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Clostridium difficile in Oncology Patients—Review of Diagnosis and Management in the Indian Setting

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Abstract

Clostridoides (formerly *Clostridium*) *difficile* (*C. difficile*) is a toxin-producing, gram-positive anaerobic bacillus, commonly implicated in antibiotic-associated diarrhea and pseudomembranous colitis. The true burden of *C. difficile* infection is unclear in India, as it is likely underdiagnosed and underreported. Its incidence is much higher in oncology patients where it can contribute significantly to morbidity and mortality. There are several challenges in the Indian setting, including lack of uniform availability of testing infrastructure, as well as therapy. Oncology patients further present with a unique set of challenges. This article will review the approach to diagnosis and management of *C. difficile*-associated diarrhea in India, with a focus on oncology patients.

Keywords
- *Clostridium difficile*
- gram-positive anaerobic bacillus

Introduction

Clostridium difficile is a toxin-producing gram-positive anaerobic bacillus, commonly implicated in antibiotic-associated diarrhea (CDAD) and pseudomembranous colitis. CDAD remains a formidable problem in healthcare facilities across the globe. In 2011, close to half a million cases of *C. difficile* infection (CDI) were reported in the United States, with the majority of cases occurring in the elderly patients (over 65 years of age).[1] There is also a financial price to pay for these infections. A meta-analysis of 42 studies published in 2016 showed that CDI placed a significant financial burden on the US healthcare system.[2] In this study, the average and incremental length of stay for CDI in-patient treatment were 11.1 (90% confidence interval [CI]: 8.7–13.6) and 9.7 (90% CI: 9.6–9.8) days respectively. Total annual CDI-attributable cost in the United States was calculated to be US$ 6.3 (range: $1.9–$7.0) billion).[2]

CDI is a common problem in oncology patients. A retrospective review found that 17.3% of the 225 patients with solid tumors admitted to a hospital with diarrhea had CDAD.[3]

A multicenter survey of oncology units showed that the pooled rate of hospital-acquired CDAD in patients with cancer was more than twice the rate reported for all patients in the United States.[4]

The incidence of CDAD has been estimated to be between 7.1 and 30% in various Indian studies.[5–7] A study published in 2017 from India showed that out of the 791 patients with nosocomial diarrhea included, 6% had CDAD. Among these patients, malignancy was found to be the most common underlying condition.[8] A 2021 study from a tertiary care center in south India showed the prevalence of CDAD in cancer patients to be 18.67%.[9]

Due to the lack of large-scale data and multicentric studies, the true burden of this problem is unknown in India. Lack of uniform availability of testing infrastructure as well as access to therapy is among the challenges faced in Indian settings. Drugs such as fidaxomicin are not available, and modalities such as fecal microbiota transplantation (FMT) are not well established in most Indian hospitals. Oncology patients further present with their unique set of challenges.

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They have multiple risk factors for the development of CDAD; chemotherapy itself can lead to dysbiosis of the gut flora. Antibiotic exposure in these patients is generally frequent and can be for longer durations. These patients also have multiple hospital encounters leading to increase in incidences of nosocomial infections.

There are no national guidelines and there is lack of clarity regarding testing protocols for CDAD in India. Also, FMT is performed in very few centers in the country and there are no established protocols regarding donor screening and administration. This article reviews the approach to diagnosis and management of CDAD in India and sheds light on how we can overcome some diagnostic and therapeutic challenges, with a focus on oncology patients. It also suggests a protocol for performing FMT, and suggests various steps that can be taken by hospitals across the country to curb the problem of CDI.

Diagnosis of CDAD in the Oncology Population in India

Population Criteria for Testing

Diarrhea in the oncology patients can have a wide range of differential diagnoses. These can include:

- Chemotherapeutic agents
- Immunotherapeutic agents
- Surgery
- Radiation therapy
- Underlying malignancy
- Infectious causes, including *C. difficile*

Clinical Practice Guidelines for CDI issued by the Infectious Disease Society of America (IDSA) in 2017 recommend testing when the patient has had three or more unformed stools in the preceding 24 hours.[10] Other causes of diarrhea in this population need to be considered carefully before ordering a stool *C. difficile* assay.

Principles of Laboratory Testing

Pathogenicity of *C. difficile* to cause CDAD is associated with production of two toxins, that is, toxin A (enterotoxin) and toxin B (cytotoxin). Not all strains of *C. difficile* possess the gene locus containing *tcdA* and *tcdB* genes to express these toxins. Hence, the diagnosis of CDI is based on the detection of these toxins and not just the detection of bacteria.

Clinical utility of any modality of laboratory testing to "rule in" (positive predictive value—PPV) or "rule out" (negative predictive value) diagnosis of CDI depends on its specificity and sensitivity, respectively. It is also decided by the prevalence of the disease in a particular population, and hence, denotes the pretest probability of the disease. Since diarrhea in oncology patients can have numerous infectious and noninfectious differential diagnoses, exclusion of these before ordering a *C. difficile* test enhances the PPV of the test.

C. difficile colonizes the large bowel of the gastrointestinal (GI) tract. It can be a part of the normal gut flora of children less than 2 years of age, in whom colonization rates can exceed 40%.[11] Colonization rates as high as 30%[12] are also seen in adults with prolonged hospitalization, such as the patients hospitalized in the oncology units. This is another reason why exclusion of other etiologies is essential for the accurate clinical interpretation of positive results.

Modalities of Laboratory Testing

Variety of testing modalities are available for the diagnosis of CDI, as summarized in ►**Table 1**.

Approach to Laboratory Testing

Testing for stool samples should be limited to selection of "loose stool that takes the shape of the container." If other causes of diarrhea have not been ruled out, a multistep algorithm that uses glutamate dehydrogenase (GDH) antigen plus toxin assay arbitrated by NAAT or nucleic acid amplification test plus toxin assay rather than NAAT alone should be followed.

If other etiologies have been excluded, which increases the pretest probability of CDAD, then NAAT alone or the GDH plus toxin assay arbitrated by NAAT or NAAT plus toxin assay rather than toxin assay alone should be used. We propose the following algorithm based on IDSA guidelines that can be applied to oncology patients in India. (►**Table 2**)

►**Table 3** describes some other important diagnostic pearls, which are valuable in the Indian setting.

Diagnostic Challenges in Oncology Patients

Oncology patients have an increased risk of *C. difficile* colonization owing to increased healthcare exposures, use of antimicrobial, and chemotherapeutic agents. Hence, distinguishing between colonization and infection is critical in these patients. However, toxin assays may have a lower sensitivity in immunocompromised patients.[13] Hence, a polymerase chain reaction (PCR) test for detecting toxigenic strains may be required. The exact reason for this phenomenon is still being studied. In these patients, even a small amount of toxin (below the limit of detection of the assay) can cause clinically significant CDAD. Also, some of these patients may receive intravenous immunoglobulins as a part of therapy for their underlying disease, which may bind *C. difficile* toxins A/B.[13] A PCR test may not be available in many laboratories across the country, and when performed as a part of a GI syndromic PCR panel (multiplex panel), may escalate the cost of diagnosis.

Management of *C. difficile*-Associated Diarrhea in Oncology Patients in the Indian Setting

Therapy for the Initial Episode of CDAD

The 2021 IDSA guidelines on the management of *C. difficile* recommend fidaxomicin as the agent of choice for the first episode of CDAD.[14] Data suggests a higher cure rate and lower rates of recurrence for fidaxomicin compared with oral vancomycin.[15] However, the cost of therapy and lack of availability in India are prohibitive factors for the use of fidaxomicin. The guidelines state that vancomycin remains an acceptable alternative when oral fidaxomicin is unavailable.[14]

Table 1 Diagnostic modalities for *Clostridium difficile*-associated diarrhea (CDAD)

Testing modality	Basic principle	Sensitivity (SS)/ specificity (SP)	Advantages	Limitations
Toxigenic culture (TC)	Inoculation of stool on a selective/chromogenic medium	SS: 22–100% SP: 90% (6)	High sensitivity. Performance of drug susceptibility testing	Cumbersome to perform Need of technical expertise Prolonged turnaround time—around 1 week Low positive predictive value (PPV) due to growth of non-toxigenic strains
Cell culture cytotoxicity neutralization assay (CCNA)	Observation of cytopathic effect (CPE), cell rounding and neutralization of CPE with antitoxin	SS: 75–85% SP: 93–100% (7)	Reference gold standard for laboratory confirmation of *C. difficile* infection (CDI) Very high specificity	High level of expertise needed
Glutamate dehydrogenase (GDH) antigen	Detection of GDH enzyme secreted by *C. difficile* using: Rapid lateral flow immunochromatography Enzyme linked immunosorbent assay (ELISA) Enzyme linked fluorescence immunoassay (ELFA)	SS: 71–95% SP: 87–90% (8)	Easy to perform Rapid results Inexpensive Excellent sensitivity, can be used as a screening test	Positive results in both toxigenic as well as non-toxigenic strains, hence low PPV
Toxin A and B immunoassays (TIA)	Detection of toxin A and B in the specimen using: rapid lateral flow immuno-chromatography ELISA ELFA	SS: 60–86% SP: 91–98% (9)	Easy to perform Rapid results Inexpensive	Inconsistent sensitivity due to variations in strains and kits Cannot be used as the sole test for the diagnosis of CDI due to false negative results.
Nucleic acid amplification test (NAAT)	Exponential amplification and detection of tcdA and tcdB genes using real-time polymerase chain reaction (PCR) Cartridge based PCR assays LAMP (ligase mediated amplification) Multiplex PCR syndromic gastrointestinal panels	SS: 82–100% SP: 90–100% (10)	High sensitivity, specificity Rapid turnaround time Excellent negative predictive value (NPV)	Positive results may be obtained with colonization and needs clinical correlation

The recommended dose of oral vancomycin in nonsevere cases is 125 mg administered every 6 hours. A meta-analysis comparing less than 2 g of oral vancomycin per day versus more than 2 g of daily oral vancomycin did not find any significant differences in the rates of recurrence in the two groups.[16] Though rare, a handful of case reports have described detectable serum levels in patients administered oral vancomycin.[17] This is usually applicable to patients with an impaired renal function or those receiving high doses of oral vancomycin.

Fulminant or severe *C. difficile* is defined as CDAD with a total leukocyte count of more than 15000/mm^3, or with more than or equal to 50% increase in the serum creatinine. However, in the oncology setting, these parameters may be difficult to use as the patients may be neutropenic and may have other causes for renal impairment. Hence, the Zar score can be used (►**Table 4**), where a score of more than or equal to 2 indicates severe CDI.

Fidaxomicin has not been evaluated in fulminant (previously known as severe, complicated CDAD), and hence, the drug of choice in fulminant CDAD remains oral vancomycin (500 mg dose administered every 6 hours). For patients with ileus, 500 mg of vancomycin in 100 mL of normal saline can be administered as retention enema every 6 hours. Also, the addition of intravenous metronidazole can be considered.

Usually, the recommended duration of therapy for the initial episode is 10 to 14 days.

CDAD Refractory or Resistant to Vancomycin

Vancomycin resistance in the case of *C. difficile* has been described. A particular strain of *C. difficile* designated as BI/NAP1/027 is characterized by the presence of a binary toxin and deletions in the regulatory gene, *tcdC* and by resistance to moxifloxacin.[18] A report from Israel found that 87.7% of the ribotype 027 isolates had a vancomycin minimum inhibitory concentration more than 2 mg/L.[19] A

Table 2 Diagnosis of CDI in oncology patients

GDH antigen	Assay for toxin A	Assay for toxin B	Recommended approach and comments
Positive	Positive	Positive	Treat as CDAD
Positive	Positive	Negative	Treat as CDAD
Positive	Negative	Positive	Treat as CDAD
Negative	Negative	Negative	Do not treat as CDAD
Positive	Negative	Negative	May indicate colonization. If high clinical suspicion, PCR for *C. difficile* should be done in oncology patients; do not treat if PCR is negative.
NAAT			
Positive	Positive	Positive	Treat as CDAD
Negative	Negative	Negative	Do not treat as CDAD
Positive	Negative	Negative	Probable colonization if pretest probability low, do not treat as CDAD Probable CDAD if pretest high, treat as CDAD
Positive	Negative	Positive	Treat as CDAD
Positive	Positive	Negative	Treat as CDAD

Abbreviations: CDAD, *Clostridium difficile*-associated diarrhea; CDI, *C. difficile* infection; GDH, glutamate dehydrogenase; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction.

Table 3 Other diagnostic pearls in the Indian setting

Do not perform repeat testing routinely within 7 days of the same episode of diarrhea, if initial test is negative
Repeat testing may be considered in patients with worsening of symptoms and a high index of clinical suspicion for CDI
Do not test for screening asymptomatic carriers
Episodes of recurrent CDI should be assessed by repeat testing
No value in testing to establish cure—more than 60% tests remain positive after successful therapy
Testing should not be routinely performed in the first 2 years of life unless clinical suspicion for CDAD is high

Abbreviations: CDAD, *Clostridium difficile*-associated diarrhea; CDI, *C. difficile* infection.

Table 4 Zar score for fulminant (severe) CDAD

Factor	Points assigned
Age > 60 years	1
Body temperature > 38.3 C	1
Albumin < 2.5 g/dl	1
Endoscopic evidence of pseudomembranous colitis	2
Treatment in the ICU	2

Abbreviations: CDAD, *Clostridium difficile*-associated diarrhea; ICU, intensive care unit.

pan European longitudinal survey from 2015 found that the epidemic ribotypes 027 and 001/072 were associated with multiple antimicrobial resistance of high levels.[20] Despite this in vitro observation, clinical response to vancomycin is noted in a majority of patients. This is likely due to the high colonic concentrations attained with proper dosages of oral vancomycin. However, this does point to a potential problem of emergence of clinically refractory cases in the future. It also highlights the need for adequate vancomycin dosing in these patients that ideally should be administered four times a day. The mechanism of resistance to vancomycin, however, remains unclear.[21] Amino acid changes in peptidoglycan biosynthesis-associated proteins such as MurG may play a potential role in the resistance to vancomycin.[22]

Therapy for *C. difficile* being refractory to vancomycin remains uncertain. Fidaxomicin as stated earlier is not freely available and its high cost is also prohibitive in the Indian setting. A prospective observational study by Popovic et al comparing the therapy of oral teicoplanin with that of oral vancomycin found that teicoplanin resulted in a significantly higher clinical cure rate compared with vancomycin.[23] Teicoplanin is freely available in India and can be a useful drug in the setting of vancomycin-refractory CDAD in India. A dose of 200 mg twice a day can be used in this setting. An ampule containing 200 mg/3 mL of teicoplanin can be directly given with 100 to 200 mL of water.

Other agents such as nitazoxanide, tigecycline, and rifaximin should only be used as salvage therapy, when other regimens have failed.

Management of Recurrent Episodes

Recurrence rates for CDAD can be as high as 25%. When available, fidaxomicin remains the drug of choice for a

recurrent episode. For the first recurrence of CDAD, vancomycin as a tapered and pulsed regimen should be used. A suggested regimen is oral vancomycin—125 mg, four times a day for 14 days; followed by 125 mg, twice a day for 1 week; then 125 mg daily for a week, later 125 mg every 2 to 3 days for 2 to 8 weeks. In a randomized control study, patients receiving rifaximin 400 mg three times daily for 20 days immediately after completing standard therapy for CDAD were found to have a lower recurrence versus those given placebo (15 vs. 31%).[24] For patients with multiple *C. difficile* recurrences, the therapeutic options include:

(i) Vancomycin as a tapered and pulsed regimen
(ii) Vancomycin (250 mg, every 6 hours for 10 days) followed by rifaximin (400 mg, every 8 hours for 20 days) and
(iii) FMT.

Should Other Antibiotics be Stopped in Oncology Patients with CDAD?

There is evidence to suggest that continuation of unorthodox antimicrobials to treat CDAD may lead to compromised initial response to CDI therapy and may reduce the durability of response.[25] However, in the case of cancer, this decision has to be taken after careful evaluation of the patient and ruling out other infections.

Monoclonal Antibody

The monoclonal antibody Bezlotoxumab (against the toxin B of *C. difficile*) is not available in India. It can be used in conjunction with antimicrobial agents that are active against *C. difficile,* especially in the elderly and immunocompromised patients.

Fecal Microbiota Transplantation (FMT) in the Indian Setting

The pathophysiology of CDAD involves intestinal dysbiosis. Hence, the use of FMT has garnered a surge in interest in the management of CDAD. Currently, FMT can be considered for the following indications:

- Recurrent CDAD
- CDAD which is refractory to antimicrobial therapy
- May be considered in severe or fulminant disease, though the data are limited

In a randomized trial of 232 patients with recurrent CDAD treated with FMT, the efficacy for one FMT was approximately 50% which increased to 75% for two FMTs performed and approximately 90% for more than two FMTs performed.[26]

FMT responses can be durable; in a retrospective study, almost 78% of the patients continued to show a good response at the end of 1 year.[27]

In the Indian setting, lack of stool banks and preformed capsules can pose a challenge. Stool inoculum from the donor needs to be freshly prepared before administration. Also, donor screening can be challenging, with high rates of bacterial colonization in the Indian population. This also needs to be balanced with cost constraints which may limit donor testing. ►**Table 5** outlines our institutional approach to selecting a donor for FMT. Scrupulous screening of the donor stool to exclude the presence of multidrug-resistant

Table 5 Suggested approach to donor selection for FMT in the Indian settings

Suggested clinical evaluation of the donor:
Should be off immunosuppressive therapy, chemotherapy, antimicrobial agents or proton pump inhibitors in the preceding 3 months
Should not have personal or family history of chronic gastrointestinal diseases
Should not have a history of HIV, syphilis, hepatitis B or C viral infections No personal history of cancer, including gastrointestinal cancers or polyposis syndrome, and first- degree family history of premature colon cancer
Previous tissue or organ transplant recipients are excluded
Suggested laboratory evaluation of the donor in the Indian setting:
Hemogram, liver function tests, CRP, ESR
HIV and VDRL
Hepatitis C antibody
Hepatitis A IgM antibody
Hepatitis B surface antigen
Routine stool examination for ova, cysts, and larvae
Stool bacterial culture and antibiotic susceptibility testing to exclude MDROs like ESBL and carbapenemase producing gram-negative bacilli, as well as vancomycin-resistant Enterococci
Modified ZN staining for cryptosporidium, isospora, and microsporidia
C. difficile assay

Abbreviations: CRP, C-reactive protein; ESBL, extended spectrum β lactamases; ESR, erythrocyte sedimentation rate; FMT, fecal microbiota transplantation; HIV, human immunodeficiency virus; IgM, immunoglobulin M; MDROs, multidrug-resistant organisms; VDRL, venereal disease research laboratory test (for syphilis); ZN, Ziehl–Neelsen.

Table 6 Suggested protocol of FMT solution preparation

At least 50 g of stool specimen is submitted by the donor on the day of FMT using sterile stool collection kit provided by the laboratory. Time of specimen voiding is noted
Donor stool sample is processed in biosafety cabinet, the technician donning aprons, impervious gown, and cap
Using sterile wooden spatula, 50 g of stools is emulsified in 250 mL of nonbuffered sterile saline (autoclaved in a screw capped glass bottle and cooled)
Emulsion is sieved through triple layered sterile gauze to filter out coarse particles (>1–2 mm). Resultant filtrate is collected in a sterile flask and transferred to the endoscopy suite with an airtight seal
FMT solution needs to be infused within 6 hours of donor voiding. The solution is stored at room temperature until the procedure
Patients should not be taking any antibiotics or probiotics 48 hours before FMT
If diarrhea persists 1 week after procedure, *C. difficile* NAAT testing should be done and repeat FMT may be considered if positive

Abbreviations: FMT, fecal microbiota transplantation; NAAT, nucleic acid amplification test.

microorganisms, parasites, and *C. difficile* is essential. ►**Table 6** gives a brief description of the protocol of FMT solution preparation followed at our center.[28]

Administration can be done via the upper or lower GI approach, though the American College of Gastroenterology 2021 guidelines favor the administration of FMT via a colonoscopy.[29] The safety of FMT in neutropenic patients has not been completely established and better-quality data are needed before this practice is adopted, especially in India. Here, donor stools may be frequently colonized with resistant pathogens increasing the risk of donor-derived infections.

Periprocedural cessation of antimicrobial agents (which is needed for FMT) can sometimes pose a challenge in immunocompromised patients.

Antimotility Agents

There is no definitive evidence to suggest that antimotility agents are contraindicated. In a retrospective study of 339 patients with hematological malignancies who had CDAD, it was found that the addition of antimotility agents to appropriate antimicrobial therapy does not pose any additional risk.[30]

Infection Control and Preventive Practices

Oncology units are especially prone to CDAD outbreaks. Asymptomatically colonized patients or healthcare workers can transmit the infection to the immunocompromised hosts.[31] Transmission can occur from a CDAD patient or an asymptomatic colonizer via the hands of the healthcare personnel. Spores of *C. difficile* can contaminate and survive on equipment, fomites, and the environment. Contaminated commode seats and bedpans are particularly associated with a high risk of transmission. Thorough and frequent disinfection of medical equipment and environmental surfaces with sporicidal agents like hydrogen peroxide or peracetic acid is an important preventive measure.[32] At our institution, we use peracetic acid for surface disinfection as well as in the event of an outbreak. Commonly used surface disinfectants like quaternary ammonium compounds or alcohol are ineffective in eradicating *C. difficile* spores.

Oncology patients who develop CDAD must be placed on contact isolation (private rooms with dedicated toilets). Barrier nursing precautions should be strictly followed entailing the use of dedicated equipment, a separate nurse for each CDAD patient, as well as the use of personal protective equipment like gown, cap, mask, and gloves. Since *C. difficile* spores resist being killed by alcohol, handwashing using soap, and water should be mandatory after contact with every patient. Contact isolation must continue for at least 48 hours after diarrhea has resolved. Surveillance of CDAD is an important aspect of infection control. Incidence of CDAD over time and in different healthcare units/wards should be monitored for timely recognition of clusters or outbreaks. This helps in focused implementation of rigorous infection control measures.

The most important preventive aspect of CDAD is the reduction in antibiotic exposure of patients. Judicious antibiotic therapy practices such as avoiding unnecessary empiric usage, culture guided treatment, timely de-escalation to narrow spectrum antibiotics, avoiding unnecessary long-term usage, and timely termination of treatment need to be followed to decrease the risk of emergence of CDAD. Robust stewardship programs must be enforced and regulated.[33]

Conclusion

CDAD can be associated with significant morbidity and mortality in oncology patients. The diagnosis needs to be made promptly and colonization must be distinguished from infection. Prompt therapy must be initiated; therapeutic options may be limited in the Indian setting. The pros and cons of administering a FMT must be weighed carefully before performing the procedure. Strict infection control protocols need to be enforced. More data are needed from India regarding the unique challenges posed by CDAD in our settings.

Conflict of Interest
None declared.

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