# How can patients with Clostridioides difficile infection on concomitant antibiotic treatment be best managed?

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# How can patients with *Clostridioides difficile* infection on concomitant antibiotic treatment be best managed?

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**Antibiotics are modifiable risk factors for *Clostridioides difficile* infection (CDI), driving pathogenesis via gut microbiome disruption. The management of patients with CDI prescribed concomitant non-CDI antibiotics is problematic and influences CDI outcome and recurrence risk. Though an assessment of the ongoing requirement for concomitant antibiotics is essential, discontinuation is often not possible. Antibiotics for other reasons might also need to be commenced during CDI therapy. Attempts to minimise the number and duration of antibiotics with a change to a low-risk class are recommended. Fidaxomicin might be preferable to vancomycin due to it having less effect on the gut microbiome; however, vancomycin is also acceptable. Metronidazole should be avoided and proton pump inhibitors discontinued. Access to fidaxomicin might be limited; hence, it should be prioritised for patients at high risk of recurrence. There is insufficient evidence to support extending anti-CDI therapy duration and concerns regarding microbiome effect remain. The addition of bezlotoxumab might be considered if multiple additional risk factors for recurrent CDI exist, though the amount of evidence is low. Investigational approaches to reduce the effect of concomitant antibiotics on the gut microbiome could further optimise CDI treatment in the presence of concomitant antibiotic use in the future.**

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## Background

Antibiotics are commonly prescribed medications in health-care settings and one of the few modifiable risk factors for *Clostridioides difficile* infection (CDI). Management of patients for whom non-CDI antibiotics are administered at the same time as anti-CDI antibiotics (ie, concomitant antibiotics) is particularly clinically challenging, both in terms of CDI management itself and also influencing the risk of future recurrences. Antibiotics drive CDI pathogenesis via disruption of the gut microbiome.[1] This disruption gives *C difficile* a selective advantage, thereby increasing the risk of CDI. On the basis of the results of a multicentre case-control study, this risk is highest during antibiotic treatment and for up to 1 month after discontinuation.[2] However, patients can remain at increased risk for recurrent CDI for several months. CDI risk declines after non-CDI antibiotics are discontinued with recovery of the gut microbiome thereafter.[1]

Given the association between an increased risk of CDI and antibiotic treatment, the continuation or initiation of antibiotics after CDI diagnosis is likely to have an unfavourable effect on CDI outcome. An observational study, published before 2000, showed that of 908 patients with CDI, discontinuing antibiotics alone was effective treatment for 135 of 154 patients.[3] However, only 569 (63%) of 898 of patients with CDI in the study population were cytotoxin positive and the distribution of these patients within the subgroup in which concomitant antibiotics were discontinued is unclear. The study does not further provide details on the proportion of patients for whom discontinuation of antibiotics was on the basis of an active treatment decision. Thus, knowledge on possible selection criteria for patients with CDI for whom cessation of antibiotics might suffice for treatment is currently lacking and unlikely to be obtained given the known risks of adverse outcomes of CDI in patients most affected. More recently, the use of concomitant antibiotics in 27% of study participants in two phase 3 studies designed to compare the efficacy of fidaxomicin and vancomycin in preventing CDI recurrence was associated with a significantly lower cure rate, longer duration of diarrhoea, and increased risk of recurrent CDI.[4] Likewise, in children hospitalised with CDI, receipt of concomitant antibiotics is associated with recurrent disease.[5] However, other studies have not confirmed an association between concomitant antibiotics and adverse CDI outcomes. A cohort study designed to compare risk factors for CDI recurrence according to ribotype (027 *vs* non-027) revealed no elevated risk for recurrence, but did not provide the definition used for concomitant antibiotics.[6] Further data on the association between concomitant antibiotic therapy during CDI treatment and outcome remain conflicting. The updated European Society for Clinical Microbiology and Infectious diseases (ESCMID) guidelines on CDI treatment acknowledges the low evidence base, yet considers patients prescribed concomitant non-CDI antibiotics after CDI diagnosis at increased risk for recurrence.[7]

## Does the choice of concomitant antibiotic effect CDI outcome?

The first step in CDI management is assessment of the ongoing requirement for concomitant non-CDI antibiotics, and if they are no longer needed to stop them. However, in many patients ongoing, antibiotic therapy is clinically indicated and therefore impossible to stop altogether. In these cases, the traditional recommendation is to consider changing the class of concomitant antibiotic to one with a lower CDI risk. The data in support of such a recommendation are conflicting. In one review, ampicillin, amoxicillin, clindamycin, cephalosporins, and fluoroquinolones were the antibiotics most commonly associated with CDI risk.[8] By contrast, in a more recent

clinical trial, carbapenems, second-generation to fourth-generation cephalosporins, fluoroquinolones, clindamycin, and extended-spectrum penicillins were classified as high-CDI-risk antibiotics.[4] In this study, clinical cure was less likely to be achieved in patients prescribed high-risk concomitant antibiotics or those prescribed two or more concomitant antibiotic classes. When cessation or changing of antibiotic therapy is not feasible, we suggest lowering the antibiotic pressure by reviewing the number of concomitant antibiotic prescriptions and shortening the duration of antibiotic therapy.[9] A retrospective cohort study showed an association between CDI risk and cumulative dose, number of antibiotics, and days of antibiotic exposure.[10] Many infections can probably be treated in a shorter timeframe than current dogma.[11]

## Choice of anti-CDI agent

The choice of the anti-CDI agent is important for patient outcome. The updated guidelines from ESCMID and the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America no longer recommend metronidazole as standard of care anti-CDI therapy irrespective of concomitant antibiotic use.[7,12] A previous retrospective study cautioned against metronidazole, recommending its use only in mild CDI after discontinuation of non-CDI antibiotics.[13] In this study, concomitant use of antibiotics increased the rates of treatment failure and 30-day all-cause mortality when patients were receiving metronidazole anti-CDI therapy. Data show that fidaxomicin is preferable to vancomycin for CDI therapy in patients on concomitant antibiotics. As part of a multicentre North American study comparing fidaxomicin and vancomycin for CDI therapy, in the subgroup of patients on concomitant antibiotics there was no significant advantage regarding recurrent CDI for fidaxomicin in both the per-protocol and the modified intention-to-treat analysis.[14] In a similar large multicentre trial in North America and Europe, patients receiving concomitant antibiotics had a longer time to diarrhoea resolution with a higher cure rate reported for those treated with fidaxomicin (46 of 51, 90·2%) than with vancomycin (33 of 45, 73·3%; p=0·031).[15] In the combined analysis of both trials, patients prescribed concurrent antibiotics during treatment with fidaxomicin or during follow-up were less likely to have recurrent CDI when compared with vancomycin (15 of 89, 16·9% *vs* 28 of 96, 29·2%; p=0·048).[4]

## Further options to reduce the risk of recurrence in patients with CDI and concomitant antibiotics

Other options for consideration in the management of patients with CDI prescribed concomitant antibiotics include extending the duration of anti-CDI therapy, consideration of faecal microbiota transplantation, and the use of bezlotoxumab—all with the intention of reducing the increased risk of recurrence in this specific circumstance. In terms of additional potentially modifiable risk factors, the risk of both incident and recurrent CDI could be further increased by the concomitant use of proton pump inhibitor therapy, in addition to non-CDI antibiotics.[16]

### Extending the duration of anti-CDI therapy

As concomitant antibiotic therapy affects a person's subsequent CDI recurrence risk, the idea of modifying this risk with an anti-CDI agent could be one potential management strategy in these patients. However, such approaches are generally not recommended because of conflicting evidence and concerns regarding the effect on the microbiome.[17] For example, metronidazole was shown to be ineffective for the eradication of asymptomatic *C difficile* faecal excretion in a randomised, placebo-controlled clinical trial,[18] most likely related to suboptimal concentrations in the gut, especially once diarrhoea ceases.[19] Similar relapse rates were observed in a retrospective study of patients treated with routine anti-CDI therapy for 10–14 days (17% relapse) versus those treated for more than 14 days (23% relapse; p=0·425).[20] However, the vast majority of patients in this study received metronidazole therapy. Extended-pulsed fidaxomicin to prevent CDI recurrence might be another potential treatment strategy. However, although patients on antibiotics for conditions other than CDI in the 90 days before the study were included in both study groups of a European multicentre randomised control trial, no specific analysis of their effect on this patient subgroup was done and information on concomitant antibiotics was not provided.[21]

### Faecal microbiota transplantation

Administration of faecal microbiota transplantation seems to be a less promising option for patients on concomitant antibiotics, mitigating the beneficial effects on reconstitution of the microbiome.[22] Furthermore, in a retrospective study designed to investigate the durability of faecal microbiota transplantation (defined as no recurrence despite additional risk factor exposure) in patients with recurrent CDI, antibiotic exposure after faecal microbiota transplantation was independently associated with decreased durability.[23]

### Bezlotoxumab

Bezlotoxumab, a monoclonal antibody directed against *C difficile* toxin B, resulted in a 10% reduced risk of recurrences in the placebo-controlled phase 3 MODIFY-I and II trials.[24] However, the use of concomitant systemic antibiotics was not a pre-specified risk factor for subgroup analysis in the post-hoc analysis, as only risk factors present at the time of randomisation were included.[25] Nevertheless, 40% of patients in the trial used concomitant antibiotics during standard-of-care CDI therapy (37% bezlotoxumab and 41% placebo), whereas non-CDI antibiotic use after standard-of-care CDI therapy was observed in 36% of patients (35% bezlotoxumab and

36% placebo). In this regard, the trial result might be considered generalisable to patients on concomitant antibiotic therapy, though further studies are required to explore the exact benefit in this subgroup.

## Future strategies: inactivation of concomitant antibiotics in the colon

A promising approach to prevent dysbiosis induced by concomitant non-CDI antibiotics includes the co-administration of compounds designed to inactivate antibiotics in the colon, such as ribaxamase or DAV-132. Ribaxamase is a recombinant β-lactamase that is orally administered in conjunction with intravenous β-lactam antibiotics. It inactivates excess antibiotics excreted into the gut via bile, preventing disruption of the gut microbiome and reducing exposure to the selective pressure of β-lactam antibiotics. In a phase 2b proof-of-concept study of 412 hospitalised patients prescribed intravenous ceftriaxone for management of lower respiratory tract infection, the incidence of CDI was reduced in patients who received ribaxamase compared to placebo (1% *vs* 3·4%, one-sided p=0·045).[26] Microbiome analysis showed a reduction of ceftriaxone-induced changes in the ribaxamase group who recovered more quickly than the placebo group. A more recent analysis showed reduced changes to the gut resistome subsequent to ceftriaxone administration in patients treated with ribaxamase.[27] DAV-132 is an enteric-coated-formulated, activated-charcoal based product designed to neutralise antibiotic residues in the proximal colon. It has been shown to selectively adsorb drug compounds in the proximal colon, without interfering with drug absorption in the proximal small intestine in a proof-of-concept study in healthy volunteers.[28] In healthy volunteers treated with moxifloxacin, DAV-132 was shown to be effective to protect the gut microbiome,[29] and a phase 2 study on safety and efficacy of DAV-132 in patients at high risk for CDI treated with fluoroquinolones was recently completed (NCT03710694).

## Conclusion

So where does that leave the clinician managing patients with CDI also requiring concomitant antibiotic therapy? This Personal View has focused specifically on CDI management of patients prescribed concomitant antibiotics. Our conclusions are based on the little literature available and on our opinion and clinical experience (panel). Certainly, every effort should be made to stop concomitant non-CDI antibiotics whenever possible. However, in many patients this measure is not possible because of an ongoing requirement for non-CDI antibiotic treatment. Therefore, the number and duration of concomitant non-CDI antibiotics should be minimised with a change to a low-risk class if possible. The revised guidelines[30] from ESCMID and the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America recommend fidaxomicin as a conditional option with moderate quality of evidence for the treatment of initial CDI and first recurrence of CDI when available and feasible, though acknowledges vancomycin as a suitable alternative.

**Panel: Key recommendations on the management of patients with *Clostridioides difficile* infection on concomitant antibiotic treatment**

- Stop concomitant non-*Clostridioides difficile* infection (CDI) antibiotics whenever possible
- If not possible, review the number and duration of concomitant non-CDI antibiotics and change to low-risk classes if possible
- Stop proton pump inhibitors whenever possible
- Do not treat CDI with metronidazole
- Fidaxomicin might be the preferred anti-CDI agent, though vancomycin is an acceptable alternative
- The addition of bezlotoxumab might be considered if multiple additional risk factors for recurrent CDI exist
- Faecal microbiota transplantation needs to be examined more for its role in this setting

We emphasise that the evidence base for providing this guidance is currently low in quality and amount, thus all recommendations need to be continuously reassessed as new data emerge.

Fidaxomicin has the narrowest spectrum of activity, with less effect on the bacterial gut microbiome than vancomycin.[31–33] However, access might be limited in some health-care systems because of its higher direct cost. In these situations, the ESCMID guidelines[7] recommend a risk stratification approach for selected fidaxomicin use in patients at high risk of recurrent CDI, such as patients older than 65 years on concomitant antibiotics. However, considerations regarding the cost of an anti-CDI agent should also include its effect on subsequent CDI-related adverse events. For example, fidaxomicin might be more cost-effective than vancomycin for the management of the initial CDI episode, due to its association with reductions in recurrent CDI.[34–39] By contrast, cost-effectiveness of fidaxomicin is lower than for vancomycin in populations with a greater proportion of BI/027 strain infections and in patients with severe CDI.[36] The Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines note that although cost-effectiveness analysis favours fidaxomicin over vancomycin for the management of the initial CDI episode, implementation can be challenging due to variations in medical insurance coverage.

Metronidazole should be avoided and is no longer recommended in these guidelines for first-line anti-CDI therapy. Both guidelines suggest consideration of concomitant administration of bezlotoxumab as adjunctive therapy, either in patients with a first recurrence of CDI (ie, according to the Infectious Diseases Society of America, the Society for Healthcare Epidemiology of

America, and ESCMID) or in patients at high risk of recurrence (ie, according to ESCMID). However, in the MODIFY trials[24] approximately a third of patients received concomitant antibiotic therapy, but there was no formal analysis on the effect of bezlotoxumab in patients on concomitant antibiotic therapy. Therefore, the decision of whether or not to add bezlotoxumab to standard-of-care antibiotics for CDI treatment might be considered in patients with additional risk factors for recurrent disease, beyond concomitant antibiotic therapy. We emphasise that the evidence base for providing this guidance is currently low in quality and amount, thus all recommendations need to be continuously reassessed as new data emerge.

In conclusion, managing patients with CDI on concomitant antibiotics remains challenging until more evidence on the benefits of newer treatment strategies in this distinct patient population emerges. In the meantime, we hope to have provided some guidance that can contribute to successful management.

#### Contributors

FF contributed to the conceptualisation of this Personal View, the literature search, and interpreting the data, and wrote the first draft of the manuscript. NS and JvP contributed to interpreting the data, editing, and revising the manuscript. ST-S contributed to the conceptualisation of this Personal View, the literature search, and interpreting the data, and edited and revised the manuscript.

#### Declaration of interests

NS reports a grant from the National Institutes of Health, outside the submitted work. ST-S is a member of the Astellas and MSD Advisory Boards for *Clostridioides difficile*, of the Pfizer Anti-infectives Advisory Board, the Menarini Scientific Advisory Board, and the Shionogi Scientific Advisory Board. She reports grants from the Swiss National Science Foundation (NRP 72 167060 and 197901), the National Center of Competence in Research AntiResist (180541), the Gottfried und Julia Bangerter-Rhyner Stiftung, the Fonds zur Förderung von Lehre und Forschung der Freiwilligen Akademischen Gesellschaft Basel, and the Jubiläumsstiftung from Swiss Life, outside the submitted work. JvP reports a grant from Merck Sharp & Dohme, outside the submitted work. FF declares no competing interests.

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