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American Society for Transplantation and Cellular Therapy Series: #5—Management of *Clostridioides difficile* Infection in Hematopoietic Cell Transplant Recipients

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A B S T R A C T

The Practice Guidelines Committee of the American Society for Transplantation and Cellular Therapy partnered with its Transplant Infectious Disease Special Interest Group to update its 2009 compendium-style infectious disease guidelines for hematopoietic cell transplantation (HCT). A completely new approach was taken with the goal of better serving clinical providers by publishing each standalone topic in the infectious disease series as a concise format of frequently asked questions (FAQ), tables, and figures. Adult and pediatric infectious disease and HCT content experts developed and then answered FAQs and finalized topics with harmonized recommendations that were made by assigning an A through E strength of recommendation paired with a level of supporting evidence graded I through III. This fifth guideline in the series focuses on *Clostridioides difficile* infection with FAQs that address the prevalence, incidence, clinical features, colonization versus infection, clinical complications, diagnostic considerations, pharmacological therapies for episodic or recurrent infection, and the roles of prophylactic antibiotics, probiotics, and fecal microbiota transplantation.

Clostridioides difficile infection (CDI) is the leading cause of infectious diarrhea among immunosuppressed hematopoietic cell transplant (HCT) recipients who are at an increased risk for the infection compared with other hospitalized populations because of iatrogenic immunosuppression, broad-spectrum antimicrobial exposure, and prolonged hospitalizations.

EPIDEMIOLOGY AND COMPLICATIONS

FAQ1: What are the major risk factors for CDI after allogeneic HCT and how do these compare to risk factors after autologous HCT?

The first line of defense against CDI is a healthy microbiome. The second line of defense is the immune response against *C. difficile* and its toxins. As such, major risk factors for CDI tend to be ubiquitous among HCT recipients and include antibiotic treatment (including fluoroquinolone prophylaxis), chemotherapeutic disruption to the bacterial microbiota and mucosa which may occur during conditioning [1], and compromised immunity, whether related to age, acuity of illness, or medical conditions such as graft-versus-host disease (GVHD). HCT studies have not consistently found additional risk factors beyond allo- (higher risk) versus auto-HCT and degree of immunosuppression [1–9].

FAQ2: At what time point after HCT are most cases of CDI diagnosed?

The incidence of CDI after allo HCT is 9% to 10% but was as high as 31% in one study and is consistently higher than that seen after auto HCT (5%-6%) [2,6,9-26]. CDI is diagnosed more frequently before engraftment versus after engraftment. After engraftment, the risk for CDI in allo-HCT is higher compared to

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auto-HCT [27,28]; about half of all CDI cases in allo-HCT occur after engraftment [6,8,18,25,29].

FAQ3: Are there secondary complications associated with CDI in the HCT population?

As with other nontransplant populations, HCT recipients with CDI may experience direct complications related to CDI, including dehydration leading to acute kidney injury, toxic megacolon, bowel perforation, death [6,30]. CDI recurrence is a potential secondary complication after a primary CDI episode. Interestingly, most studies have not found a higher incidence of recurrent CDI compared to other patient populations [6,12,31-33].

CDI may also increase the risk for bacteremia with enteric organisms during HCT [34,35]. It is postulated that compromised gut mucosal integrity from chemotherapy and/or GVHD is contributory in the setting of immunocompromise. *C. difficile* toxins further impair colonic mucosal integrity, potentially facilitating translocation of gut bacteria into the bloodstream. GVHD has been found to be both a risk factor for, and a potential complication of, CDI in allo-HCT (Supplementary Table S1 [93–96]) [6,13,36,37]. GVHD and its treatment increase the risk for infection, which leads to antibiotic exposures, both of which increase the risk for CDI. CDI may increase the risk for GVHD because the damage caused by *C. difficile* toxins may expose host antigens to donor immune cells, inciting an immune response.

CLINICAL FEATURES

FAQ4: What are the key clinical features associated with C. difficile *infection in HCT?*

Like other patient populations, unexplained, new-onset diarrhea (≥3 loose bowel movements in a 24-hour time period) or acute worsening of chronic diarrhea is the primary symptom and may be accompanied by abdominal cramping/pain, nausea, vomiting, and fever. More severe CDI is associated with elevated serum creatinine because of dehydration or sepsis. Scoring systems for severity of CDI in the general population have not been validated in HCT recipients [38–41]. For example, leukocytosis, used as a predictor of severity in the general population, may be absent in HCT recipients due to recent conditioning chemotherapy or underlying disease, and signs of inflammation or pain may be absent due to immunosuppressants.

FAQ5: How can CDI be distinguished from other potential causes of diarrhea after HCT?

CDI can coexist with noninfectious diarrhea, the latter includes medications (oral magnesium supplements, laxatives, oral contrast) or increasing the rate of enteral formula feeds as common examples. The relatively high frequency of post-transplantation diarrhea and *C. difficile* colonization (See FAQ6) can confound the interpretation of test results for CDI.

In general, the first step in evaluation of diarrhea should include a comprehensive review of medications and removal of any potentially offending agents. If the degree of diarrhea and associated symptoms and clinical parameters are within expectations based on the treatment(s) received, and the patient is clinically stable, it is reasonable to monitor the patient. If the degree of diarrhea or its associated symptoms are worse than would otherwise be expected, then testing for *C. difficile* is warranted (AIII) [38]. Other enteric pathogens (viral, bacterial, and parasitic) could also be considered based on host risk and exposures. Infectious diseases or gastroenterology consultation may be helpful in determining whether additional stool testing is warranted, particularly in cases where the presentation of CDI is atypical, or where the patient is not responding as expected to CDI therapy. In these instances, alternative diagnoses such as gastrointestinal GVHD or infectious colitis may be considered, and additional work-up such as endoscopy with biopsies may be needed to solidify a diagnosis.

DIAGNOSIS

FAQ6: How does colonization confound the diagnosis of C. difficile *infection?*

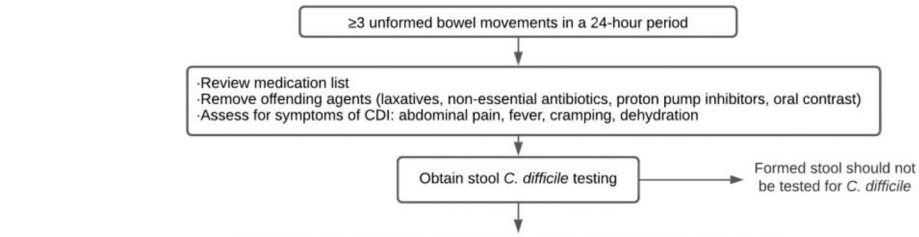
Colonization with toxigenic *C. difficile* has been detected in 11% to 39% of allo-HCT candidates before transplant. Colonization may increase the risk of early CDI, but relevant studies are confounded by use of nucleic acid amplification tests (NAATs; see FAQ7) as the diagnostic method and CDI being associated with conditioning regimens that are more likely to cause diarrhea. In other words, diarrhea may be from the conditioning regimen and NAAT detects pre-existing colonization [12]. Colonization in children is more common than in adults. Up to 50% of infants <1 year of age carry toxigenic strains of *C. difficile* [42–44] and *C. difficile* toxins can be found in the stool of asymptomatic infants [45,46]. Whether *C. difficile* can cause disease in children <2 years of age is unclear. In <1-year-olds, it is not recommended to routinely test for *C. difficile* (AIII) [38]. For 1- and 2-year-olds, testing should only be done after excluding other causes of diarrhea, when there is a high suspicion for CDI and should be limited to diarrheal stool specimens (AIII) [38].

FAQ7: What is the optimal method for diagnosis of C. difficile *infection in HCT?*

The optimal method to diagnose CDI has not been established, and clinicians typically do not have the ability to determine which diagnostic assays will be used. As such, it is important to be familiar with the diagnostics available, which one(s) are used at your facility, and their interpretation (Figure 1). There are 3 primary categories of commercially available tests for *C. difficile* used in the United States; NAATs (the most widely used being polymerase chain reaction), enzyme immunoassays (EIAs) for toxins A and B, and glutamate dehydrogenase (GDH) assays. Less frequently used in the United States, but at times more commonly used outside of the United States, are cytotoxicity cell assays and stool culture for *C. difficile*. Below we discuss characteristics consistent within a class of diagnostic assay, but the reader should be aware that differences may exist across manufacturers, platforms, and there can be inter-person variability in assay performance.

Current assays detect *C. difficile* toxins (toxin EIA and cytotoxicity cell assay) or the organism (GDH, NAAT, culture), but none are diagnostic for CDI. CDI is a clinical diagnosis based on presence of clinically significant diarrhea alongside other signs/symptoms of CDI *plus* temporally associated evidence of toxigenic *C. difficile* or its toxins in the stool. Simply detecting *C. difficile* or its toxins in stool without associated CDI symptoms does not indicate CDI because colonic *C. difficile* colonization most commonly is asymptomatic. Therefore testing for the presence of *C. difficile* in formed stools is not recommended. Risk factors for colonization are the same as those for CDI [47–49]. Interpreting a diagnostic assay result must take into account both patient and performance characteristics of the assay(s) used.

In general, methods that detect the organism are more sensitive than methods that detect toxins, but methods that detect toxins are more specific for CDI. Currently in the United States, many laboratories use NAAT as a standalone test [50]. These are highly sensitive for detecting the gene that encodes *C. difficile* toxin production in stool. They have an excellent negative



Possible *C. difficile* testing results and interpretation

NAAT-based algorithms	Toxin test	Interpretation
NAAT+	Positive	Patient likely has CDI.
NAAT-	Not performed	Patient does not have CDI.
NAAT+	Not performed	Patient may have CDI. In appropriate setting, treatment may be considered if high clinical suspicion.
NAAT+	Negative	Patient may have CDI or colonization with toxigenic strain. In appropriate setting, treatment may be considered if high clinical
Not performed	Positive	Patient likely has CDI. For children <2 years of age, see FAQ 6.
PCR (polymerase chain reaction) is a type of Nucelic Amplification Test (NAAT) that detects the gene encoding toxin B.		
Toxin tests include: Enzyme immunoassay (EIA) for *C. difficile* toxins (A, B, or A+B) or tissue culture cytotoxicity assays. They detect the toxins that cause CDI. Cytotoxicity assay uses cell culture to determine if there is cytopathic effect when stool is added; an antisera is added to neutralize the cytopathic effect. **When positive, a positive toxin tests usually indicates a patient with CDI if that patient has an appropriate clinical syndrome.**		
GDH-based algorithms	**Toxin test**	**Interpretation**
GDH+	Positive	Patient likely has CDI.
GDH -	Not performed	Patient does not have CDI.
GDH+	Negative	Arbitrated by NAAT. Patient may have CDI or *C. difficile* colonization without CDI. Clinical judgment should be used to determine if treatment is needed.
GDH (glutamate dehydrogenase) is an enzyme produced by toxigenic and non-toxigenic strains of *C. difficile*. This detects all strains of *C. difficile* (both toxigenic and non-toxigenic strains).		
Other methods		**Interpretation**
Toxigenic culture	Positive	Patient may have CDI or colonization with toxigenic strain. In appropriate setting, treatment may be considered if high clinical suspicion.
Toxigenic culture is an anaerobic culture of the organism. It cannot distinguish between a toxin-producing strain and a non-toxin-producing strain.		

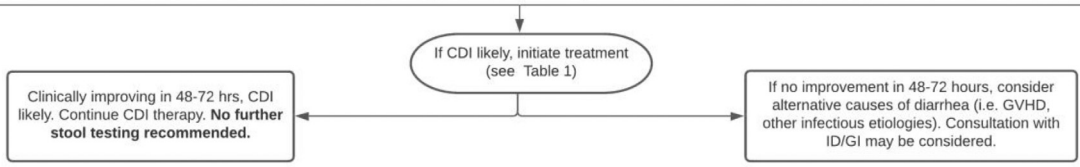


Figure 1. Possible *C. difficile* testing results and interpretation.

predictive value for CDI (~99%); however, because of the high sensitivity, they have a poor positive predictive value for CDI (50% to 60%) [38]. GDH assays should not be used alone to determine who has CDI because bacteria (other than toxin-producing strains of *C. difficile*) that produce GDH may result in a positive assay. GDH assays are typically paired with a toxin EIA. GDH assays are very sensitive, and negative GDH assays have excellent negative predictive value for CDI (~99%) [38]. A positive GDH assay paired with a positive toxin EIA has very good positive predictive value for CDI (~85%) [38]. Most patients with a positive GDH but negative toxin EIA do not have CDI. Some laboratories will reflexively use a NAAT for stools that test positive for GDH and negative by toxin EIA. Approximately 50% of patients with a positive NAAT will have CDI, so clinical judgement is needed when determining which patients with a positive GDH, negative toxin EIA, and positive NAAT should receive treatment for CDI.

PHARMACOLOGIC TREATMENT

FAQ8: What are first-line treatments for an initial episode of CDI? (Table 1)

Table 1

Discontinuation of inciting antibiotic agent(s) as soon as possible should always be considered as their continued use has been shown to decrease clinical response and increase recurrence rates (AII) [51,52]. Discontinue unnecessary proton-pump inhibitors when possible because some studies suggest an epidemiologic association between proton-pump inhibitor use and CDI risk (BIII) [53,54].

- Recommended first-line treatment is oral fidaxomicin, or vancomycin as an alternative agent if fidaxomicin is not available (AI) [38,55-58]. Although there are no randomized controlled trials specific to the stem cell transplant population, randomized trials in adults, which included patients with cancer, suggested higher cure and sustained response rates and fewer recurrences associated with fidaxomicin use [59]. Furthermore, when compared with oral vancomycin, fidaxomicin may cause less disruption to the gut microbiome, a factor that may influence the treatment decision-making process, particularly early during the transplant course (See FAQ 13) [60–62]. The choice of CDI treatment may be individualized based on shared informed-decision making between the provider and patient, taking into consideration factors such as the local epidemiology, the patient's risk for recurrent CDI, and other factors such as drug coverage benefits.
- Fidaxomicin is dosed at 200 mg by mouth twice per day for 10 days for adults (AI) [55,59]. The dosing for pediatric patients <6 years old is 16 mg/kg oral suspension twice

Table 1
Treatment Options for *C. difficile* Infection in Adult and Pediatric Stem Cell Transplant Recipients

	Ways Supplied	Indication/Dosing	Comment
Agent			
Fidaxomicin	Oral tablet oral suspension (pediatrics)	First Episode CDI: Standard dosing (adults): 200 mg twice a day × 10 days Standard dosing (pediatrics): 16 mg/kg/dose (max 200 mg) twice a day for 10 days Recurrent CDI: Standard dosing (adults): 200 mg twice a day × 10 days Extended dosing (adults): 200 mg twice a day from days 1-5, then every other day from days 7-25 Tapered-pulsed (adults): 200 mg twice a day × 10 days, once a day for 7 days, every other day for 26 days (total 40 capsules) Recurrent CDI (pediatrics): 16 mg/kg/dose (max 200 mg) twice a day for 10 days	The package insert for fidaxomicin provides additional information regarding pediatric dosing according to body weight.
Vancomycin	Oral capsule oral reconstituted solution IV solution administered orally IV solution administered per rectum	First Episode CDI: Standard dosing (adults): 125 mg four times a day × 10 days Standard dosing (pediatrics): 10 mg/kg (125 mg max dose) by mouth every 6 hours × 10 days Recurrent CDI: Standard dosing (adults): 125 mg four times a day × 10 days (only if metronidazole used in prior episode) Tapered-pulsed (adults)* Recurrent CDI (pediatrics)† Fulminant CDI: Standard dosing (adults): Vancomycin 500 mg 4 times daily by mouth or by nasogastric tube (in addition to IV metronidazole 500 mg q8 hours) Standard dosing (pediatrics): 10 mg/kg (500 mg max dose) by mouth or by nasogastric tube every 6 hours (in addition to IV metronidazole 10 mg/kg/dose q8h, max 500 mg/dose)	Per rectum vancomycin (500 mg VAN in 100 mL NS via retention enema every 6 hours) can be considered in patients with fulminant disease.
Metronidazole	Oral tablet oral capsule IV	PO (adults): 500 mg every 8 hours (if VAN or FDX are not available) × 10 days IV (adults): (as an adjunctive agent for fulminant CDI in patients receiving VAN or FDX) 500 mg every 8 hours Pediatric dosing: 7.5 mg/kg/dose 3 times a day or 4 times a day (max 500 mg per dose) × 10 days IV (pediatrics): (as an adjunctive agent for fulminant CDI in patients receiving VAN or FDX) 10 mg/kg/dose q8h, max 500 mg/dose	Generally considered to be less efficacious than VAN or FDX. Used as an adjunct to oral vancomycin for fulminant CDI.
Adjunctive Therapies‡			
Bezlotoxumab	IV	Adults: Monoclonal antibody indicated for the prevention of recurrence in at-risk patients on CDI therapy	Supplied as a single 10 mg/kg dose [69]. Safety and efficacy have not been evaluated in pediatric patients; a study in children is currently recruiting subjects.
MRT	PO, endoscopically	No standardized dosing available	Has not been studied in larger randomized trials in immunocompromised patients. Potential risk of bacteremia associated with the product in immunosuppressed patients.

VAN indicates vancomycin; NS, normal saline; FDX, fidaxomicin; PO, per os.

* Tapered and pulse regimen: one approach after completing a 10-day treatment course of 125 mg four times per day would be to decrease to once per day for 4 weeks, then 125 mg every other day for 2 weeks, and then 125 mg once every 3 days for 2 weeks.

† Vancomycin tapered regimen in pediatrics: 10 mg/kg (125 mg max dose) 4 times per day for 10–14 days, followed by 10 mg/kg 2 times per day for 7 days, then 10 mg/kg once per day for 7 days, then 10 mg/kg by mouth every 2 or 3 days for 2–8 weeks.

‡ Consideration for adjunctive therapies should be made in consultation with an infectious disease specialist.

daily (maximum 400 mg/d), and 200 mg twice per day for ≥6 years of age (AI) [63]. The phase 3 trials in adults comparing fidaxomicin to oral vancomycin for patients experiencing a first episode of CDI or a first recurrence found fidaxomicin to be noninferior to vancomycin for initial cure but superior for sustained clinical response (i.e., both initial cure plus no recurrence at 30 days after treatment was stopped) [59,64]. Although not powered for efficacy, a safety study done in children found no difference for initial cure, but fidaxomicin was associated with a significantly better sustained clinical response compared to oral vancomycin [63].

- Vancomycin is dosed at 125 mg by mouth 4 times per day for 10 days (AI) [39,65-67]. Intravenous (IV) vancomycin is

unable to treat CDI because of insufficient penetration into the colon when administered by IV.
- Oral metronidazole is no longer recommended as a first-line agent because it was found to be inferior to oral vancomycin in double blinded randomized trials in adults (DI) [39,67].
- In adults, bezlotoxumab (human monoclonal antibody against *C. difficile* toxin B), given as a single intravenous infusion (10 mg/kg) during active CDI treatment, may be used as an adjunct to standard antibacterial therapy for CDI to reduce the risk of recurrent CDI (rCDI) (BI). Two Phase III studies found a significant reduction in recurrent CDI among immunocompromised subjects receiving the infusion when compared to placebo [58,68,69]. In addition to patients with a history of immunocompromise (such as post-HCT), patients who are above the age of 65, who have severe CDI, or who have a history of prior CDI may further benefit from the addition of bezlotoxumab to standard of care antibiotics [68,70].
- For patients with fulminant CDI (i.e., hypotension or shock, ileus, or megacolon), a regimen of vancomycin 500 mg 4 times daily by mouth or by nasogastric tube in addition to intravenous metronidazole (500 mg every 8 hours) should be administered. For patients with an ileus, in whom there is no contraindication to rectal installation, consider adding a rectal instillation of vancomycin [38].

FAQ9: What are the major treatment options for recurrent CDI?

Recurrent CDI is defined as a new episode of symptom onset consistent with CDI and a positive assay after a successfully treated episode of CDI with an onset ranging from within days up to 4 to 12 weeks after cessation of treatment for the prior episode [38]. Consultation with an infectious diseases specialist should be considered for all patients with rCDI.

First recurrence

- Recommended treatments for a first episode of rCDI are a 10-day treatment course of oral fidaxomicin 200 mg twice per day (BI), or an extended course of fidaxomicin (200 mg twice per day for 1 to 5 days, then every other day for days 7 to 25) (BI) [38,56-58,64].
- An oral vancomycin taper-pulse is an acceptable alternative for a first recurrence (BII). Vancomycin tapers have not been standardized, so the optimal duration and taper strategy are not known. Typically, the daily number of doses of vancomycin are reduced over time down to once per day, followed by pulse dosing to every other day and once every 3 days. A retrospective, observational study suggests extending dosing to once every 3 days is associated with fewer recurrences than once every other day dosing [38,71,72].
- If not previously administered, bezlotoxumab, given as a single intravenous infusion (10 mg/kg) during active CDI treatment, may be used as an adjunct to standard antibacterial therapy for CDI to reduce the risk of rCDI (BI) [68,73]. There are no data on the efficacy and safety of additional doses of bezlotoxumab.

Second or greater recurrence

The optimal therapy for second or greater CDI recurrence has not been defined. There are a variety approaches to subsequent rCDI, including:

- Standard dosing of fidaxomicin (200 mg twice per day for 10 days) [38,55-57] (CIII)
- Extended dosing of fidaxomicin (200 mg twice per day for 1 to 5 days, then every other day for days 7 to 25)[57] (CIII)
- Taper-pulse of fidaxomicin (for example: 200mg twice per day for 10 days, once per day for 7 days, then once every other day for 26 days [total 40 capsules]) [74] (CIII)
- Taper-pulse of oral vancomycin (CIII) [38,71,72]
- Microbiota restoration therapy (MRT)/fecal microbiota transplantation (FMT) to address associated gut dysbiosis (see FAQ10) (DIII)
- If not previously administered, bezlotoxumab, given as a single intravenous infusion (10 mg/kg) during active CDI treatment, may be used as an adjunct to standard antibacterial therapy for CDI to reduce the risk of rCDI (BI) [68,75]

OTHER MANAGEMENT CONSIDERATIONS

FAQ10: Can MRT be administered after HCT and what are the potential associated risks?

Although there are reports of successful intestinal MRT/FMT for rCDI in HCT recipients [76], there is insufficient safety and tolerability data in this context [77–79]. HCT recipients may be at increased risk for bacterial translocation from bacteria transferred with MRT, resulting in an invasive bloodstream infection, unanticipated immunologic consequences of MRT on GVHD, and procedure-associated risks [80]. With these uncertainties, MRT is not routinely recommended as a treatment option for rCDI in HCT recipients, especially neutropenic patients (DIII). Use of MRT/FMT in HCT needs to be individualized with a careful assessment of the risks and benefits. An infectious diseases consultation is recommended to determine whether this is appropriate for individual patients.

FAQ11: What other supportive care can be considered?

Probiotics have not been found to be helpful to prevent CDI or rCDI in well done studies [38]. In addition, bacteria and fungi found in probiotics can cause infection after HCT [81]. Because of the lack of benefit and potential risk, the use of probiotics are not recommended in HCT recipients for prevention of CDI (DIII). Addition of an anti-motility agent (e.g., loperamide) as an adjunct to specific antibacterial therapy for CDI may be safe, although no prospective or randomized studies are available (C-III) [38].

SPECIAL CONSIDERATIONS

FAQ12: How should asymptomatic carriers of* C. difficile *be detected and managed?

Whether patients should be screened for colonization on admission to the hospital to prevent transmission to other patients is an area of ongoing study. However, if a patient is found to be a carrier of *C. difficile* but without CDI, then contact precautions are recommended (BII). This is because carriers without active CDI can be a source of *C. difficile* transmission to other patients in the hospital [82–85].

The treatment of asymptomatic carriers is not recommended because the risks and benefits for this approach are not known (DIII). CDI treatment disrupts the microbiome and facilitates colonization and infection caused by other enteric organisms, such as vancomycin-resistant enterococcus, candida, or resistant Gram negatives. Microbiome disruption is also associated with worse outcomes after allo HCT [86,87].

FAQ13: Is there a role for primary and secondary CDI prophylaxis in HCT?

Fidaxomicin 200 mg once per day was evaluated in a double-blinded randomized controlled adult study for primary prevention of CDI [88]. The study did not meet its primary composite endpoint, which was prophylaxis failure through 30 days after discontinuation of the study drug. Downsides to prophylaxis include promotion of resistance to fidaxomicin [89]. There are insufficient data to recommend fidaxomicin for CDI prophylaxis at this time: (CI).

Oral vancomycin as primary prophylaxis was shown to reduce CDI in one retrospective adult study [90], but this has not been validated in randomized controlled trials. Retrospective studies on secondary prophylaxis with oral vancomycin in non HCT settings have yielded mixed results. Oral vancomycin is highly disruptive to the microbiome, and microbiome disruption has been associated with worse outcomes after allogeneic HCT [86,87]. Oral vancomycin also facilitates colonization and infection caused by other enteric organisms (See FAQ12). There are insufficient data to recommend for the use of oral vancomycin for CDI prophylaxis at this time: (CII). Metronidazole should not be used for CDI prophylaxis because of lack of efficacy and risk of toxicity with extended use [91,92]: (EIII).

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jtct.2022.02.013.

APPENDIX 1. GRADING OF STRENGTH OF RECOMMENDATION AND LEVEL OF EVIDENCE

	Grade	Supporting
FAQ1 to FAQ7 Recommendation		
If diarrhea or its associated symptoms are worse than would otherwise be expected, then testing for CDI is warranted.	AIII	[38]
In <1 year-olds, it is not recommended to routinely test for *C. difficile*.	AIII	[38]
For 1- and 2-year-olds, testing should be done only after excluding other causes of diarrhea, when there is a high suspicion for CDI, and should be limited to diarrheal stool specimens.	AIII	[38]
Discontinuation of inciting antibiotic agent(s) as soon as possible should always be considered as their continued use has been shown to decrease clinical response and increase recurrence rates.	AII	[51,52]
Discontinue unnecessary proton-pump inhibitors when possible.	BIII	[53,54]
FAQ8 Recommendation		
Recommended first-line treatment is oral fidaxomicin or vancomycin as an alternative agent if fidaxomicin is not available.	AI	[38,55-58,64]
	AI	[56,64]
Fidaxomicin is dosed at 200 mg by mouth twice per day for 10 days for adults.	AI	[63]
Fidaxomicin dosing for pediatric patients <6 years old is 16 mg/kg oral suspension twice daily (maximum 400 mg/d) and 200 mg twice per day for ≥6 years of age.	AI	[39,65,66,97]
Vancomycin is dosed at 125 mg by mouth 4 times per day for 10 days.	DI	[39,67]
Oral metronidazole is no longer recommended as a first-line agent because it was found to be inferior to oral vancomycin in double- blinded randomized trials in adults.	BI	[58,68,69]
Bezlotoxumab, given as a single intravenous infusion (10 mg/kg) during active CDI treatment, may be used as an adjunct to standard antibacterial therapy for CDI to reduce the risk of rCDI.	AII	[38]
For fulminant CDI, a regiment of vancomycin 500 mg 4 times daily by mouth or by nasogastric tube in addition to intravenous metronidazole (500 mg every 8 hours) should be considered. Consider adding a rectal instillation of vancomycin if ileus present.	Grade	Supporting
FAQ9 to FAQ11 Recommendation	BI	[38,56-58,64]
For first episode of rCDI, recommended treatments are a 10-day treatment course of oral fidaxomicin 200 mg twice per day or an extended course of fidaxomicin (200 mg twice per day for 1-5 days, then every other day for days 7-25).	BII	[38,71,72]
An acceptable alternative for first recurrence of CDI is an oral vancomycin taper-pulse.	CIII	[38,55-57]
Optimal therapy for second or greater CDI recurrence has not been defined. In such cases, standard dosing of fidaxomicin could be used.	CIII	[57]
Optimal therapy for second or greater CDI recurrence has not been defined. In such cases, extended dosing of fidaxomicin could be used.	CIII	[74]
Optimal therapy for second or greater CDI recurrence has not been defined. In such cases, taper-pulse of fidaxomicin could be used.	CIII	[38,71,72]
Optimal therapy for second or greater CDI recurrence has not been defined. In such cases, taper-pulse of oral vancomycin could be used.	DIII	[77–80]
Routine use of MRT is not routinely recommended as a treatment option for rCDI in HCT recipients, especially neutropenic patients.	DIII	[81]
Probiotics are not routinely recommended for prevention of CDI in HCT recipients.	BI	[68,73]
In patients with rCDI, bezlotoxumab may be used as an adjunct to standard antibacterial therapy for CDI to reduce the risk of rCDI.	CIII	[38]
There are insufficient data to recommend for or against the addition of an anti-motility agent as an adjunct to specific antibacterial therapy for CDI.		
FAQ12 to FAQ13 Recommendation		
Contact precautions are recommended for patients who test positive for *C. difficile*.	BII	[82–85]
Treatment of asymptomatic *C. difficile* carriers is not recommended.	DIII	[86,87]
There are insufficient data to recommend for or against the use of fidaxomicin for CDI prophylaxis in HCT recipients.	CI	[88,89]
There are insufficient data to recommend for or against the use of oral vancomycin for CDI prophylaxis in HCT recipients.	CII	[90]
Metronidazole should not be used for CDI prophylaxis due to lack of efficacy and risk of toxicity with extended use.	EIII	[91,92]

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