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Review

Diagnosis and Treatment of *Clostridioides difficile* Infection

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Clostridioides difficile infection (CDI) remains a leading cause of healthcare-associated diarrhea worldwide, with high morbidity, recurrence, and healthcare burden. Timely and accurate diagnosis, effective treatment, and preventive strategies are critical in improving patient outcomes. This review presents a comprehensive overview of CDI and focuses on diagnostic criteria, severity classifications, recurrence risk prediction, and therapeutic approaches, emphasizing both international and Japanese perspectives. The use of the Bristol Stool Scale and appropriate stool testing protocols helps ensure diagnostic accuracy and avoid overtreatment. Japan's adoption of the MN severity criteria, which incorporate clinical, laboratory, and imaging findings, contrasts with laboratory-based classifications in international guidelines. While both structured diagnostic algorithms and evidence-based treatment guidelines offer prognostic value, MN criteria may better reflect real-world clinical decision-making in Japan. CDI recurrence remains a significant clinical challenge. This review highlights two predictive models—CHIEF score and the novel Days of Antibiotic Spectrum Coverage (DASC) metric—developed in Japanese cohorts. Both tools enable early identification of high-risk patients and support decisions on prophylactic or tailored therapy. Therapeutic options include fidaxomicin (FDX), vancomycin, and metronidazole (MTZ). Recent international guidelines favor FDX due to its superior microbiota-sparing properties and reduced recurrence rates. However, MTZ remains an option for mild cases in Japan because of cost considerations and differences in CDI strain prevalence. By comparing local and global practices, this review underscores the importance of region-specific data in optimizing CDI management and encourages further integration of emerging risk stratification tools and treatment strategies to improve care across diverse clinical settings.

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Introduction

Clostridioides difficile (CD) infection (CDI) is one of the most common infections encountered in hospitals and requires appropriate treatment and strict infection control measures. Therefore, accurate diagnosis and prompt intervention are essential. Even with appropriate treatment, CDI has a high recurrence rate: recurrence develops in approximately 25% of patients after the initial episode and in up to 65% after multiple episodes[1]. Recurrent CDI not only worsens clinical outcomes but also places a substantial economic burden on healthcare systems. Thus, early identification of high-risk patients and implementation of preventive strategies are crucial.

Given the ongoing evolution in CDI management—including novel diagnostics, therapeutics, and preventative recurrence—our motivation is to provide an up-to-date review that summarizes current practices and bridges perspectives from international and Japanese guidelines. We emphasize differences between Japanese and international practices, especially in our review of studies conducted in Japan. This includes epidemiology, the Japan-specific severity criteria (MN criteria) and their evalu-

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Table 1 Stool characteristics based on BSS are useful for accurate diagnosis of CDI[3]

Stool type	Stool characteristics	Interpretation
1	Separate hard lumps, like nuts, difficult to pass	Severe constipation
2	Sausage-shaped but lumpy	Mild constipation
3	Like a sausage but with cracks on the surface	Normal
4	Like a sausage or snake; smooth and soft	Normal
5	Soft blobs with clear-cut edges	Mild diarrhea
6	Fluffy pieces with ragged edges; a mushy stool	Moderate diarrhea
7	Watery, no solid pieces; entirely liquid	Severe diarrhea

ation, and Japanese studies on recurrence risk predictors (e.g., a recurrent CDI prediction score which includes carbapenem, hematological malignancy, irritable bowel disease, enteral feeding, and fluoroquinolone [CHIEF] and Days of Antibiotic Spectrum Coverage [DASC]-based analyses). Additionally, we highlight therapeutic strategies aimed at reducing recurrence risk. In doing so, we aim to provide clinicians with a comprehensive and up-to-date resource that offers new insights and clarifies how regional differences in practice can inform optimal CDI management.

Bristol Stool Scale and Diagnosis of CDI

Healthcare facility-onset CDI is defined as an infection in patients aged ≥2 years who have been hospitalized for more than 3 days, experience three or more episodes of loose or watery stools within 24 hours or an increase in stool frequency from baseline, and test positive for stool toxins or a toxigenic CD isolate[2]. To ensure consistency in identifying diarrhea, the Bristol Stool Scale (BSS)[3] is recommended (**Table 1**)[2]. When CDI is suspected, stool samples with a BSS score of 5 or higher should be submitted for testing. The BSS offers several advantages. First, it improves selection of appropriate stool specimens and reduces unnecessary testing. Because asymptomatic colonization of CD occurs in approximately 0–15% of healthy adults and 4–29% of hospitalized patients[4], testing of stools without diarrhea may lead to false-positive results. Second, using the BSS helps avoid overtreatment in patients without true CDI, thus promoting appropriate antimicrobial stewardship. Finally, it reduces unnecessary infection control measures in patients without active diarrhea. It is important to note that CDI can present with ileus (toxic megacolon) in severe cases, where little to no diarrhea occurs[5]. In such instances, a high index of suspicion is needed despite the absence of frequent loose stools. Patients with CDI-related ileus may have significant abdominal distension and systemic toxicity; radiologic findings (e.g., colonic distension on imaging) and toxin assays on minimal stool or rectal swab can aid diagnosis. Recognizing this atypical presentation ensures that CDI is not overlooked in patients with severe illness.

International guidelines (e.g., Infectious Diseases Society of America / Society for Healthcare Epidemiology of America [IDSA/SHEA], European Society of Clinical Microbiology and Infectious Diseases [ESCMID]) similarly recommend limiting CDI testing to patients with ≥3 unexplained new-onset unformed stools in 24 hours[6,7]. The Japanese guidelines uniquely highlight the use of the BSS to objectively define stool consistency, aiming to standardize sample selection[2]. This approach is consistent with global efforts to avoid testing formed stool and reduce false positives. The emphasis on BSS in Japan may stem from local observations of high asymptomatic colonization rates (4.2–15.3%)[8], necessitating stricter criteria to prevent overdiagnosis. In essence, while core diagnostic criteria are similar across regions, Japanese guidance places additional practical measures (like BSS) to improve diagnostic accuracy, reflecting epidemiological differences and a commitment to antimicrobial stewardship and infection control.

Rapid CDI diagnosis typically relies on three tests[2,6,7]: glutamate dehydrogenase (GDH) antigen detection, enzyme immunoassays (EIAs) for toxins A and B, and nucleic acid amplification tests (NAATs) (**Table 2**)[9–16]. A meta-analysis of 42 studies with over 29,000 samples by Arimoto et al.[17] reported the pooled sensitivity and specificity of GDH testing at 91.1% and 91.2%, respectively, with a positive likelihood ratio of 10.4, a negative likelihood ratio of 0.098, and an area under the curve (AUC) of 0.970, demonstrating excellent diagnostic accuracy. This large study firmly established GDH as an effective, cost-effective, and sensitive first-line screening method for CDI. Similar analyses have confirmed these findings: a recent systematic review in Korea reported GDH EIA sensitivity of approximately 92.7% and specificity of approximately 94.6%, whereas toxin A/B EIAs showed much lower sensitivity (~58%) but higher specificity (~

Table 2 Key characteristics of CDI diagnostic methods

Diagnostic test	Detects	Approx. Sensitivity	Approx. Specificity	Key Pros/Cons
GDH antigen EIA[9-12]	*C. difficile* glutamate dehydrogenase (common antigen)	High (88–94%)	Moderate (89–94.4%)	Pros: Excellent screening tool; very sensitive and quick. A negative GDH effectively rules out CDI (high NPV). Cons: Not specific for toxigenic strains; requires confirmatory toxin test. Does not indicate active infection on its own.
Toxin A/B EIA[9, 10, 13, 14]	*C. difficile* toxins (A and/or B)	Moderate (45.5–87%)	Very High (94.1–98%)	Pros: High specificity—a positive result confirms toxin-mediated disease. Rapid turnaround. Cons: Moderate sensitivity—many false negatives; negative result does not exclude CDI if suspicion is high.
NAAT (PCR)[10, 15, 16]	Toxin gene (e.g., tcdB) DNA	Very High (91–100%)	High (96–100%)	Pros: Detects toxigenic *C. difficile* with high accuracy; rapid. Useful for discordant GDH/toxin results. Cons: Cannot distinguish infection from colonization; must be used judiciously with clinical context.

GDH, glutamate dehydrogenase; EIA, enzyme immunoassay; NAAT, nucleic acid amplification test; PCR, polymerase chain reaction; DNA, deoxyribonucleic acid; NPV, negative predictive value.

97%)[18]. Another global meta-analysis reported GDH EIA sensitivity of around 82% (95% confidence interval [CI]: 79–84%), reflecting some variation across different settings[19]. Despite these minor differences, all studies confirm that GDH has high sensitivity as a CDI rule-out test, whereas toxin EIAs, though highly specific, can miss a substantial proportion of true positives. The significance of the Arimoto et al.[17] study lies in its scale and resulting confidence in using GDH as the initial screen in multistep diagnostic algorithms. In clinical practice, these algorithms often include confirmatory NAATs for GDH-positive but toxin-negative cases, enhancing diagnostic accuracy. However, while NAATs have high sensitivity and specificity (85–100% and 90–95%, respectively)[12,14], they detect genes rather than active toxins, necessitating careful interpretation in asymptomatic carriers.

A positive *C. difficile* test in a patient without CDI symptoms generally indicates colonization rather than infection. Such patients should not be treated for CDI in the absence of clinical illness. Instead, infection control measures (e.g., hand hygiene protocols) should be implemented to prevent transmission, and the patient should be monitored for any development of symptoms. This principle underscores why current guidelines discourage testing formed stool or asymptomatic individuals[2,6,7]: diagnostic assays must be applied only in patients with compatible clinical signs to avoid overdiagnosis and overtreatment of carriers (**Figure 1** shows the CDI diagnosis flowchart).

Risk Factors for CDI and Its Recurrence (Table 3)

CDI is associated with several well-established risk factors, including recent antibiotic exposure[20], advanced age[4], underlying comorbidities[21], and hospitalization[22]. In contrast, known risk factors for recurrent CDI include age ≥65 years[23], antibiotic exposure[23], use of antacids[21,23], renal dysfunction[21], and prior CDI[24]. A key shared risk factor for both initial and recurrent CDI is antibiotic exposure[23], as certain antibiotics markedly increase the risk of disrupting gut microbiota and promoting *C. difficile* overgrowth. The lincosamide clindamycin is consistently identified as one of the highest-risk agents and is associated with substantial CDI incidence in community and healthcare settings[25]. Among β-lactams, broad-spectrum agents such as third- and fourth-generation cephalosporins (e.g., ceftriaxone, cefepime) and carbapenems (e.g., meropenem) significantly elevate CDI risk[26]. Broad-spectrum penicillins combined with β-lactamase inhibitors, including amoxicillin–clavulanate and piperacillin–tazobactam, also confer high risk, comparable to later-generation cephalosporins[25,27]. Fluoroquinolones, notably ciprofloxacin and levofloxacin, have been linked to CDI outbreaks and continue to pose a significant risk[28]. These agents not only contribute to CDI onset but also to its recurrence when re-exposure occurs[29]. After initial CDI, subsequent antibiotic exposure greatly increases the risk of recurrence by impairing microbiome recovery and promoting *C. difficile* spore germination[30]. In contrast, narrow-spectrum antibiotics such as tetracyclines and macrolides (e.g., azithromycin) exhibit lower CDI risk[25], as they disrupt the microbiome less extensively, making them preferable when clinically appropriate.

Several predictive scoring systems have been explored for CDI outcomes. The ATLAS score (Age, Treatment with systemic antibiotics, Leukocyte count, Albumin, and Serum creatinine) was originally developed to predict treatment response and severity[31]. While it has been evaluated for recurrence risk, its positive predictive value

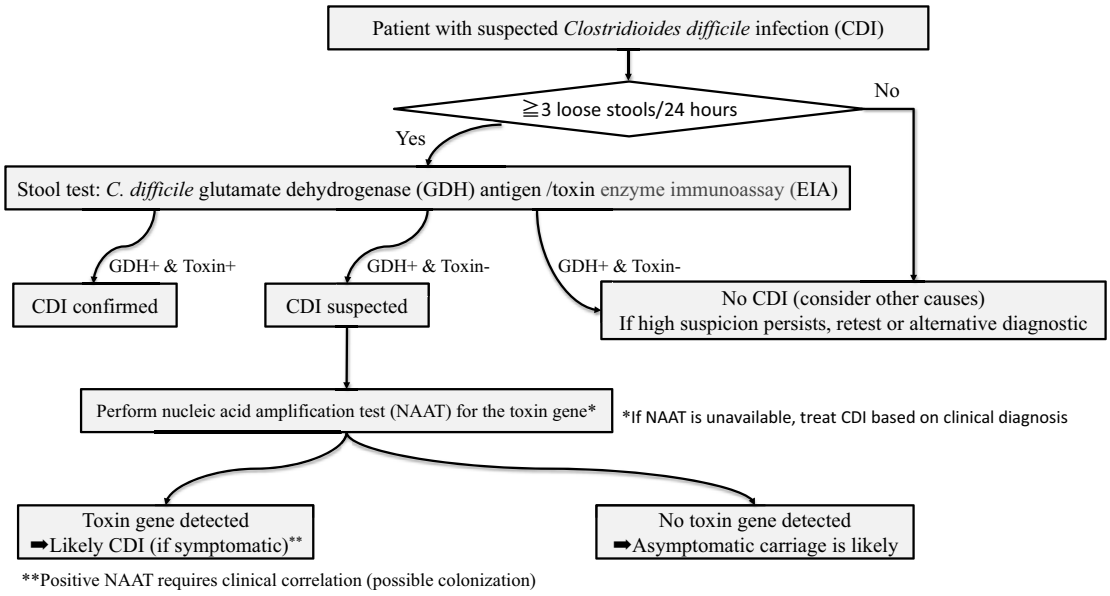

Figure 1 Submitting stool tests for diagnosing *Clostridioides difficile* infection and interpreting the results of genetic tests, antigen tests, and stool cultures

Table 3 Risk factors for onset and recurrence of CDI

Risk factors for onset
Elderly[4]
History of antibiotic administration[20]
Past hospitalization within 3 months prior to CDI onset[22]
History of digestive tract surgery[23]
Presence of inflammatory bowel disease[4]
Nasogastric tube feeding[24]
Use of antacids such as proton pump inhibitors and H_2 blockers[21, 25]
Use of non-steroidal anti-inflammatory drugs[26]
Hypoalbuminemia[27]
Risk factors for recurrence
Age ≥65 years[25]
Antimicrobial use (concomitant use during treatment of initial CDI episode, or after CDI treatment) [25, 29, 30]
Chronic kidney disease[21]
History of CDI[28]
Use of antacids such as proton pump inhibitors and H_2 blockers[21, 25]
Hospitalization within 3 months prior to CDI onset[28]
Presence of solid malignancy or hematologic cancer[31]
History of abdominal surgery[32]
Admission to intensive care unit at time of CDI diagnosis[31]
Presence of inflammatory bowel disease[33]
Steroid use[34]
Severe CDI[35]
Enteral feeding[36]

for recurrent CDI is modest. To date, no single scoring system has been universally adopted for predicting recurrence. In this review, we focus on two newly developed risk stratification tools specific to CDI recurrence. Mori et al.[32] developed the CHIEF score in a Japanese cohort, incorporating five variables: carbapenem use, hematologic malignancy, inflammatory bowel disease (IBD), enteral feeding, and fluoroquinolone use. This model had a high negative predictive value (NPV) of 93.3% and an AUC of 0.722. IBD and enteral feeding are strong predictors of relapse, because of intestinal dysbiosis and immune dysregulation, making CHIEF a clinically useful tool for ruling out high recurrence risk and identifying patients who may benefit from relapse-preventive therapies, such as FDX or bezlotoxumab[33,34], as recommended by international guidelines. We also discuss the novel DASC metric. Introduced by Kakiuchi et al.[35], DASC quantifies antibiotic exposure by spectrum and duration. Broader-spectrum and longer-duration antibiotics are more likely to disrupt the microbiome and increase CDI risk, and the DASC metric, which quantifies the spectrum and duration of antibiotic exposure, may also be applicable in assessing the risk of initial or recurrent CDI onset. In a cohort study, Mori et al.[36] reported that higher DASC scores within 30 days before CDI onset were significantly associated with increased recurrence risk (DASC 89−148: relative risk [RR], 9.9; >148: RR, 11.8), whereas post-diagnosis DASC scores were not predictive. Building on this concept, Nagaoka et al.[37] later developed a combined scoring system using DASC, age, and creatinine level, achieving an AUC of 0.70. The DASC thresholds of 36 and 66 identified patients at increased risk. These results support the use of DASC as a practical quantitative tool for predicting recurrent CDI (rCDI) risk.

Table 4 MN criteria[2]

Variables/score	0	1	2	3
Age (years)	<65	≥65	-	-
Abdominal distension or pain	No	Yes		
Body temperature (°C)	>37	37.0–37.4	37.5–38.4	≥38.5
Diarrhea (BSS ≥5) frequency per day. (if bloody stools are present, add 1 point)	0–2	3–9	≥10	-
White blood cell count (/μL)	<12,000	12,000–14,999	15,000–19,999	≥20,000
eGFR (mL/min/1.73 m²)	≥80	50–79	30–49	<30 or Hemodialysis
Serum albumin (g/mL)	≥3.0	2.5–2.9	2.0–2.4	<2.0
Imaging findings*	No	-	Yes	-

The severity of MN criteria is as follows—Mild: ≤4, Moderate: 5–9, Severe: 10–13, Very severe: ≥14.
In cases involving hypotension, shock, ileus, or toxic megacolon, these conditions are classified as fulminant.
*The presence of intestinal dilatation, intestinal wall thickening, peri-intestinal fatty tissue infiltration, unexplained ascites, and pseudomembrane.
eGFR, estimated glomerular filtration rate.

Criteria for Classifying CDI Severity: Global vs. Japanese Standards

Accurate assessment of disease severity is essential for optimal management of CDI, especially for guiding treatment decisions and predicting prognosis. However, the criteria for classifying CDI severity differ across regions. International guidelines, such as those from the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID)[38], propose laboratory-based definitions, whereas Japan uses a unique system known as the MN criteria, proposed as the first Japanese CDI severity scoring system in 2017[2].

According to the 2021 IDSA/SHEA[6] and ESCMID guidelines[7], non-severe CDI is defined as a white blood cell (WBC) count of ≤15,000 cells/μL and a serum creatinine level <1.5 mg/dL (IDSA/SHEA) or ≤50% elevation from baseline (ESCMID). Severe CDI includes cases with a WBC count of >15,000 or elevated creatinine above the threshold, and severe-complicated (fulminant) CDI encompasses hypotension, ileus, toxic megacolon, and multi-organ failure.

In contrast, the MN criteria (**Table 4**), developed in Japan, assess CDI severity by using clinical symptoms, laboratory data, and imaging and classifies cases as mild, moderate, or severe[2]. This approach was designed to align more intuitively with clinical decision-making in Japanese practice. Yamada et al.[39] found that a higher MN severity was significantly associated with increased 30-day mortality, supporting its prognostic value in real-world settings. Similarly, Asaoka et al.[40] showed that the MN criteria correlated well with treatment intensity and outcomes in Japanese hospitals, demonstrating clinical practicality despite differences from international standards. In a study of 66 non-fulminant CDI cases, the MN criteria achieved a sensitivity of 1.00 and specificity of 0.89 for predicting adverse events such as death, colectomy, and intensive care unit admission. These findings suggest that the MN criteria effectively stratify the severity of CDI. Future studies comparing the MN and international scoring systems may help determine their respective predictive strengths and inform global CDI management strategies. Although currently used mainly in Japan, the MN criteria—or elements thereof—could be applicable globally, as components such as ileus or radiological evidence of toxic megacolon are universally relevant for assessing CDI severity. This contrasts with international guidelines (e.g., IDSA/SHEA, ESCMID), which often rely on laboratory thresholds (WBC count, creatinine) that may not fully capture clinical realities, such as patients with normal lab values but severe colitis evident on imaging. Future studies directly comparing the MN criteria with international severity scoring systems in diverse populations may help determine their respective predictive strengths and inform global CDI management strategies.

Treatment of CDI

Treatment options for CDI include FDX, vancomycin (VCM), and metronidazole (MTZ). FDX is recommended as the first-line therapy for patients with CDI, regardless of disease severity (severe or non-severe) or episode type (initial or recurrent)[38]. This broad recommendation reflects a central feature of the recent international guidelines. The 2021 IDSA/SHEA and ESCMID guidelines

identify FDX as the preferred first-line treatment across these clinical scenarios; VCM is an alternative when FDX is unavailable or contraindicated[6,7]. MTZ is generally not recommended.

In the Japanese guidelines[2], FDX is also recommended as a first-line therapy for patients with a high recurrence risk, such as older adults, immunocompromised patients, and those with renal impairment or recurrent cases. FDX or VCM is recommended for severe cases. However, unlike guidelines in other countries, Japanese guidelines include MTZ as an option for non-severe cases.

Differences in severity definitions across guidelines can influence first-line therapy choices[2,6,7]. For instance, under IDSA/SHEA criteria a CDI case with a WBC of 16,000/μL would be classified as severe and treated with FDX or VCM as the first-line treatment, whereas Japanese guidelines (using MN criteria) might classify the same case as "moderate" if there are no significant clinical or radiologic signs, thus potentially treating with metronidazole. In general, recent international guidelines advocate FDX as first-line for all severities (non-severe and severe) because of its superior recurrence outcomes, with VCM as an alternative[6,7]. In Japan, however, MTZ remains an option for mild cases, partly because the Japanese MN criteria incorporate clinical context, such as symptoms and imaging findings, rather than relying solely on laboratory values. As a result, some cases that would be classified as severe under international guidelines may instead be considered moderate in Japan, allowing for more conservative treatment approaches, including MTZ. Thus, a patient's treatment can differ in relation to the severity assessment used. This discrepancy is gradually decreasing as more data support the use of FDX, but this highlights why we discuss severity scoring: how severity is defined (lab-only vs. comprehensive criteria) can change whether a narrow-spectrum, recurrence-preventing agent such as FDX is used initially or not.

However, unlike guidelines in North America and Europe[6,7], Japanese guidelines continue to include metronidazole as a first-line option for non-severe CDI[2]. This discrepancy exists for several reasons. First, fidaxomicin was approved and adopted later in Japan than elsewhere, and its high cost has limited its widespread first-line use[41]. Considering resource constraints, the inexpensive generic drug MTZ has remained a practical choice for mild cases. Second, epidemiologic differences in Japan—particularly the low prevalence of the hypervirulent BI/NAP1/027 strain—meant that metronidazole outcomes in Japanese patients were not as poor as those observed during Western outbreaks[42]. The hypervirulent 027 strain is associated with high toxin production and treatment failure but is rare in Japan. Consequently, Japanese clinicians historically found that MTZ could effectively manage many mild CDI cases. Finally, guidelines often lag behind emerging data; Japan's 2022 guidance took a conservative approach, still permitting MTZ in low-risk scenarios but with explicit caveats[2]. It is clearly not recommended for severe or fulminant CDI in Japan, aligning with global practice. Overall, the continued (limited) use of MTZ in Japan reflects a balance of efficacy evidence, local strain prevalence, and cost considerations. As fidaxomicin becomes more accessible and further data, particularly on recurrence reduction, accumulate, Japanese practice is expected to increasingly align with international standards favoring fidaxomicin or vancomycin over metronidazole.

Figure 2 presents a stepwise algorithm for selecting the appropriate antibiotic therapy for CDI, which is based on Japanese guidelines. Treatment decisions are guided by three key considerations: (1) whether oral administration is feasible, (2) whether the case is recurrent or involves risk factors for recurrence, and (3) infection severity. If a patient cannot take oral medication, intravenous MTZ is recommended. FDX is the first-line treatment for recurrent or high-risk cases, whereas high-dose VCM or tapered/pulsed VCM therapy is the second-line option. For severe CDI, first-line therapy includes VCM or FDX, and second-line options include combination therapy with VCM plus MTZ or high-dose VCM. In patients without risk factors for recurrence or non-severe disease, oral MTZ remains the first-line treatment option, with VCM and FDX as alternatives. If ileus or other obstructions are present, consult a surgeon to determine the need for colectomy[43].

Characteristics of Each Treatment Drug for CDI

The position of each drug in the CDI treatment guidelines is shown in **Table 5**. FDX is a macrocyclic antibiotic that inhibits the bacterial RNA polymerase in CD[44]. It has minimal systemic absorption, exhibits a narrow antimicrobial spectrum, preserves commensal gut flora, and reduces spore formation[44]. The recurrence rate is significantly lower than those for VCM and MTZ[45]. Recent international guidelines recommend FDX as the first-line therapy for CDI[6,7,46]. A meta-analysis of six randomized controlled trials compared FDX and VCM for CDI treatment[47]. The primary outcome was global cure (clinical resolution without recurrence). FDX significantly im-

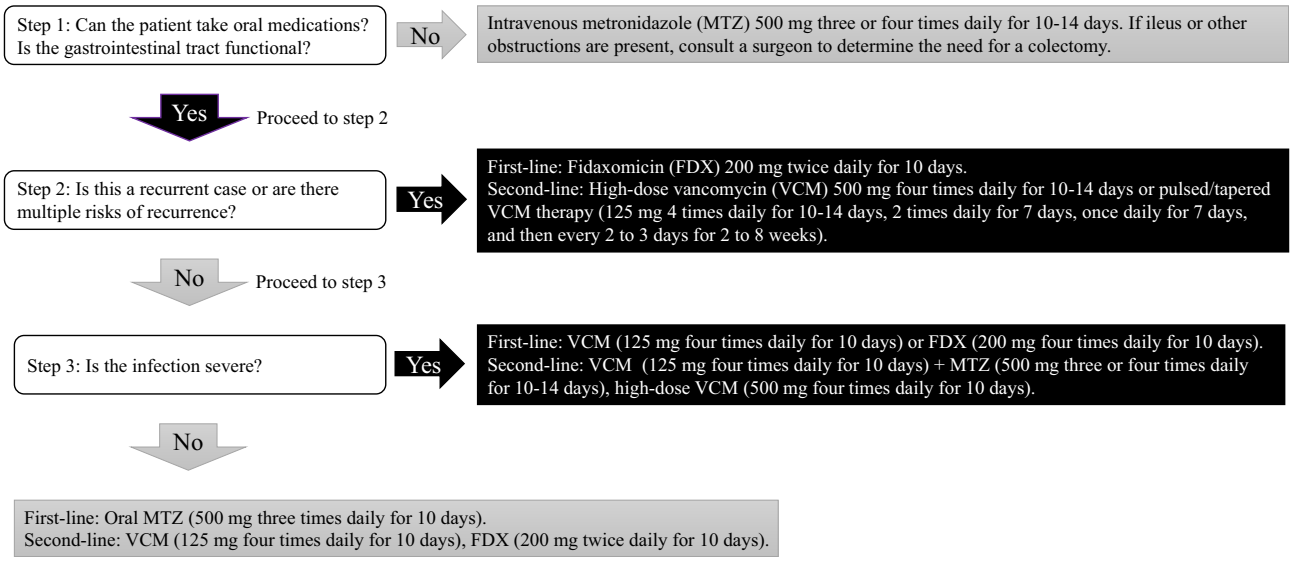

Figure 2 Stepwise algorithm for selecting appropriate antibiotics for treatment of *Clostridioides difficile* infection in Japan

Table 5 Recommendations for drug selection in the CDI treatment guidelines

Therapeutic agent	Japan[2]	America[6]	Europe[7]
Fidaxomicin	First choice for cases with a risk of recurrence and recurrent cases.	First choice for both initial and recurrent cases.	First choice for both initial and recurrent cases.
Vancomycin	First choice for severe cases without a risk of recurrence	Alternative drugs for both initial and recurrent cases.	Alternative drugs for both initial and recurrent cases.
Metronidazole	Use only in non-severe cases without a risk of recurrence.	Not generally recommended.	Not generally recommended.

proved global cure (RR: 1.18, 95% CI: 1.09−1.26) and reduced recurrence (RR: 0.59, 95% CI: 0.47−0.75). Initial cure (RR: 1.02, 95% CI: 0.99−1.05) and adverse events (RR: 1.01, 95% CI: 0.94−1.09) did not significantly differ. Subgroup analyses confirmed the benefits of FDX in multiple scenarios, including initial CDI, non-severe disease, and infections caused by non-BI/NAP1/027 strains[47]. This last point is epidemiologically important for Japan, as the hypervirulent 027 strain that drove increased severity and recurrences in the United States and Europe is rare in Japan[48,49]. In Western countries, widespread 027 outbreaks revealed MTZ's limitations, prompting rapid adoption of VCM and FDX as first-line therapies. Japan, with predominantly less virulent strains (e.g., toxin A−/B +017 and others)[48,49], did not experience the same urgency to shift therapy, which partly explains why MTZ persisted longer in guidelines. Nevertheless, fidaxomicin is beneficial in reducing recurrence regardless of strain. In pivotal trials, FDX significantly lowered recurrence even in non-027 strain infections[50]. Thus, even though Japan's CDI cases tend to involve strains with lower toxin production and severity, use of FDX can further reduce recurrence and is increasingly recognized as beneficial. The low prevalence of 027 in Japan likely contributed to historical treatment patterns, but ongoing epidemiologic surveillance and outcomes data support a global trend toward FDX because of its consistent effectiveness against both typical and hypervirulent strains.

VCM is a glycopeptide antibiotic that inhibits cell-wall synthesis in gram-positive bacteria[51]. When orally administered for CDI, it remains within the intestinal lumen with minimal systemic absorption, effectively reducing the CD burden. Oral VCM has long been the mainstay of CDI treatment and offers a high initial cure rate. However, its recurrence rate is higher than that of FDX, owing to its broader antimicrobial activity, which disrupts normal gut microbiota and lacks direct action against spores[38]. Widespread use of VCM has been linked to the emergence of VCM-resistant enterococci (VRE), posing significant infection control concerns[38]. The potential to promote antimicrobial resistance must be considered when selecting CDI therapy. Current guidelines continue

Table 6 Characteristics of drugs used for CDI treatment

Therapeutic agent	Mechanism & spectrum	Notable considerations*
Fidaxomicin	Inhibits bacterial RNA polymerase; narrow spectrum (largely confined to *C. difficile* in gut). Minimally absorbed from the intestine[53].	Advantages: Preserves gut commensals; associated with significantly lower recurrence rates. Disadvantages: High cost; not as widely available in some settings.
Vancomycin	Inhibits cell wall synthesis; moderate spectrum (active against Gram-positive bacteria in the gut). Not systemically absorbed[51].	Advantages: High initial cure rates; effective for severe CDI. Disadvantages: Broader antimicrobial activity leads to higher recurrence and VRE colonization risk.
Metronidazole	Generates DNA-damaging radicals under anaerobic conditions; broad spectrum against anaerobes[52]. Systemically absorbed[52].	Advantages: Oral and intravenous forms available; inexpensive. Disadvantages: Inferior efficacy in moderate-to-severe CDI; collateral damage to gut flora.

*Notable considerations are described in references 2, 6, 7, and 55.
DNA, deoxyribonucleic acid.

to recommend oral VCM as the standard CDI treatment, although it is often a second-line option after FDX[6,7,46]. The 2021 IDSA/SHEA guidelines list VCM as an acceptable alternative for the initial episodes[6]. For the first recurrence, a tapered and pulsed regimen is recommended if FDX is not administered. The ESCMID 2021 guidelines also recommend VCM (125 mg four times a day for 10 days) as the first-line therapy when FDX is unavailable or contraindicated[7]. In Japan, VCM is considered the first-line treatment for severe CDI, alongside FDX[2]. For fulminant or life-threatening cases (e.g., with shock, hypotension, or ileus), high-dose VCM (500 mg four times a day, orally or via a nasogastric tube) is used with intravenous MTZ to ensure adequate coverage[2,38]. In summary, VCM remains a critical treatment for CDI, especially for severe or fulminant cases and when FDX is inaccessible. However, its higher recurrence rate and the risk of promoting VRE make FDX the preferred option when available.

MTZ, a nitroimidazole antibiotic, exhibits bactericidal activity in anaerobic environments by inducing DNA strand breaks[52]. It has been used for decades to treat CDI, primarily mild cases, owing to its broad anaerobic coverage and oral bioavailability. However, the emergence of hypervirulent strains (e.g., BI/NAP1/027) and evidence of inferior outcomes for severe CDI have prompted a reevaluation of its role. Recent guidelines no longer recommend MTZ as a first-line agent when FDX or VCM is available[38]. The 2021 ESCMID update explicitly advises against its use as first-line therapy[7]. Similarly, the IDSA/SHEA guidelines now restrict MTZ to exceptional cases such as the first episode of non-severe CDI in low-risk patients when VCM or FDX is unavailable[6]. The 2022 Japanese guidelines weakly recommend MTZ only for non-severe initial episodes without risk factors for recurrence or severe progression[2]. This limits the use of MTZ to relatively mild cases, particularly in younger patients without major comorbidities. Other agents are preferred, even in such cases. Notably, MTZ is not recommended for severe CDI in any guideline owing to its high failure rates; in fulminant cases, it is used only as an adjunctive intravenous therapy[2,6,7,38]. Overall, MTZ use in CDI should be minimized because it has higher recurrence and lower sustained cure rates than VCM and FDX. **Table 6** summarizes the properties of each therapeutic agent for CDI.

Impact of CDI Therapies on the Gut Microbiota

CDI therapies, namely FDX, VCM, and MTZ, differ markedly in their effects on the intestinal microbiota, a factor closely associated with the risk of CDI recurrence. In a murine CDI model, Yamaguchi et al.[53] reported that 7-day treatment with FDX maintained significantly higher microbial diversity (134.2 operational taxonomic units [OTUs]) than VCM (26.2 OTUs), indicating better maintenance of the gut microbiota. Other studies have demonstrated that FDX spares key bacterial taxa, such as *Bacteroidia* and *Clostridia*, which support gut homeostasis and are associated with lower recurrence rates and sustained clinical response[53,54]. VCM has broader-spectrum activity and disrupts the gut microbiota more extensively than FDX, thereby increasing recurrence risk[53]. MTZ, a nitroimidazole that targets anaerobes, also exerts wide-ranging effects on the gut flora. It disrupts diverse anaerobic commensals, including members of the phyla Firmicutes and Bacteroidetes, both of which are essential for microbial balance[55]. These two dominant bacterial phyla contribute to colonization resistance and mucosal health: for example, Firmicutes (like Ruminococcaceae and Lachnospiraceae) ferment dietary fibers into short-chain fatty acids that nourish enterocytes, while Bacteroidetes (like Bacteroides spp.) break down complex polysaccharides and help regulate immune responses. Disruption of these

groups can lead to loss of colonization resistance against pathogens such as *C. difficile*[55]. In animal models, MTZ significantly decreases microbial richness and diversity, with dysbiosis persisting beyond the treatment window[53,54,56]. In summary, FDX provides the best microbiota-sparing profile of the three agents, reinforcing its role as a preferred option, particularly in patients at high risk for recurrence. In contrast, VCM—and especially MTZ—induce substantial loss of beneficial Firmicutes and Bacteroidetes, delay microbiota recovery, and increase the likelihood of recurrence, which supports their more limited use in recent guidelines.

Conclusion

CDI continues to impose a substantial clinical and economic burden, necessitating refined strategies for accurate diagnosis, effective treatment, and recurrence prevention. As discussed in this review, the use of objective tools like the BSS improves diagnostic accuracy by avoiding unnecessary testing in colonized but asymptomatic individuals. Incorporation of the MN criteria in Japan provides a clinically practical method of assessing severity, reflecting the real-world complexity of CDI presentation beyond simple laboratory thresholds.

Prediction of recurrence remains central to improving long-term outcomes. The CHIEF score and DASC metric—both developed and validated in Japanese clinical cohorts—offer promising frameworks for identifying patients at high risk for recurrence and tailoring treatment strategies accordingly. These tools enable clinicians to consider broader factors, such as comorbidities, antibiotic exposure duration and spectrum, and microbiota disruption, thereby facilitating the selection of optimal therapies, including fidaxomicin and bezlotoxumab.

Therapeutic choices are evolving globally: fidaxomicin is emerging as the preferred agent due to its narrow spectrum, superior microbiota preservation, and lower recurrence rates. While vancomycin remains a viable alternative, use of metronidazole is increasingly limited to mild cases, especially in Japan, where its historical efficacy and cost-effectiveness are considered.

Ultimately, this review demonstrates that optimal management of CDI requires integration of global evidence and regional epidemiology. Japanese-specific severity criteria and recurrence predictors provide valuable insights, and their wider validation may contribute to more nuanced and effective treatment algorithms. Moving forward, continued surveillance, comparative research, and real-world data will be critical to advancing personalized CDI care.

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