

# Recent Progress for the Effective Prevention and Treatment of Recurrent *Clostridium difficile* Infection

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Isobel Ramsay, Nicholas M Brown and David A Enoch

Clinical Microbiology & Public Health Laboratory, National Infection Service, Public Health England, Addenbrooke's Hospital, Cambridge, UK.

**ABSTRACT:** Recurrence occurs in approximately 25% of all cases of *Clostridium difficile* infection (CDI) and poses a unique clinical challenge. Traditionally, treatment options of CDI have been limited to regimes of established antibiotics (eg, pulsed/tapered vancomycin) but faecal transplantation is emerging as a useful alternative. In recent years, promising new strategies have emerged for effective prevention of recurrent CDI (rCDI) including new antimicrobials (eg, fidaxomicin) and monoclonal antibodies (eg, bezlotoxumab). Despite promising progress in this area, obstacles remain for making the best use of these resources due to uncertainty over patient selection. This commentary describes the current epidemiology of rCDI, its clinical impact and risk factors, some of the measures used for treating and preventing rCDI, and some of the emerging treatment options. It then describes some of the obstacles that need to be overcome.

**KEYWORDS:** Recurrent *Clostridium difficile* infection, risk factors, bezlotoxumab, fidaxomicin, faecal microbiota transplantation

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**CORRESPONDING AUTHOR:** David A Enoch, Clinical Microbiology & Public Health Laboratory, National Infection Service, Public Health England, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK. Email: David.enoach@addenbrookes.nhs.uk

## Introduction

*Clostridium difficile* infection (CDI) continues to be a major cause of morbidity and mortality and remains the commonest cause of nosocomial diarrhoea in the developed world.<sup>1</sup> Managing patients with recurrent CDI (rCDI) remains a significant challenge. The decreasing efficacy of metronidazole<sup>2</sup> and the increasing incidence of multiply recurrent disease<sup>3</sup> have driven investigation into new approaches to preventing and treating rCDI. This commentary describes the current epidemiology of rCDI, its clinical impact and risk factors, some of the measures used for treating and preventing rCDI, and some of the emerging treatment options. It then describes some of the obstacles that need to be overcome.

## Current Recurrence Rate

Recurrent CDI can be defined as reappearance of symptoms following the completion of a course of therapy resulting in complete resolution of those symptoms. European guidelines define recurrence as symptoms occurring within 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment.<sup>4</sup> However, studies offer different definitions. Louie et al<sup>5</sup> and Cornely et al<sup>6</sup> defined clinical recurrence as the reappearance of more than 3 diarrhoeal stools per 24-hour period within 4 weeks after the cessation of therapy, *C difficile* toxin in stool and a need for retreatment for CDI. Heimann et al<sup>7</sup> defined it as above but between 14 days and 12 weeks after cessation of CDI treatment. Lübbert et al<sup>8</sup> did not require a positive toxin result but diarrhoea recurring within 11 to 60 days of follow-up. Events within 0 to 10 days of follow-up were not counted as recurrences because standard CDI drug therapy

extends for 10 days, whereas events occurring after 60 days were counted as a new index event. Around a quarter of all patients with confirmed CDI will develop a recurrence.<sup>8</sup> Those patients who have had a first recurrence are at increased risk of further recurrence (or multiply rCDI) – up to 60% of patients with a second recurrence will have further infections.<sup>8</sup> Recurrence can occur either as a relapse with the same strain or as a reinfection with a different strain.

## Impact of Recurrence

A recent case-control study comparing patients with recurrent infection, those without infection, and those with non-recurrent infection, demonstrated both greater use of hospital resources and increased mortality. Patients with rCDI had a 48% higher rate of emergency department visit (relative risk, 1.48 [95% confidence interval (CI), 1.40–1.57]), and have longer hospital days (1.65 [1.55–1.76]), and intensive care unit days (1.30 [1.12–1.52]) than matched patients who had non-rCDI. Comparing patients with rCDI with matched controls without CDI, there was a 155% increase in 1-year mortality in the recurrent infection group.<sup>9</sup> This is supported by a single-centre US study<sup>10</sup> showing a significantly higher mortality within 180 days in those with recurrent infection compared with non-recurrent infection hazard ratio 1.33; [95% CI, 1.12 to 1.58].

## Risk Factors for Recurrence

The key to preventing recurrent infection is identifying those patients at the greatest risk. Factors accepted to present a risk of initial CDI include older age and comorbidities. Proton



pump inhibitor (PPI) and antibiotic use have also been implicated in risk of recurrence.

### *Patient factors*

As with initial infection, the risk of recurrence increases with increasing age. Poor baseline health status has also been identified as a risk factor.

Two systematic reviews identified older age, use of PPI, and continued antibiotic use as significant risk factors for recurrence.<sup>11,12</sup> Abdelfatah et al<sup>13</sup> in a retrospective case-control study identified higher Charlson comorbidity score, chronic kidney disease (CKD), use of corticosteroids, and PPIs as risk factors by univariate analysis. Multivariate analysis showed that CKD, PPI, and corticosteroid use were significant risk factors.

There has been conflicting data regarding the effect of PPI use on rCDI. Tariq et al<sup>14</sup> in a recent meta-analysis of 16 studies suggested that it contributed to increased risk, although the studies included were largely observational in nature. Other observational studies have not shown an association.<sup>15</sup> Past exposure to health care has also been found to be a significant risk factor – in particular, Eyre et al<sup>16</sup> identified previous admission to a gastroenterology ward as significant, although this may reflect the burden of inflammatory bowel disease (in itself a possible risk factor for CDI). Previous dialysis or chemotherapy was found to increase risk of recurrence at older ages.

### *Infection factors*

Characteristics of the initial infection have also been shown to be important in predicting recurrence risk. Eyre et al<sup>16</sup> showed significant recurrence risk associated with emergency admissions and those who had elevated inflammatory markers (eg, C-reactive protein).

Whether individual strains carry a higher risk of recurrence is unclear with some studies suggesting higher recurrence rates with the NAP1/BI/027 type 1 strain.<sup>17,18</sup>

## **Treating and Preventing Recurrence**

### *Established antibiotics*

Traditionally, preventing recurrence has focussed on judicious use of antibiotic therapy for treatment of infection. Oral vancomycin or metronidazole (for mild to moderate infection) has been the mainstay of treatment.<sup>4</sup> Although metronidazole has been shown to be inferior to vancomycin for clinical cure in severe infection, a recent retrospective cohort study did not show a difference in the risk of recurrence between these 2 antibiotics.<sup>19</sup> There is limited evidence from small studies for the use of pulsed/tapered vancomycin regimes in treating recurrent infection.<sup>20</sup> This strategy is mainly based on favourable experience and the theoretical rationale that spores can still germinate long after the clinical symptoms have resolved. McFarland et al<sup>20</sup> retrospectively compared a standard course

of antibiotics, vancomycin taper strategies (gradually decreasing the daily dose of vancomycin by 125–750 mg per day from varying starting doses) and vancomycin pulse strategies (125–500 mg of vancomycin every 2–3 days during a period of usually 3 weeks). They found the recurrence rate to be lowest in pulse regimens (14%), followed by taper regimens (31%) and the standard regimen of vancomycin (54%; average for all dose groups). No other studies investigating taper or pulse regimens have been published.

### *Fidaxomicin*

Fidaxomicin is a narrow-spectrum bactericidal antibiotic which is reportedly less disruptive to the normal intestinal flora than vancomycin.<sup>21</sup> Cornely et al in a randomised controlled trial across North America, Europe, and Canada found fidaxomicin to be non-inferior to vancomycin for treatment of infection.<sup>6</sup> Louie et al<sup>5</sup> compared fidaxomicin with vancomycin for treatment of initial CDI and also found comparable efficacy but although a reduced rate of recurrence in those treated with fidaxomicin compared with vancomycin (15.4% versus 25.3% in a modified intention to treat analysis  $P=.005$ ). A similar distinction has been seen in patients being treated for their first recurrence where the rate of second recurrence was lower with fidaxomicin.<sup>22</sup> In a study of cost-effectiveness when compared with vancomycin, fidaxomicin proved cost-effective both for treatment of severe infection and for treatment of first recurrence.<sup>23</sup> As well as preventing reinfection with the same strain, fidaxomicin may also be of use in preventing recurrence due to different strains of *C difficile*.<sup>24</sup> Extended treatment regimens have also been performed with fidaxomicin.<sup>25</sup> This recent randomised controlled, open-label study compared fidaxomicin (200 mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7–25) with vancomycin (125 mg oral capsules, 4 times daily on days 1–10).<sup>25</sup> The primary endpoint was sustained clinical cure 30 days after end of treatment. About 124 (70%) of 177 patients receiving extended-pulsed fidaxomicin achieved sustained clinical cure 30 days after end of treatment, compared with 106 (59%) of 179 patients receiving vancomycin (difference 11% [95% CI, 1.0–20.7],  $P=.030$ ; odds ratio 1.62 [95% CI, 1.04–2.54]). Fewer patients in the extended-pulsed fidaxomicin had rCDI at days 40, 55, and 90 compared with the vancomycin arm.<sup>25</sup> There are currently no prospective randomised controlled trials investigating the efficacy of fidaxomicin in patients with multiple recurrences of CDI.

### *Strategies to normalise faecal flora*

The normal intestinal flora play a protective role in the prevention of CDI and it is notable that patients with rCDI undergo progressive reductions in the diversity of their intestinal microbiome.<sup>26</sup> Treating infection and preventing recurrence by altering the makeup on the intestinal flora have therefore engendered interest.

### Probiotics

Despite moderate-quality evidence supporting use of probiotics in primary prevention of CDI,<sup>27</sup> there is a lack of compelling evidence for the use of probiotics in the prevention of recurrent infection. Given that patients with recurrent as opposed to primary infection may have greater disruption to their normal flora, it may be more difficult to restore normality. In the meta-analyses of trials looking at probiotics in recurrent infection, there are conflicting reports regarding potential benefit.<sup>28,29</sup>

### Faecal microbiota transplantation

Reintroduction of the normal gut flora via faecal transplantation has been used as a strategy in the treatment of rCDI. A randomised controlled trial was discontinued early after finding that infusion of donor faeces was significantly more effective than vancomycin for treating rCDI.<sup>30</sup> In the short term, faecal microbiota transplantation (FMT) appears to have a favourable safety profile but there is a lack of longitudinal studies to assess any potential longer-term effects. Data on identifying those most likely to benefit, preferred donors, delivery methods, and preparations continue to be unclear. In comparison with fidaxomicin, vancomycin, or metronidazole, FMT is highly cost-effective.<sup>31</sup> The National Institute for Health and Care Excellence (NICE) in the United Kingdom found that 'current evidence on the efficacy and safety of FMT for recurrent CDI is adequate to support the use of this procedure provided that normal arrangements are in place for clinical governance, consent and audit'.<sup>32</sup> They suggest that it should only be considered for patients with rCDI who have failed to respond to antibiotics and other treatments. However, in a recent study, Hota et al compared a tapered vancomycin regime with oral vancomycin followed by faecal transplantation for rCDI. The study was stopped early after finding no difference between the 2 approaches for prevention of recurrence and a futility analysis suggested that further pursuing the planned study would not alter the outcome.<sup>33</sup>

### Microbiome therapeutics

Employing a similar strategy to FMT, specific microbiome therapeutics are in development. For example, SER109, a mixture of 50 different firmicute spores isolated from donor stool has been used successfully in a small cohort for prevention of recurrence.<sup>34</sup> There has also been interest in using the purified spores of non-toxigenic strains of *C. difficile* to prevent recurrence which has had promising results in phase 2.<sup>35</sup>

## New and Emerging Therapies

### Monoclonal antibodies

**Bezlotoxumab.** Bezlotoxumab is a human monoclonal antibody directed against *C. difficile* toxin B and has been recently

approved by the Food and Drug Administration (FDA) in the United States to prevent rCDI in patients at high risk of recurrence. Randomised, double-blind, placebo-controlled trials (MODIFY 1 and 2)<sup>36</sup> involving 2655 patients showed a significant decrease in recurrence rate in patients with risk factors for recurrence who received a single infusion of bezlotoxumab alongside standard antibiotic therapy for CDI (17% versus 28%; 95% CI, -15.9 to -4.3;  $P < .001$  in MODIFY 1 and 16% versus 26%; 95% CI, -15.5 to -4.3;  $P < .001$ ). Recurrence was defined as a new episode within 12 weeks of the initial bezlotoxumab infusion. These initial studies suggest that bezlotoxumab appears to be well tolerated with a similar adverse event rate in the placebo arms. Diarrhoea and nausea were the most common side effects noted. In addition, bezlotoxumab carries a caution for use in patients with pre-existing congestive cardiac failure due to a higher rate of adverse events seen during the trials in this group. The addition of the anti-toxin A compound actoxumab conferred no additional benefit.

### Obstacles

One of the major obstacles to using these newer strategies in practice is identifying those patients most likely to benefit, ie, identifying those who will have a recurrence. Escobar et al<sup>37</sup> demonstrated the difficulty in predicting recurrent infection in a recent evaluation of 150 predictors in a large retrospective patient cohort through use of electronic patient data. Despite the large cohort, none of their prediction models discriminated well between patients who had or did not have a recurrence.

Second, identification of patients who have developed recurrent infection may prove difficult. There are many potential causes of diarrhoea other than CDI, particularly in the hospital setting. In addition to this, *C. difficile* toxin tests may remain positive for at least 3 to 6 weeks following successful treatment.<sup>38</sup> Distinguishing between true recurrence and colonisation can therefore be difficult.

### Conclusions

Treatment and prevention of rCDI remain difficult. Although newer strategies are available or in the pipeline, further studies are required to identify those patients in whom these treatments are likely to be both clinically and cost-effective.

### Author Contributions

IR, NMB and DAE agreed the design, methodology (search terms) and drafting of the manuscript.

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