiotics	34 (14.1)	3 (23.1)	8 (57.1)	45 (16.8)	
Duration of systemic antibiotics + 1 wk	143 (59.3)	4 (30.8)	5 (35.7)	152 (56.7)	
Other[a]	25 (10.4)	1 (7.7)	0 (0.0)	26 (9.7)	
Unsure	4 (1.7)	1 (7.7)	0 (0.0)	5 (1.9)	
Would randomize patients to vancomycin prophylaxis vs placebo					
Yes	249 (86.2)	29 (69.0)	23 (82.1)	301 (83.8)	NT

The bold values denote statistical significance.

Abbreviations: BID, twice daily; CDI, *Clostridioides difficile* infection; DIE, once daily; QID, 4 times daily.

[a]Defined according to the participant.

due to cost, availability, safety concerns with concomitant heart failure [17], and limited data on its value when combined with fidaxomicin [18]. Since the conduct of this survey, bezlotoxumab has been discontinued [20], which will likely further reduce its use. There is a lack of consensus on the backbone agent and its dose, adjunctive agent, and use of intrarectal vancomycin for fulminant CDI. Vancomycin 500 mg PO QID was preferred in North America, whereas 125 mg PO QID was preferred in Europe. Adjunctive intravenous metronidazole was also more often used in North America. This is also reflective of local guidelines and, probably, the complete lack of RCT data for this indication [21]. Taken together, our results underscore the need for additional RCTs evaluating the optimal antibiotic and regimen, adjunctive agents, and sequential ordering of treatments [22] for both uncomplicated and fulminant CDI. Such a trial would ideally employ a platform design to address multiple questions in parallel, akin to the SNAP trial for *S. aureus* bacteremia [11].

For our primary objective, our results identified significant practice variation in the use and application of secondary CDI prophylaxis during antibiotic re-exposure, which mirrors discordant guideline recommendations. The ESCMID [6] advises against prophylaxis and the IDSA [8] refrains from making a recommendation, whereas the ACG [4] and AMMI Canada [5] recommend consideration in certain circumstances (Supplementary Table 1). Additionally, these guidelines diverge on the optimal dose and duration of prophylaxis. This discordance likely results from the low-quality observational evidence base supporting secondary vancomycin prophylaxis, which is highlighted in our recent meta-analysis [12]. The use of secondary vancomycin prophylaxis was highest in North America, which could be related to its conditional recommendation by the ACG and AMMI Canada and because the first study on its use originated from Canada [23]. Given the observed practice variation, observational evidence suggesting a potential benefit, and the support for an RCT in most respondents, there is clear equipoise for conducting an RCT comparing secondary vancomycin prophylaxis vs placebo. Assuming that it is efficacious, further studies will be needed to establish the optimal dose, duration, and time frame of use, considering the inconsistent clinical practice and guidelines.

This study is subject to certain limitations. First, participation from outside North America was limited, which is potentially attributable to the availability of the survey exclusively in English or French. Second, geographic differences in the distribution of *C. difficile* strains, like NAP1, which is more common in North America and is associated with increased disease severity, mortality, and recurrence [24–26], may also influence practice. Third, it is possible that ineligible participants completed the survey under false pretenses. However, this risk was mitigated by removing duplicate or nonsensical responses and by not incentivizing participation. Fourth, although CDI practices are influenced by local drug availability, cost, and local guidelines, which may contribute to practice heterogeneity, these were not specifically evaluated in our survey. Fifth, nonresponse bias could not be quantified due to the voluntary nature of this online survey. Sixth, sampling bias remains a possibility; however, this was mitigated by our multimodal recruitment strategy, which potentially enhanced the representativeness of the sample. Seventh, inherent to self-reported data, there may be response bias. Nevertheless, to our knowledge this study reflects the first and most comprehensive international clinician survey on CDI practices.

CONCLUSIONS

There exists significant practice variation in the diagnosis, treatment, and use of secondary prophylaxis for CDI both within and across geographic regions, which is mirrored in discrepant international guideline recommendations. Our results identify numerous knowledge gaps and suggest clinical equipoise and need for further study, ideally with RCTs, to establish harmonized international best practices for this common, costly, and morbid infection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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References

1. Balsells E, Shi T, Leese C, et al. Global burden of *Clostridium difficile* infections: a systematic review and meta-analysis. J Glob Health **2019;** 9:010407.
2. Guh AY, Mu Y, Winston LG, et al. Trends in U.S. burden of *Clostridioides difficile* infection and outcomes. N Engl J Med **2020;** 382:1320–30.
3. Zhang S, Palazuelos-Munoz S, Balsells EM, Nair H, Chit A, Kyaw MH. Cost of hospital management of *Clostridium difficile* infection in United States—a meta-analysis and modelling study. BMC Infect Dis **2016;** 16:447.
4. Kelly CR, Fischer M, Allegretti JR, et al. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. Off J Am Coll Gastroenterol ACG **2021;** 116:1124–47.
5. Loo VG, Davis I, Embil J, et al. Association of Medical Microbiology and Infectious Disease Canada treatment practice guidelines for *Clostridium difficile* infection. Off J Assoc Med Microbiol Infect Dis Canada **2018;** 3:71–92.
6. van Prehn J, Reigadas E, Vogelzang EH, et al. European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults. Clin Microbiol Infect **2021;** 27:S1–21.

7. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. Clin Microbiol Infect **2014;** 20:1–26.
8. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis **2018;** 66:e1–48.
9. Johnson S, Lavergne V, Skinner AM, et al. Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. Clin Infect Dis **2021;** 73:e1029–44.
10. Westgeest AC, Buis DTP, Sigaloff KCE, et al. Global differences in the management of *Staphylococcus aureus* bacteremia: no international standard of care. Clin Infect Dis **2023;** 77:1092–101.
11. Tong SYC, Mora J, Bowen AC, et al. The *Staphylococcus aureus* Network adaptive platform trial protocol: new tools for an old foe. Clin Infect Dis **2022;** 75:2027–34.
12. Prosty C, Bortolussi-Courval É, Dubé L-R, Lee TC, McDonald EG. Oral vancomycin prophylaxis for the prevention of recurrent *Clostridioides difficile* infection during re-exposure to systemic antibiotics: a systematic review and meta-analysis. CMI Commun **2024;** 1:105041.
13. Sharma A, Minh Duc NT, Luu Lam Thang T, et al. A Consensus-based checklist for Reporting Of Survey Studies (CROSS). J Gen Intern Med **2021;** 36:3179–87.
14. Mapping Global Data. rworldmap. **2023**. Available at: https://cran.r-project.org/web/packages/rworldmap/index.html. Accessed December 9, 2024.
15. RAWGraphs. Available at: https://www.rawgraphs.io/. Accessed 9 December 2024.
16. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med **2011;** 364:422–31.
17. Johnson S, Gerding DN. Bezlotoxumab. Clin Infect Dis **2019;** 68:699–704.
18. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. N Engl J Med **2017;** 376:305–17.
19. Patel D, Senecal J, Spellberg B, et al. Fidaxomicin to prevent recurrent *Clostridioides difficile*: what will it cost in the USA and Canada? JAC Antimicrob Resist **2023;** 5: dlac138.
20. Food and Drug Adminisration. Drug shortages. Available at: https://dps.fda.gov/drugshortages/discontinuations/bezlotoxumab-injection. Accessed March 21, 2025.
21. Pipitone G, Iaria C, Granata G, Cascio A, Maraolo AE. Which trials do we need? Fidaxomicin plus either intravenous metronidazole or tigecycline versus vancomycin plus either intravenous metronidazole or tigecycline for fulminant *Clostridioides difficile* infection. Clin Microbiol Infect **2024;** 31: 315–8.
22. van Prehn J, van Werkhoven CH, Skinner AM, Guery B, Dubberke ER, Kuijper EJ. Which trial do we need? A sequential multiple assignment randomized trial to determine the optimal *Clostridioides difficile* treatment sequence. Clin Microbiol Infect **2024;** 30:165–9.
23. Carignan A, Poulin S, Martin P, et al. Efficacy of secondary prophylaxis with vancomycin for preventing recurrent *Clostridium difficile* infections. Off J Am Coll Gastroenterol ACG **2016;** 111:1834–40.
24. Loo VG, Bourgault A-M, Poirier L, et al. Host and pathogen factors for *Clostridium difficile* infection and colonization. N Engl J Med **2011;** 365: 1693–703.
25. Marsh JW, Arora R, Schlackman JL, Shutt KA, Curry SR, Harrison LH. Association of relapse of *Clostridium difficile* disease with BI/NAP1/027. J Clin Microbiol **2012;** 50:4078–82.
26. See I, Mu Y, Cohen J, et al. NAP1 strain type predicts outcomes from *Clostridium difficile* infection. Clin Infect Dis **2014;** 58:1394–400.