Guideline for the management of *Clostridioides difficile* infection in pediatric patients with cancer and hematopoietic cell transplantation recipients: 2024 update

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Summary

Our objective was to update a clinical practice guideline for the prevention and treatment of *Clostridioides difficile* infection (CDI) in pediatric patients with cancer and hematopoietic cell transplantation recipients. We reconvened an international multi-disciplinary panel. A systematic review of randomized controlled trials (RCTs) for the prevention or treatment of CDI in any population was updated and identified 31 new RCTs. Strong recommendations were made to use either oral metronidazole or oral vancomycin for non-severe CDI treatment, and to use either oral vancomycin or oral fidaxomicin for severe CDI. A strong recommendation that fecal microbiota transplantation should not be routinely used to treat CDI was also made. The panel made two new good practice statements to follow infection control practices including isolation in patients experiencing CDI, and to minimize systemic antibacterial administration where feasible, especially in patients who have experienced CDI.

Keywords: Practice guideline; *Clostridioides difficile* infection; Prevention; Treatment; Pediatric oncology

Introduction

Clostridioides difficile is a common cause of infectious diarrhea in pediatric patients with cancer and hematopoietic cell transplantation (HCT) recipients.[1] Rates of new and recurrent *Clostridioides difficile* infection (CDI) have increased over the past decade with the appearance of new virulent strains.[2] Recent antibiotic exposure, chemotherapy exposure and prolonged hospitalization are risk factors for CDI among pediatric oncology and HCT patients.[3–8] The prevalence of CDI in pediatric oncology patients is variable depending on the type of cancer diagnoses and treatment. Some studies have reported rates ranging from 1.2 to 11%.[3,8–10] The clinical

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Research in context

Evidence before this study

A clinical practice guideline (CPG) for the management of *Clostridioides difficile* infection (CDI) in pediatric patients with cancer and hematopoietic cell transplantation (HCT) recipients was developed in 2018. The original recommendations were based on a systematic review of 65 randomized controlled trials (RCTs) evaluating interventions for the prevention or treatment of CDI in any population and considered the directness of the evidence to pediatric patients with cancer and HCT recipients.

Added value of this study

In this CPG update the systematic review was updated and a total of 96 randomized controlled trials (RCTs) were included to form the evidence base. This CPG made the following strong recommendations: (1) Use either oral metronidazole or oral vancomycin for the treatment of non-severe CDI, (2) Use either oral vancomycin or oral fidaxomicin for the treatment of severe CDI, and (3) Do not use fecal microbiota transplantation routinely to treat CDI. The panel made two new good practice statements to follow infection control practices including isolation in patients experiencing CDI, and to minimize systemic antibacterial administration where feasible, especially in patients who have experienced CDI.

Implications of all the available evidence

There are an increasing number of RCTs conducted for interventions used to prevent and treat CDI. However, direct evidence for the pediatric immunocompromised population, and specifically pediatric cancer patients and HCT recipients, where risk for CDI is high remains limited.

presentation of *Clostridioides difficile* infection (CDI) can range from mild enterocolitis to severe cases with toxic megacolon and death.[3] Given the potential for substantial negative consequences as a result of CDI, there is a need to focus on prevention and treatment optimization.

An important component of improving evidence-based clinical care is the development of clinical practice guidelines (CPGs). We previously developed a CPG in 2018 for the prevention and treatment of CDI in pediatric patients with cancer and HCT recipients.[11] It is important to periodically evaluate new evidence to determine if recommendations should be modified. Consequently, the objective was to update the 2018 CDI CPG.

Methods

Panel constitution

We reconvened a multi-disciplinary and multi-national panel with representation from the following groups: pediatric oncology, pediatric HCT, pediatric infectious diseases, nursing, pharmacy, patient advocates and guideline methodologists (Appendix 1). Panel members were selected based on scientific or content expertise, or patient lived experience. Each panel member declared conflicts of interest (Appendix 2). No member had conflicts that precluded panel participation or recusal from specific recommendation deliberation.

General CPG development procedures

As with the 2018 CDI CPG, we followed standard procedures for creating CPGs.[12] The CPG development process was led by the Pediatric Oncology Group of Ontario (POGO) Guidelines program. The key clinical question to be addressed by the CPG was: "What interventions should be used for the prevention and treatment of CDI in pediatric patients with cancer and HCT recipients?" The CPG recommendations are intended for children and adolescents 1–18 years of age with cancer and those undergoing HCT. We excluded infants younger than 1 year of age as *C. difficile* detection typically represents asymptomatic colonization rather than CDI in this population. The target users are pediatric oncology and HCT physicians, pediatric infectious diseases physicians, nurse practitioners, physician assistants, nurses, pharmacists, and other healthcare professionals who manage CDI in the target population such as general pediatric, emergency room and intensive care unit clinicians.

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to describe level of evidence and generate recommendations.[13] Level of evidence (high to very low) reflects our certainty of intervention effects in the target population and is influenced by precision, consistency, lack of bias and directness. With the GRADE approach, recommendations may be strong or conditional. Strong recommendations are made when the benefits of an intervention clearly outweigh the downsides or vice versa. Strong recommendations should generally be implemented as a matter of policy in most settings. Conversely, conditional recommendations are made when the benefits and downsides of the intervention are closely matched, or when there is considerable uncertainty about their estimates. Values, preferences and resources will determine whether conditional recommendations are implemented.

Search strategy and selection criteria

Both the 2018 CDI CPG and 2024 CDI CPG update were based on randomized controlled trials (RCTs) of interventions for the prevention or treatment of CDI conducted in any population. The panel considered directness to pediatric immunocompromised patients with neutropenia when deliberating recommendations.

Facilitated by a library scientist, we conducted a systematic review and searched for RCTs indexed from March 15, 2018 (end date of the 2018 CDI CPG search) to February 29, 2024. The following databases were searched: MEDLINE including Epub ahead of print, in-process and other non-indexed citations, Embase, and the Cochrane Central Register of Controlled Trials; Appendix 3 shows the full search strategy. The following inclusion criteria were applied: (1) participants were human subjects; (2) fully published RCT with a parallel group design; and (3) evaluated an intervention for the prevention or treatment of CDI. Exclusion criteria were as follows: (1) for prevention studies, CDI was not a study endpoint or was reported as an adverse event; and (2) for treatment studies, the study population had less than 90% of patients with CDI. There was no exclusion by language.

Titles and abstracts of studies identified by the search strategy were independently screened by two reviewers (PP, PDR, AM, NE or AA). Potentially relevant articles were retrieved, and eligibility was applied independently to full text publications by two reviewers (PP, PDR, AM, NE or AA). If there was disagreement, the two reviewers met to reach consensus. If consensus could not be achieved, a third reviewer (PDR or LS) arbitrated. Agreement in study inclusion was described using the Kappa statistic.[14]

One reviewer (PP, SC, NE, KN, or AA) abstracted the following data: study-level characteristics, details of the intervention and control groups, *a priori* determined important outcomes, and risk of bias assessment. A second reviewer (PP or PDR) confirmed the abstracted elements. If there was disagreement, the reviewers met to come to consensus and if consensus could not be achieved, adjudication was by a third reviewer (LS). Study-level characteristics were as follows: prevention vs. treatment study, year of publication, age of participants (adult, pediatric or both), immune status (immunocompetent only, any immunocompromised participant but not known to be neutropenic, any immunocompromised participant known to be neutropenic, or not reported), cancer or HCT population and number of randomized participants. We also abstracted details of the intervention and control groups. Intervention group types were CDI-directed antibacterial therapy, fecal microbiota transplantation (FMT), monoclonal antibody, probiotic and other. Control group types were placebo, usual care and other interventions.

The panel determined outcomes important to recommendation formulation prior to data abstraction. For prevention studies, the outcome was occurrence of CDI. CDI was defined as the presence of diarrhea and detection of *C. difficile* toxin from stool using the study-specified approach to toxin detection such as enzyme immunoassay or polymerase chain reaction. For treatment studies, outcomes were cure at the end of the treatment period, cure at the end of the follow-up period and recurrence. We defined cure as the resolution of diarrhea. If we were unable to abstract cure using this definition, we used the study's definition of cure, which sometimes included resolution of abdominal pain or a negative *C. difficile* toxin test. The Cochrane Collaboration's tool was used to assess risk of bias.[15]

We previously identified invasive infection attributed by study authors to probiotic administration by conducting a systematic review of observational studies in pediatric oncology or HCT patients.[11] We did not update the systematic review since new studies would not have influenced recommendations.

Statistical analysis

We synthesized outcomes when there were at least three studies evaluating the same intervention and the same outcome. In studies with three or more randomized groups, data for distinct intervention groups were abstracted and compared against a single control group. For studies that evaluated more than one dosing regimen for the same agent, we abstracted data from the most intensive (dose or frequency) group as the intervention group. The control group was placebo, no therapy or standard of care. In the absence of these approaches, we defined the control group as the least intensive regimen. For studies of FMT, we separately analyzed by whether the product was fresh vs. frozen and by whether the product traversed the stomach (oral or naso-gastric tube) or by whether the product was delivered directly to the small or large intestine (naso-duodenal/jejunal tube, colonoscopy or enema).

Intervention effects were described using the risk ratio (RR) and the corresponding 95% confidence intervals (CI). Effect sizes were weighted by the Mantel-Haenszel method, and a random effects model was used as we anticipated heterogeneity in effects. Meta-analyses were conducted using Review Manager 5.4 (Cochrane Collaboration, Nordic Cochrane Centre).[16] All tests of significance were two-sided, and statistical significance was defined as $P < 0.05$. Publication bias was explored by visual inspection of funnel plots when at least 10 studies were available for synthesis.[15] If there was evidence of publication bias, the trim and fill approach was used to evaluate whether the magnitude of bias might influence interpretation.[15]

Formulating recommendations

Evidence and recommendations were considered for prevention and treatment studies separately. We described RCTs included in the 2018 CDI CPG and those newly added to this 2024 CDI CPG update. Evidence tables of synthesized results were then created. These tables were reviewed in two video-conference calls. The panel decided whether to maintain previous recommendations, modify them or add new recommendations. The panel also considered making good practice statements.[17] Good practice statements may be

contemplated when there is compelling indirect evidence from multiple sources that strongly support the action, and when the alternative action would not conform to ethical norms.[17] The patient advocates used their lived experiences to make suggestions to support or not support the proposed recommendations or good practice statements.

Statements were drafted and voted upon by panel members. The statement was accepted if at least 80% of panel members agreed with each statement. Draft versions of the recommendations and manuscript were then developed, circulated and revised until approved by all authors. Rather than sending the final CPG for external review, we used the peer review process during manuscript submission as a rigorous and efficient approach to external review. A guideline update is planned in five years or sooner in the event of publication of important new information.

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Results
Table 1 presents the 2024 CDI CPG recommendations and describes changes from the 2018 CDI CPG. Some recommendations are stratified by CDI severity. Severe CDI may be defined as the presence of colitis, pneumatosis intestinalis, pseudomembranous colitis, ileus or surgery for CDI.[18] Table 2 illustrates the characteristics of RCTs included in the 2018 CDI CPG (n = 65), new RCTs added to the 2024 CDI CPG update (n = 31) and the total number of RCTs considered in the 2024 CDI CPG update (n = 96). There were 35 RCTs evaluating prevention strategies and 61 RCTs evaluating treatment strategies for CDI. In total, there were 10 studies conducted in pediatric population only, seven in the prevention setting and three in the treatment setting. There were 21 studies that included immunocompromised patients who were not known to be neutropenic and four studies that included immunocompromised patients who were known to be neutropenic. Among the studies including neutropenic patients, two also included pediatric patients.

Among all studies, the most commonly studied intervention group type was CDI-directed antibacterial therapy followed by probiotics and FMT. The flow diagram of study identification, selection and reasons for exclusion is provided in Appendix 4. Agreement in study inclusion/exclusion was perfect (Kappa = 1.0). Appendix 5 shows the characteristics and outcomes of CDI prevention trials (N = 35). The number of new RCTs by intervention group type were as follows: CDI-directed antibacterial therapy (n = 5), FMT (n = 2), probiotic (n = 6) and other (n = 3). Table 3 shows the synthesized results for probiotic prevention studies, the only prevention intervention amenable to synthesis.

Appendices 6 and 7 show the characteristics and outcomes of CDI treatment trials excluding FMT. The number of new RCTs by intervention group type were as follows: CDI-directed antibacterial therapy (n = 7), monoclonal antibody (n = 1), probiotic (n = 1) and other (n = 1). Appendices 8 and 9 show the characteristics and outcomes of FMT treatment trials with seven new RCTs. Table 4 shows the synthesized results for treatment studies, including which estimates were revised compared to the 2018 CDI CPG. Knowledge gaps are presented in Table 5.

Recommendation 1
We suggest that probiotics not be used routinely for the prevention of CDI in pediatric patients with cancer and HCT recipients (conditional recommendation, low quality evidence).

Literature review and analysis
The 2018 CDI CPG made a conditional recommendation against routine use of probiotics to prevent CDI. Although the previous synthesis suggested benefit in reducing CDI compared to placebo, none of the probiotic RCTs included immunocompromised children. For the previous 2018 CDI CPG, we conducted a systematic review of observational studies to identify if there were invasive infections associated with probiotic administration in pediatric cancer and HCT patients. There were three cases of invasive infection in pediatric patients receiving cancer treatment that were attributed by the study authors to a probiotic, namely *Lactobacillus* bacteremia,[19] absidiomycosis[20] and *Saccharomyces* fungemia.[21] The conditional recommendation against routine probiotic use was influenced by the observed attribution of invasive infection to either a probiotic itself or contamination of the probiotic in pediatric patients with cancer. The panel was also concerned that the benefits of probiotics were primarily seen in RCTs of immunocompetent adults.

For the 2024 CDI CPG update, there were 23 RCTs of probiotic administration for CDI prevention, six of which were new to this CPG update (Appendix 5). While we previously included the single prebiotic study with probiotics, we have now separated them in this CPG update since, unlike probiotics, prebiotics do not contain live organisms. All studies administered probiotics as primary prophylaxis with the exception of the VE303 study,[22] which administered the probiotic as primary and secondary prophylaxis. There were 12 studies that evaluated a probiotic containing a single organism (10 of which were compared against placebo) and 11 studies that evaluated a probiotic containing multiple organisms (10 of which compared against placebo). Two RCTs included immunocompromised patients not known to be neutropenic[23,24] and although

Health Questions and Recommendations	2024 Update Status and Remarks
What interventions should be used for the prevention of CDI in pediatric patients with cancer and HCT recipients?	
1. We suggest that probiotics not be used routinely for the prevention of CDI in pediatric patients with cancer and HCT recipients (conditional recommendation, low quality evidence)	Although there were new RCTs of probiotics evaluating CDI prevention, there remained few conducted in immunocompromised patients and none in pediatric patients receiving cancer therapies. Given the small but documented risk of probiotic-associated invasive infection, the 2018 recommendation was maintained.
What interventions should be used for the treatment of CDI in pediatric patients with cancer and HCT recipients?	
2. Use either oral metronidazole or oral vancomycin for the treatment of non-severe CDI in pediatric patients with cancer and HCT recipients (strong recommendation, low quality evidence)	No new RCTs; the 2018 recommendation was maintained.
3. Use either oral vancomycin or oral fidaxomicin for the treatment of severe CDI in pediatric patients with cancer and HCT recipients (strong recommendation, low quality evidence)	There were new RCTs supporting the benefit of fidaxomicin vs. vancomycin to increase cure and reduce recurrence plus direct data in pediatric cancer patients with neutropenia. Fidaxomicin benefits are likely more important in severe vs. non-severe CDI; thus, fidaxomicin was added as an option in this setting.
4. Consider fidaxomicin for the treatment of recurrent CDI in pediatric patients with cancer and HCT recipients (conditional recommendation, moderate quality evidence)	The new RCTs supporting the benefit of fidaxomicin vs. vancomycin and new data in pediatric patients with cancer in the non-recurrent CDI setting led to increasing the quality of evidence from low in the 2018 CPG to moderate in the 2024 update.
5. Do not use FMT routinely for the treatment of CDI in pediatric patients with cancer and HCT recipients (strong recommendation, low quality evidence)	While there were new RCTs of FMT, the strong recommendation against routine use was based on uncertainty regarding benefits and risks, heterogeneity of evaluated products and routes of administration, and the lack of direct data. Thus, the 2018 recommendation was maintained.
6. We suggest that monoclonal antibodies not be used routinely for the treatment of CDI in pediatric patients with cancer and HCT recipients (conditional recommendation, moderate quality evidence)	There was a new RCT evaluating bezlotoxumab, the only monoclonal antibody generally available. While bezlotoxumab reduced recurrent CDI overall, a benefit was not observed in the new trial consisting of pediatric patients with cancer and HCT recipients. The conditional recommendation against routine use was also based upon the requirement for intravenous administration, limited data in immunocompromised patients and availability of alternatives including vancomycin and fidaxomicin. Thus, the 2018 recommendation was maintained although the quality of evidence was increased to moderate.
7. We suggest that probiotics not be used routinely for the treatment of CDI in pediatric patients with cancer and HCT recipients (conditional recommendation, low quality evidence)	While there was a new RCT of probiotics for the treatment of CDI, there were no RCTs conducted in pediatric patients and thus, the 2018 recommendation was maintained.
Good Practice Statements	
1. In pediatric patients with cancer and HCT recipients experiencing CDI, follow infection control practices including isolation according to jurisdictional policies.	This new good practice statement reflects the importance of isolation to reduce spread of CDI.
2. In pediatric patients with cancer and HCT recipients, especially those who have experienced CDI, minimize systemic antibacterial administration where feasible.	This new good practice statement recognizes the importance of removing risk factors for CDI where feasible.

Abbreviations: CDI, *Clostridioides difficile* infection; HCT, hematopoietic cell transplantation; FMT, fecal microbiota transplantation; RCT, randomized controlled trial; CPG, clinical practice guideline.

Table 1: **Summary of recommendations and changes from 2018 recommendations.**

seven RCTs included pediatric patients, none included immunocompromised pediatric patients, or more specifically, neutropenic pediatric patients receiving intensive chemotherapy.

Probiotics, when compared to placebo, significantly reduced the risk of CDI (RR 0.47, 95% CI 0.31–0.72; Table 3). When stratified by single or multiple organisms vs. placebo, the P interaction was 0.06, with a larger reduction in CDI among multiple organism probiotic (RR 0.34, 95% CI 0.19–0.61) compared to single organism probiotic (RR 0.74, 95% CI 0.42–1.30). There was no suggestion of heterogeneity of effect by adult vs. pediatric (P interaction 0.74). Funnel plot for probiotics vs. any control suggested the possibility of publication bias (Appendix 10). The trim and fill analyses did not influence interpretation (Appendix 10).

The conditional recommendation against the routine use of probiotics to prevent CDI was based upon the lack of direct data supporting efficacy and safety in neutropenic pediatric patients with cancer and HCT recipients, and the previously identified rare but documented potential for invasive infection. Thus, the 2018 recommendation was maintained. Probiotic administration in this population should continue to be restricted to the research setting, especially in severely neutropenic patients. If a probiotic is administered, it is important to understand the potential for bacterial or fungal contamination.

Recommendation 2

Use either oral metronidazole or oral vancomycin for the treatment of non-severe CDI in pediatric patients with cancer and HCT recipients (strong recommendation, low quality evidence).

Literature review and analysis

The 2018 CDI CPG strong recommendation to use oral metronidazole or oral vancomycin for the treatment of non-severe CDI was based upon five RCTs comparing vancomycin to metronidazole.[25–28] None of these RCTs included pediatric patients and only two studies included patients with cancer (65 in total). The strong

Characteristic	All studies, n (%)			Prevention, n (%)			Treatment, n (%)		
	Previous 2018 CPG	New 2024 update	Total RCTs	Previous 2018 CPG	New 2024 update	Total RCTs	Previous 2018 CPG	New 2024 update	Total RCTs
Total number RCTs	N = 65	N = 31	N = 96	N = 19	N = 16	N = 35	N = 46	N = 15	N = 61
Study population									
Adult	56 (86)	26 (84)	82 (85)	14 (74)	14 (88)	28 (80)	42 (91)	12 (80)	54 (89)
Pediatric	6 (9)	4 (13)	10 (10)	5 (26)	2 (13)	7 (20)	1 (2)	2 (13)	3 (5)
Both	3 (5)	1 (3)	4 (4)	0 (0)	0 (0)	0 (0)	3 (7)	1 (7)	4 (7)
Immune status									
Immunocompetent only	21 (32)	13 (42)	34 (35)	12 (63)	10 (63)	22 (63)	9 (20)	3 (20)	12 (20)
Any immunocompromised, not known to be neutropenic	17 (26)	4 (13)	21 (22)	2 (11)	2 (13)	4 (11)	15 (33)	2 (13)	17 (28)
Any immunocompromised, known to be neutropenic	0 (0)	4 (13)	4 (4)	0 (0)	1 (6)	1 (3)	0 (0)	3 (20)	3 (5)
Not reported	27 (42)	10 (32)	37 (39)	5 (26)	3 (19)	8 (23)	22 (48)	7 (47)	29 (48)
Cancer or HCT									
Cancer included	13 (20)	6 (19)	19 (20)	2 (11)	3 (19)	5 (14)	11 (24)	3 (20)	14 (23)
HCT included	0 (0)	3 (10)	3 (3)	0 (0)	1 (6)	1 (3)	0 (0)	2 (13)	2 (3)
Intervention group type[a]									
CDI-directed antibacterial therapy	33 (51)	12 (39)	45 (47)	1 (5)	5 (31)	6 (17)	32 (70)	7 (47)	39 (64)
FMT	10 (15)	9 (29)	19 (20)	0 (0)	2 (13)	2 (6)	10 (22)	7 (47)	17 (28)
Monoclonal antibodies	7 (11)	1 (3)	8 (8)	0 (0)	0 (0)	0 (0)	7 (15)	1 (7)	8 (13)
Probiotic	19 (29)	7 (23)	26 (27)	17 (89)	6 (38)	23 (66)	2 (4)	1 (7)	3 (5)
Other	5 (8)	4 (13)	9 (9)	1 (5)	3 (19)	4 (11)	4 (9)	1 (7)	5 (8)
Control group type									
Placebo	26 (40)	16 (52)	42 (44)	17 (89)	13 (81)	30 (86)	9 (20)	3 (20)	12 (20)
Usual care	2 (3)	3 (10)	5 (5)	2 (11)	3 (19)	5 (14)	0 (0)	0 (0)	0 (0)
Other intervention	37 (57)	12 (39)	49 (51)	0 (0)	0 (0)	0 (0)	37 (80)	12 (80)	49 (80)
Risk of bias adequacy[b]									
Sequence generation	32 (49)	20 (65)	52 (54)	11 (58)	12 (75)	23 (66)	21 (46)	8 (53)	29 (48)
Allocation concealment	30 (46)	17 (55)	47 (49)	11 (58)	10 (63)	21 (60)	19 (41)	7 (47)	26 (43)
Participants blinded	42 (65)	13 (42)	55 (57)	15 (79)	8 (50)	23 (66)	27 (59)	5 (33)	32 (52)
Outcome assessors blinded	32 (49)	17 (55)	49 (51)	11 (58)	13 (81)	24 (69)	21 (46)	4 (27)	25 (41)
Lack of attrition bias	55 (85)	25 (81)	80 (83)	15 (79)	11 (69)	26 (74)	40 (87)	14 (93)	54 (89)
Free of selective reporting	52 (80)	25 (81)	77 (80)	13 (68)	14 (88)	27 (77)	39 (85)	11 (73)	50 (82)

Abbreviations: CPG, clinical practice guideline; FMT, fecal microbiota transplantation; HCT, hematopoietic cell transplantation; RCTs, randomized controlled trials; CDI, *Clostridioides difficile* infection. [a]Trials could have more than one intervention group and thus, totals do not always add up to 100%. [b]Number of studies adjudicated to have these attributes and thus, at reduced risk of bias.

Table 2: **Characteristics of included randomized trials focused on *Clostridioides difficile* infection prevention or treatment.**

Outcome	Revised	N	No. of Patients	RR	95% CI	I^2 (%)	P value
Probiotic main							
Probiotic vs. Any Control	New	23	8154	0.43	0.28–0.65	19%	<0.0001
Probiotic vs. Placebo	Yes	20	7600	0.47	0.31–0.72	19%	0.0005
Probiotic vs. Placebo stratified							
Probiotic type							Pint = 0.06
Single organism	New	10	2095	0.74	0.42–1.30	0%	0.29
Multiple organisms	New	10	5505	0.34	0.19 –0.61	26%	0.0003
Adult or pediatric							Pint = 0.74
Adult only	Yes	14	6338	0.46	0.26–0.82	40%	0.009
Pediatric only	Yes	6	1262	0.39	0.18–0.86	0%	0.02

Abbreviations: N, Number of studies; RR, risk ratio; CI, confidence interval; Pint, P value for interaction.

Table 3: **Efficacy of interventions for the prevention of *Clostridioides difficile* infection.**

Outcome	Revised	N	No. of patients	RR	95% CI	I^2 (%)	P value
Antibacterial therapy							
Vancomycin vs. Metronidazole (all)							
Cure at the end of antibiotic treatment	No	5	856	1.05	1.00–1.11	0%	0.07
Cure at the end of follow-up	No	5	856	1.07	0.97–1.19	33%	0.19
Recurrence	No	5	705	0.89	0.65–1.23	0%	0.48
Vancomycin vs. Metronidazole (severe)							
Cure at the end of antibiotic treatment	No	3	234	1.22	1.05–1.42	0%	0.01
Recurrence	No	3	176	0.95	0.37–2.34	50%	0.91
Fidaxomicin vs. Vancomycin							
Cure at the end of antibiotic treatment	Yes	7	1989	1.01	0.97–1.06	15%	0.59
Cure at the end of follow-up	Yes	8	2027	1.18	1.10–1.25	0%	<0.00001
Recurrence	Yes	7	1659	0.53	0.41–0.70	20%	<0.00001
Surotomycin vs. Vancomycin							
Cure at the end of antibiotic treatment	No	3	1280	0.98	0.93–1.03	0%	0.41
Cure at the end of follow-up	No	3	1280	1.06	0.96–1.17	17%	0.28
Recurrence	No	3	1056	0.80	0.62–1.03	25%	0.09
Cadazolid vs. Vancomycin							
Cure at the end of antibiotic treatment	Yes	3	1253	0.97	0.92–1.01	0%	0.16
Cure at the end of follow-up	Yes	3	1247	1.04	0.96–1.14	0%	0.34
Recurrence	Yes	3	1040	0.76	0.59–1.00	0%	0.05
Fecal Microbiota Transplantation							
Fresh with Direct Administration[a] vs. Vancomycin							
Cure at the end of follow-up	Yes	3	97	1.83	0.70–4.78	78%	0.21
Frozen with Direct Administration[a] vs. Vancomycin							
Cure at the end of follow-up	Yes	3	122	1.53	0.64–3.63	82%	0.34
Monoclonal Antibodies							
Bezlotoxumab vs. Placebo							
Cure at the end of treatment	New	3	1693	0.99	0.92–1.06	70%	0.75
Cure at the end of follow-up	New	3	1693	1.13	0.98–1.30	69%	0.08
Recurrence	New	3	1378	0.63	0.52–0.76	0%	<0.00001
Actoxumab + Bezlotoxumab vs. Placebo							
Recurrence	No	3	1389	0.57	0.42–0.77	51%	0.0003
Probiotic							
Probiotic vs. Placebo							
Recurrence	Yes	3	172	0.58	0.38–0.90	0%	0.02

Abbreviations: N, Number of studies; RR, risk ratio; CI, confidence interval. [a]Direct administration was defined as product delivery directly to the small or large intestine via naso-duodenal/jejunal tube, colonoscopy or enema.

Table 4: **Efficacy of interventions for the treatment of *Clostridioides difficile* infection.**

Among pediatric patients with cancer and hematopoietic cell transplantation recipients:

- Confirm or revise definition of severe CDI
- Conduct randomized controlled trials to evaluate the benefits and risks of different prophylactic and therapeutic strategies specifically in this population for patients with non-severe and severe CDI
- Identify treatment strategies for those who cannot tolerate oral antibacterial therapy
- Determine the safety and efficacy of currently available and newer formulations of probiotics and fecal microbial transplantation in this population, particularly among those with severe neutropenia and severe immunosuppression
- Determine the cost effectiveness of fidaxomicin vs. metronidazole and vancomycin for the treatment of initial and recurrent CDI
- Determine if the duration of CDI antibacterial therapy should change in the presence of concurrent systemic antibacterial therapy
- Determine the risk of recurrence during the initial CDI episode

Abbreviation: CDI, *Clostridioides difficile* infection.

Table 5: **Identified knowledge gaps.**

recommendation that either oral metronidazole or oral vancomycin may be used for non-severe CDI was based on similar cure and recurrence rates observed among all analyzed patients.[11]

For the 2024 CDI CPG update, there were 39 RCTS that evaluated CDI-directed antibacterial therapy for the treatment of CDI, with seven new studies added to the update (Appendices 6 and 7). The new studies compared fidaxomicin vs. vancomycin (n = 4), cadazolid vs. vancomycin (n = 2) and ridinilazole vs. vancomycin (n = 1). As there were no new RCTs comparing metronidazole and vancomycin, the 2018 CPG recommendation was maintained. Given that a statistically significant benefit of cadazolid was not shown against vancomycin (Table 4) and since it is no longer currently marketed, the panel did not make a recommendation regarding its use.

Recommendation 3

Use either oral vancomycin or oral fidaxomicin for the treatment of severe CDI in pediatric patients with cancer and HCT recipients (strong recommendation, low quality evidence).

Literature review and analysis

The 2018 CDI CPG made a strong recommendation to use oral vancomycin for the treatment of severe CDI in pediatric patients with cancer and HCT recipients based on an analysis of three of the vancomycin vs. metronidazole studies that reported outcomes for a subset of patients with severe CDI.[25,26] In this analysis, vancomycin significantly increased the cure rate at the end of the antibiotic treatment compared to metronidazole (RR 1.22, 95% CI 1.05–1.42).[11] The likely better tolerability of oral vancomycin compared to oral metronidazole also contributed to the recommendation.

For the 2024 CDI CPG update, there were no new RCTs comparing metronidazole to vancomycin. There were eight RCTs comparing fidaxomicin vs. vancomycin for CDI treatment, four of which were new to this CPG update (Appendices 6 and 7). One new study enrolling 148 pediatric patients in total included patients with cancer and HCT recipients, and some participants were known to be neutropenic.[29] Fidaxomicin, when compared to oral vancomycin, significantly increased cure at the end of follow-up (RR 1.18, 95% CI 1.10–1.25) and significantly decreased recurrence (RR 0.53, 95% CI 0.41–0.70; Table 4). These data support the option of fidaxomicin for initial CDI treatment. Fidaxomicin benefits are likely more important in severe vs. non-severe CDI. Consequently, fidaxomicin was added as an option in this setting. Vancomycin was retained as an option for severe CDI because rates of cure at the end of antibiotic treatment were comparable and because of its established efficacy and safety in this population.

Recommendation 4

Consider fidaxomicin for the treatment of recurrent CDI in pediatric patients with cancer and HCT recipients (conditional recommendation, moderate quality evidence).

Literature review and analysis

The 2018 CDI CPG made a conditional recommendation to consider fidaxomicin administration for recurrent CDI based on better efficacy of fidaxomicin compared to vancomycin in achieving cure at the end of the follow-up period and in reducing CDI recurrence in adult RCTs.[11]

The new studies comparing fidaxomicin vs. vancomycin were summarized in Recommendation 3 above. The increase in number of RCTs and direct data in pediatric cancer patients increased the quality of evidence to moderate from low in the 2018 CDI CPG. However, the recommendation remained conditional since fidaxomicin was not studied specifically in the recurrent CDI setting and since many patients treated with oral vancomycin for recurrent CDI are expected to have good outcomes.

Recommendation 5

Do not use FMT routinely for the treatment of CDI in pediatric patients with cancer and HCT recipients (strong recommendation, low quality evidence).

Literature review and analysis

The 2018 CDI CPG made a strong recommendation against routine use of FMT for the treatment of CDI based on nine adult RCTs of FMT. Only one included children (n = 3), none of whom had cancer.[30] There were three studies that compared fresh FMT vs. vancomycin, with disparate findings.[31–33] Two studies were stopped early for efficacy[31,33] while one study was stopped early for futility.[32] The strong recommendation against routine use of FMT was based upon uncertainty regarding the efficacy of fresh FMT compared to vancomycin, absence of direct data in pediatric patients with neutropenia and challenges related to administration such as need for colonoscopy and bowel preparation.

For the 2024 CDI CPG update, there were 16 RCTs evaluating FMT for CDI treatment, seven of which were new to this CPG update (Appendices 8 and 9). The FMT products were as follows: fresh FMT (n = 6), frozen FMT (n = 10) and both fresh and frozen FMT (n = 1). Across all studies, there was heterogeneity in control group type and route of FMT administration. There remained only one study that included pediatric patients[30] and none of the patients were known to be neutropenic. Table 4 shows the synthesis when fresh or frozen and approach to administration were analyzed separately. The effect on cure at the end of follow-up was

uncertain for three studies comparing fresh FMT with direct intestinal administration vs. vancomycin (RR 1.83, 95% CI 0.70–4.78; Table 4) and three studies comparing frozen FMT with direct intestinal administration vs. vancomycin (RR 1.53, 95% CI 0.64–3.63; Table 4). Given these data and the ongoing concerns about safety and logistical considerations, the 2018 CDI CPG recommendation was maintained. The highest concern is during periods of neutropenia and immunosuppression. Thus, once patients have completed therapy and are no longer immunosuppressed, FMT may be a reasonable option.

Recommendation 6

We suggest that monoclonal antibodies not be used routinely for the treatment of CDI in pediatric patients with cancer and HCT recipients (conditional recommendation, moderate quality evidence).

Literature review and analysis

The 2018 CDI CPG made a conditional recommendation against the routine use of monoclonal antibodies for the treatment of CDI in pediatric patients with cancer and HCT recipients based on four RCTs.[34–36] The combination of actoxumab and bezlotoxumab significantly reduced CDI recurrence vs. placebo; no pediatric patients were included in these RCTs. While these RCTs were conducted using the combination of actoxumab and bezlotoxumab, only bezlotoxumab is approved by the United States Food and Drug Administration[37] and the European Medicines Agency.[38]

For the 2024 CDI CPG update, one new pediatric RCT evaluating bezlotoxumab monotherapy was identified. In this study, 101/139 (73%) participants were immunocompromised and it included patients with cancer and HCT recipients.[39] While bezlotoxumab reduced recurrent CDI vs. placebo based on the synthesis of the two adult and one pediatric RCTs (RR 0.63, 95% CI 0.52–0.76; Table 4), a benefit was not observed in this new pediatric RCT. The conditional recommendation against routine use was also based upon the requirement for intravenous administration and availability of other effective therapies including vancomycin and fidaxomicin. Thus, the 2018 recommendation was maintained although the quality of evidence was increased to moderate.

Recommendation 7

We suggest that probiotics not be used routinely for the treatment of CDI in pediatric patients with cancer and HCT recipients (conditional recommendation, low quality evidence).

Literature review and analysis

In the 2018 CDI CPG, the panel made a conditional recommendation against the routine use of probiotics as an adjunct to CDI-directed antibacterial therapy based on three RCTs that examined probiotics or prebiotics for the treatment of CDI.[40–42] The recommendation was based on the absence of pediatric patients in the included RCTs and the same invasive infection considerations discussed in Recommendation 1.

With the 2024 CDI CPG update, the prebiotic study was removed from the probiotic synthesis and one new study[43] was identified. The new study only included adult patients and severely immunocompromised patients were excluded (Appendices 6 and 7). When synthesized, probiotics, when compared to placebo, significantly reduced the risk of CDI recurrence (RR 0.58, 95% CI 0.38–0.90; Table 4). The conditional recommendation against routine use of probiotics to treat CDI was related to the absence of direct pediatric data combined with the potential risk of invasive infection in severely immunocompromised patients. Thus, the 2018 recommendation was maintained.

Good practice statement 1

In pediatric patients with cancer and HCT recipients experiencing CDI, follow infection control practices including isolation according to jurisdictional policies.

Rationale

This statement acknowledges the importance of isolation to limit the spread of CDI and that specific policies may differ by jurisdiction.

Good practice statement 2

In pediatric patients with cancer and HCT recipients, especially those who have experienced CDI, minimize systemic antibacterial administration where feasible.

Rationale

This statement acknowledges that exposure to systemic antibacterial therapy is a known risk factor for CDI in pediatric patients with cancer and HCT recipients.[3,44] It also recognizes the importance of antibiotic stewardship.

Discussion

In the 2024 CDI CPG update, we identified additional RCTs for the prevention or treatment of CDI published since 2018. Recommendations were modified from the 2018 CDI CPG accordingly. While the number of RCTs has increased, it is notable that the number conducted in pediatric populations, particularly those who are neutropenic due to cancer therapies, remains limited. This lack of representation contrasts with the acknowledgement that pediatric patients receiving intense cancer treatments including HCT are at increased risk of CDI.[45] Thus, new RCTs in pediatric patients receiving cancer treatments should be prioritized and are particularly important since interventions such as products that include live organisms may have a different safety profile in this population compared to

immunocompetent populations. As evidence becomes available in the future, it will be important to revisit and revise these recommendations so that they are appropriately informed by contemporary published data. Although not considered in this CPG, pediatric specific criteria for diagnosing CDI, including both testing and clinical signs and symptoms, need to be established as they are important to the systematic implementation of treatment recommendations.

In summary, we present the 2024 CDI CPG update for the prevention and treatment of CDI in pediatric patients with cancer and HCT recipients.

Outstanding questions

An important question that remains is the ideal definition for severe CDI in pediatric patients with cancer and undergoing HCT. More direct RCT evidence is also needed to evaluate the benefits and risks of different prophylactic and therapeutic strategies specifically in this population for patients with non-severe and severe CDI. In addition, questions around the safety of probiotics and FMT in patients who are severely neutropenic and immunocompromised remain. A list of the identified gaps can be found in Table 5.

Contributors

Study concepts and design: PP, PDR, BTF, RP, JEM, TL, SK, CK, GMH, AE, CE, ND, CD, EC, MPB, RAA, LLD, LS.

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Data interpretation: PP, PDR, BTF, RP, JEM, TL, SK, CK, GMH, AE, CE, ND, CD, EC, MPB, RAA, LLD, LS.

Drafting the manuscript or revising it critically for important intellectual content: PP, PDR, BTF, RP, JEM, TL, SK, CK, GMH, AE, CE, ND, CD, EC, MPB, RAA, LLD, LS.

Final approval of version to be published: PP, PDR, BTF, RP, JEM, TL, SK, CK, GMH, AE, CE, ND, CD, EC, MPB, RAA, LLD, LS.

Agreement to be accountable for all aspects of the work: PP, PDR, BTF, RP, JEM, TL, SK, CK, GMH, AE, CE, ND, CD, EC, MPB, RAA, LLD, LS.

PP, PDR, BTF, RP, JEM, TL, SK, CK, GMH, AE, CE, ND, CD, EC, MPB, RAA, LLD, LS have read and approved the final version of the manuscript.

Data sharing statement

The authors declare that all of the results of the systematic review used to inform the recommendations in this clinical practice guideline are presented within the article and appendices. No original study data are presented.

Declaration of interests

BTF has served on a data safety monitoring board for Astellas and BTF's institution has received grant support from Allovir and Pfizer as well as CDC, FDA and NIH for research performed.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102604.

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