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Comparison of the 2010 and 2017 IDSA guidelines on the diagnosis and treatment of *Clostridium difficile* infection

Mark H. Wilcox, Christopher M Rooney

Microbiology, Leeds Teaching Hospitals NHS Trust & University of Leeds, Leeds, UK

Corresponding author:

Professor Mark H. Wilcox

Microbiology,
Old Medical School,
Leeds General Infirmary,
Leeds LS1 3EX,
W. Yorks., UK.

mark.wilcox@nhs.net

Tel +44 113 392 6818
Fax +44 113 392 2696

Abstract

Purpose of review: To highlights the key changes in the updated Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines with respect to the diagnosis and treatment of CDI.

Recent findings: CDI continues as a major threat to healthcare institutions and as a community associated infection related primarily to antibiotic exposure. IDSA/SHEA produced extensive CDI guidelines in 2010; in 2018, updated guidance has been published. The new guidelines include key changes with respect to the treatment and diagnosis of CDI.

Summary: Updated, evidence guidelines allow optimisation of the diagnosis of CDI and the use of therapeutic interventions, in particular to reduce the risk of recurrent infection.

Key points:

- **Metronidazole is no longer recommended as a first line treatment option in CDI**
- **Fidaxomicin is recommended as a first line alternative treatment option to vancomycin for patients with CDI**
- **FMT is a recommended treatment option in patients with multiple (≥3) recurrences of CDI**
- **There is an increased emphasis of the importance of using a toxin test as part of laboratory algorithms for CDI diagnosis**
- **CDI testing should never be routinely recommended for infants ≤12 months of age with diarrhoea**

Background

The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) issued clinical practice guidelines for *Clostridium difficile* infection (CDI) in 2010;[1] update guidelines have recently been published in 2018.[2] CDI has

continued to increase as a global threat in the last decade, and as a result CDC has identified *C. difficile* as one of the top three antibiotic resistant pathogens (with *Neisseria gonorrhoea* and carbapenem resistant enterobacteria).[3] The latest IDSA/SHEA guidelines examined new information published between 2009 and 2016, and used the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) system to categorise the strength of evidence for each recommendation.[2] In addition, unlike the earlier version,[1] the new guidelines contain pediatric specific recommendations.[2] This review highlights the key changes in the updated guidelines with respect to the diagnosis and treatment of CDI.[1,2]

CDI severity classification

Changes to the terminology and CDI severity definitions, including the assessment of acute renal impairment, which can be associated with CDI, are highlighted in Table 1. These definitions are used to guide the treatment recommendations, as in 2010, according to disease severity.[1,2]

CDI treatment recommendations

The updated 2017 treatment recommendations are compared with the earlier versions in Table 2. The two most prominent changes are the removal of metronidazole as a first line treatment option for CDI, and the addition of fidaxomicin (for either non-severe or severe CDI) as an alternative to vancomycin.[2] Metronidazole used to be the most often prescribed CDI treatment option. It was believed to be non-inferior to vancomycin, and was inexpensive. New data demonstrate, however, that metronidazole is clearly inferior to vancomycin (and so, it is reasonably assumed, also to fidaxomicin).[4-6] Two phase 3 clinical trials compared the treatment of primary CDI with tolevamer (a toxin binding polymer), vancomycin or metronidazole.[4] Whilst tolevamer was not effective, there was a significantly superior clinical response rate (resolution of diarrhoea and absence of severe abdominal discomfort for >2 consecutive days) to vancomycin compared with metronidazole (81.1% versus 72.7%, P = .02). Furthermore, a post-hoc multivariate analysis showed that vancomycin therapy was strongly associated with a successful response. These clinical

efficacy results are likely at least partly explained by the very poor penetration of metronidazole into the lumen of the colon. The clinical relevance of increasing reports of *C. difficile* isolates with reduced susceptibility to metronidazole is unclear, but is a worrying trend.[7] Of note, a recent US insurance database study (not reviewed in the latest guidelines, concluded that the risk of 30-day mortality was significantly reduced in patients with CDI treated with vancomycin as opposed to metronidazole.[8]

Fidaxomicin achieves similar initial clinical cure rates to vancomycin, but sustained cure is superior with the former antibiotic. This difference is driven by an ~50% reduced risk of recurrence in fidaxomicin recipients (i.e. from ~25% to 13%), particularly in the first two weeks after treatment cessation.[9] Fidaxomicin is associated with less disturbance of the gut microbiota during/following administration compared with vancomycin. Also, non-specific binding of fidaxomicin to *C. difficile* spores may provide protection against recurrent infection due to residual spores following antibiotic therapy.[10-12] Fidaxomicin has a relatively high acquisition cost, but has been shown to be a cost-effective alternative to vancomycin, due to the savings associated with lower recurrence rates.[13]

Faecal microbiota transplantation (FMT) has become widely practised in between the 2010 (when it was not advocated)[1] and the updated 2017 guidelines.[2] The 2017 guidelines discuss in detail the evidence for the use of FMT, highlighting their prime niche for patients with multiple recurrences of CDI who have failed to resolve their infection, despite conventional antibiotic-based treatment attempts. A key point here is whether/when to consider FMT (considering the multiple pharmacological alternatives), notably given remaining unknowns regarding the long term safety associated with transfer of the gut microbe of one individual to another. There are many unanswered questions about the optimal use of FMT in patients with recurrent CDI, including the optimal 'dose', formulation (e.g. capsulated/frozen faeces), route of instillation, and the use autologous versus donor faeces. There are no robust data to indicate how many attempted antibiotic treatments should occur before FMT is considered for a patient with recurrent CDI. The latest guidelines recommend that at least 2 recurrences (i.e. 3 CDI episodes) should have occurred before FMT is considered.[2] The guidelines highlight that there are limited data on the use of FMT in patients with severe, refractory CDI.

Given the 2016 cut-off date used to examine published evidence for the latest CDI guidelines,[2] two key therapeutic options (bezlotoxumab and extended fidaxomicin) missed being included. Briefly, bezlotoxumab has been shown to significantly reduced the risk of CDI recurrence in predefined groups at high risk of recurrent disease and/or poor outcome (≥65 years of age, previous CDI, immunocompromised, severe CDI; but not in CDI due to ribotype 027).[14,15] Notably, bezlotoxumab was associated with a significant reduction in 30-day CDI-associated readmission rate (4.0% versus 9.6%; difference -5.7%, 95% CI -8.8, -2.7).[16] A novel extended/pulsed regimen of fidaxomicin, using conventional 200 mg oral twice daily dosing on days 1-5, followed by (200 mg oral) once daily antibiotic on alternate days (days 7-25), was compared with conventional vancomycin (125 mg po, four times daily on days 1-10).[17] Extended-pulsed fidaxomicin therapy was followed by a significantly reduced risk of recurrent CDI compared with vancomycin (4% versus 17% patients, respectively), and the time to event was longer after antibiotic treatment ended with the novel regimen ($p<0.0001$).

Diagnosis

Since the 2010 CDI guidelines,[1] the use of nucleic acid amplification tests (NAATs, e.g. PCR) to detect C. difficile toxin (B) gene has become commonplace in some (e.g. US) but not all (e.g. Europe) settings. The 2010 guidelines stated 'Polymerase chain reaction (PCR) testing appears to be rapid, sensitive, and specific and may ultimately address testing concerns.[1] More data on utility are necessary before this methodology can be recommended for routine testing.' The 'testing concerns' here referred to the sub-optimal sensitivity of (faecal) *C. difficile* toxin detection methods. However, it has become clear that switching to using considerably more sensitive NAATs, is associated with over-diagnosis of CDI. For example, the largest CDI diagnosis study of its type ever performed found that there was an 81% (95% CI 77-85%) increase in the positivity rate of the *C. difficile* toxin gene NAAT (10.7%) compared with the faecal toxin rate (5.9%).[18] Furthermore, this study found that *C. difficile* toxin positive patients with diarrhoea had significantly increased white cell counts (reflecting the host response to infection) and significantly higher mortality compared with patients with diarrhoea and a positive NAAT result. Thus, the positive predictive value of the toxin gene NAAT is low (e.g. 54% in this study), due the inability of these tests to

distinguish between patients with diarrhoea who are colonised by a toxin gene positive strain as opposed to those who have CDI (due to toxin production).[18-21] Such poor accuracy for CDI has important potential sequelae for patients (unnecessary treatment, isolation, and label/stigma, which could affect their future medical management) and for healthcare institutions.[21]

Consequently, the 2017 guidelines reflect he drawbacks of using NAATs a standalone tests, and advocate the use of stool toxin test as part of a multistep algorithm (i.e. glutamate dehydrogenase [GDH] plus toxin; GDH plus toxin, arbitrated by nucleic acid amplification test [NAAT]; or NAAT plus toxin).[2] The guidelines offer a compromise for settings where there are pre-agreed institutional criteria for stool submission (i.e. frequent diarrhea and absence of other factors such as laxatives), which are intended to increase the predictive value of NAAT alone use; however, such an approach still risks considerable over-diagnosis of true CDI.[13-16] Lastly, as there is a high chance that toxigenic strains of *C. difficile* can be carried asymptomatically in infants, the guidelines make a strong recommendation that testing for CDI should never be routinely recommended for neonates or infants ≤12 months of age with diarrhea.[2]

Conflict of interest

MHW has received: consulting fees from Actelion, Astellas, bioMerieux, Cambimune, Da Volterra, Ferring, MedImmune, Menarini, Merck, Meridian, Pfizer, Qiagen, Sanofi-Pasteur, Seres, Spero, Summit, Synthetic Biologics and Valneva; lecture fees from Alere, Astellas, Merck & Pfizer; and grant support from Actelion, Astellas, bioMerieux, Da Volterra, Merck, Motif Biosciences, Nabriva, Paratek, Pfizer, Sanofi-Pasteur, Seres and Summit.

Table 1

CDI severity terminology and definitions used in 2010 and updated 2017 IDSA/SHEA guidelines

2010		**2017**	
Clinical definition	**Supportive clinical data**	**Clinical definition**	**Supportive clinical data**
Mild or moderate	Leukocytosis with a white blood cell count of 15,000 cells/mL or lower and a serum creatinine level less than 1.5 times the premorbid level	**Non-severe**	Leukocytosis with a white blood cell count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL
Severe	Leukocytosis with a white blood cell count of 15,000 cells/mL or higher or a serum creatinine level greater than or equal to 1.5 times the premorbid level	**Severe**	Leukocytosis with a white blood cell count of ≥15 000 cells/mL or a serum creatinine level >1.5 mg/dL
Severe, complicated	Hypotension or shock, ileus, megacolon	**Fulminant**	Hypotension or shock, ileus, megacolon

Table 2

CDI treatment recommendations in 2010 and updated 2017 IDSA/SHEA guidelines

2010		2017		
Clinical definition	**Treatment recommendation**	**Clinical definition**	**Treatment recommendation**	
Mild or moderate	Metronidazole, 500 mg 3 times per day by mouth for 10–14 days	**Non-severe**	Vancomycin 125 mg given 4 times daily for 10 days OR Fidaxomicin 200 mg given twice daily for 10 days Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	
Severe	Vancomycin, 125 mg 4 times per day by mouth for 10–14 days	**Severe**	Vancomycin, 125 mg 4 times per day by mouth for 10 days OR Fidaxomicin 200 mg given twice daily for 10 days	
Severe, complicated	Vancomycin, 500 mg 4 times per day by	**Fulminant**	Vancomycin, 500 mg 4 times per day by	

	mouth or by nasogastric tube, plus metronidazole, 500 mg every 8 hours intravenously. If complete ileus, consider adding rectal instillation of vancomycin		mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present.	
1st recurrence	Same as for initial episode	**1st recurrence**	Vancomycin 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode OR Use a prolonged tapered and pulsed vancomycin regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per	

			day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks) OR Fidaxomicin 200 mg given twice daily for 10 days if vancomycin was used for the initial episode	
2nd recurrence	Vancomycin in a tapered and/or pulsed regimen	**2nd recurrence**	VAN in a tapered and pulsed regimen, OR Weak/Low Vancomycin, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days OR Fidaxomicin 200 mg given twice daily for 10 days OR Faecal microbiota	

			transplantation**	

*Randomized trials have compared 10-day treatment courses; as some patients (particularly those treated with metronidazole) may have delayed response to treatment, consideration should be given to extending treatment duration to 14 days in such circumstances.

**The opinion of the expert panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e. 3 CDI episodes) should be tried before offering faecal microbiota transplantation.

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