

Antibiotic therapy and *Clostridium difficile* infection – primum non nocere – first do no harm

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Abstract: Treatment options for *Clostridium difficile* infection (CDI) remain limited despite this usually nosocomial infection posing an urgent threat to public health. A major paradox of the management of CDI is the use of antimicrobial agents to treat infection, which runs the risk of prolonged gut microbiota perturbation and so recurrence of infection. Here, we explore alternative CDI treatment and prevention options currently available or in development. Notably, strategies that aim to reduce the negative effects of antibiotics on gut microbiota offer the potential to alter current antimicrobial stewardship approaches to preventing CDI.

Keywords: treatment, prevention, CDI, SYN-004, vaccine, beta-lactams

Introduction

Over the last three decades, our understanding of the pathophysiology, epidemiology, diagnosis, and treatment of *Clostridium difficile* infection (CDI) has grown, notably as the incidence and severity of infections have increased dramatically.¹ From 1935, when first cultured by Hall and O'Toole, until the 1970s, when its role in antibiotic-associated diarrhea and pseudomembranous colitis was elucidated, the *C. difficile* bacterium was believed to be relatively unimportant in clinical significance.^{2,3} The initiation of antibiotic therapy usually leads to perturbation of the intestinal microbiota. Cessation of therapy gradually enables a return to a pretreatment state, a concept called colonization resistance or community resilience. However, this resilience is not necessarily complete, and the resultant patient's intestinal microbiota may remain perturbed for months after antibiotic cessation.⁴⁻⁶ *C. difficile* can exploit the niche created by the effects of antibiotics on the intestinal microbiota, either by the expansion of strain already present before antimicrobial therapy commenced or following the acquisition of a strain while colonization resistance remains perturbed.

The rise to prominence of *C. difficile* as a cause of infective diarrhea was heightened by the emergence of the NAP1/BI/027 strain in the early to mid-2000s and its association with more severe CDI.⁷ The recognition of community-acquired CDI has added another new dimension of concern.⁸ Today *C. difficile* is widely recognized as the leading cause of infective nosocomial diarrhea globally and is associated with significant morbidity and mortality.⁹⁻¹¹ These facts, coupled with the probability that CDI might be substantially underdiagnosed in some settings, serve to support its designation by the CDC as an urgent public health threat.¹²⁻¹⁴

The resident microbiota of the gastrointestinal tract plays a crucial role in protecting against invading pathogenic microorganisms via colonization resistance.^{15,16} Any exposure to an antibiotic is a major risk factor for the development of CDI; enhanced

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CDI risk has been shown to persist for up to 3 months postexposure.^{17,18} This is particularly true with clindamycin, the penicillins ampicillin or amoxicillin, cephalosporins, and fluoroquinolones.^{19–22} In an effort to minimize exposure to these selected classes of drugs, interventions have been made to substitute one class (eg, a ureidopenicillin) for another (eg, an oxyimino-cephalosporin) in an attempt to reduce rates of CDI.²⁰ Additionally, there is evidence that the class of drug is not the only parameter to consider when selecting a particular agent. Another important determinant of CDI risk is the cumulative antibiotic exposure as measured by length of therapy and number of different antibiotics used, either simultaneously or sequentially.²³

As stated in the Infectious Disease Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines for developing an institutional program to enhance antibiotic stewardship, “The primary goal of antimicrobial stewardship is to optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *C. difficile*), and the emergence of resistance”.²⁴ As previously stated, the use of broad-spectrum (workhorse) antimicrobials such as penicillins, cephalosporins, and fluoroquinolones as empiric agents is associated with subsequent CDI development. This concept is sometimes referred to as “collateral damage”. Ideally, the use of these higher CDI risk antimicrobial classes should be minimized or avoided entirely, but this is not always practical. Furthermore, restriction of whole antibiotic classes will likely lead to less diversity of antimicrobial prescribing, which is associated with increased risk of resistance.^{25,26} Notably, however, the collateral damage caused by antibiotic use may be more serious than the original infection. Furthermore, many patients, particularly the elderly with multiple comorbidities, are recipients of antibiotic polypharmacy, possibly starting in the community setting and then continuing after hospitalization.

Should CDI occur, the first step in treatment is the discontinuation of all antibiotics, if possible. This is usually impractical, especially in patients with serious and/or multiple comorbidities.^{27–29} The 2014 European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines recommend metronidazole as initial therapy for mild-to-moderate CDI, with oral vancomycin reserved for more severe cases (Table 1).³⁰ However, recently published data show that vancomycin was superior to metronidazole in achieving clinical success for all patients in a combined Phase III database.³¹ For severe, complicated cases of CDI, oral vancomycin, with or without IV metronidazole, plus

Table 1 Therapeutic regimens for CDI

First-line option	Second-line option
Nonsevere CDI	
Metronidazole (500 mg TID 10 days)*	Vancomycin (125 mg QID 10 days)** Fidaxomicin (200 mg BID 10 days)**
Severe CDI	
Vancomycin (125 mg QID 10 days)*	Fidaxomicin (200 mg BID 10 days)**
First recurrence	
Vancomycin (125 mg QID 10 days)** Fidaxomicin (200 mg BID 10 days)**	Metronidazole (500 mg TID 10 days)**

Notes: For information on rates of recurrence for each therapeutic regimen, please refer ESCMID guidelines. *Indicates strong support for recommendation of use; **Indicates moderate support for recommendation of use; ***Indicates marginal support for recommendation of use. Data from Debast et al.³⁰

Abbreviations: CDI, *Clostridium difficile* infection; TID, three times daily; QID, four times a day; BID, twice daily.

a vancomycin retention enema if *ilius* is present is recommended (Table 1).

Fidaxomicin was approved by the FDA in 2012 for the treatment of *C. difficile*-associated diarrhea in adults (≥ 18 years of age). Fidaxomicin is a narrow-spectrum agent with minimal systemic absorption when administered orally, possesses low activity against normal gut microbiota, and is active against *C. difficile*, most strains of staphylococci, and enterococci.^{32,33} Fidaxomicin has been shown to be noninferior to vancomycin for initial cure in patients with CDI and was associated with a lower recurrence rate and superior sustained clinical response.^{34,35} Adverse event rates were similar; overall, 5.9% of patients on fidaxomicin and 6.9% on vancomycin withdrew from trials as a result of adverse events. Fidaxomicin was demonstrated to be superior to vancomycin in patients with non-NAP1/BI/027 strains.³⁶ In the United Kingdom, use of fidaxomicin should be considered in patients with severe CDI who are considered at high risk of recurrence or not responding to vancomycin therapy. It is also the recommended option for patients with a first recurrence of CDI (Table 1).³⁷ Use of fidaxomicin, however, has remained limited due to its high price, a negative attribute further exacerbated by the recent availability of a generic version of oral vancomycin in the United States.³⁸

It is important to note that current standards of care for CDI (metronidazole, vancomycin, or fidaxomicin) are associated with at least 12%–20% levels of recurrence, with further recurrences more likely in those who require follow-up treatment.³⁹ High gut concentrations of conventional CDI therapeutic agents can adversely affect the microbiota, leading to secondary infections (relapses and reinfections) of CDI and selection of other potential pathogens, such as enterococci.⁴⁰

Our approach to CDI management needs to be multifactorial and incorporate improved diagnostics, epidemiology,

infection control, antibiotic stewardship, and prevention and treatment options. Currently, there are multiple antimicrobial agents (eg, cadazolid [Actelion], surotomycin [Cubist], SMT19969 [Summit Corporation], and CR3123 [Crestone]) in various stages of development for the treatment of CDI.^{39,41} In addition to this traditional CDI management strategy, several different approaches to the prevention and treatment of CDI that do not utilize antibiotic agents to treat established infections are in development (Table 2). Although all differ from each other on a mechanistic level, most are grounded on the principle of attempting to spare, protect, or repair the endogenous gut flora.⁴²

The microbiological supplementation approach, notably fecal microbiota transplant and Rebiotix oral preparation (Table 2), addresses the high rates of recurrence and particularly the debilitating impact of multiple recurrences following treatment with either vancomycin or metronidazole by attempting to restore the “normal” gut flora. With the exception of VP20621, none of the approaches listed are aimed at preventing the initial episode of CDI. Additionally, because

the infective process can still be active and the need for antibiotic cover still exists, these strategies are primarily aimed at present for the treatment of CDI recurrence. Furthermore, the administration of antibiotics could obviate such therapies, as this would reinterrupt the gut microbiota.

The nonmicrobial biological approach (Table 2) encompasses passive immunization and vaccination and target the toxins produced by the *C. difficile* bacterium. Monoclonal antibodies given in addition to either metronidazole or vancomycin were superior to standard treatment alone for the prevention of recurrence in a Phase II study; Phase III studies are nearing completion.⁴³ The therapy with this adjuvant antibody did not, however, improve the severity of illness, the length of hospitalization, or the time to resolution of diarrhea.

There are multiple key issues to be addressed for the development of an effective vaccine for CDI, including antigen(s) selection, delivery system, patient selection, and immunoresponsiveness, particularly in the elderly.^{44,45} In addition, the requirement for multiple doses of vaccine impacts negatively on the development and success of a toxoid vaccine.⁴⁶ Additionally, current vaccines do not inhibit colonization by *C. difficile*.³⁹

The third approach, antibiotic inactivation (Table 2), is targeted at eliminating the collateral damage associated with the initial antibiotic exposure, thereby potentially reducing the risk of CDI.³⁹ As antibiotics are often necessary, the co-administration of an agent such as SYN-004 can inactivate the antibiotic in the large intestine, thereby allowing the systemic distribution of the active agent but avoiding the damage associated with the antibiotic to the intestinal microbiota, thereby preventing CDI. As such, the antibiotic inactivation approach is a novel strategy that could not only prevent the initial episode of CDI but also allow the continued use of broad-spectrum penicillins and cephalosporins, which are widely prescribed for empiric treatment of serious infections.

Recently, there was a call by Gerding and Johnson for “inside the box” and “outside the box” thinking in treating CDI.⁴⁷ “Inside the box” agents include vancomycin, metronidazole, fidaxomicin, and the other agents previously listed that are to be used to treat CDI. “Outside the box” approaches to CDI treatment and prevention include the microbiological, nonmicrobiological, and antibiotic inactivation approaches discussed earlier. These avoid “the continued suppression of normal bacterial microbiota that occurs with antimicrobial management”.⁴⁷

In closing, our understanding of the importance of *C. difficile* has been transformed in the three decades since its discovery as a human pathogen; it is now considered to

Table 2 Alternative *Clostridium difficile* infection preventative and therapeutic approaches

Approach	Product	Development stage
Microbiological	• Microbiota supplementation (fecal microbiota transplant)	n/a
	• RBX2660 (Rebiotix; an oral preparation of live microbes)	Phase II
	• SER109 (SeresHealth; an orally delivered combination of spores)	Phase I/II
	• VP20621 (Shire [formerly ViroPharma]; spores of NTCD strain M3)	Phase II
Nonmicrobial biological	• Passive immunization (MK3415A [Merck])	Phase III
	• Vaccines:	
	<i>C. diffense</i> (Sanofi Pasteur)	Phase III
Antibiotic inactivation	PF-06425090 (Pfizer)	Phase II
	IC84 (Valneva)	Phase I
	• SYN-004 (Synthetic Biologics; a synthetic Class A β -lactamase enzyme for use with IV cephalosporins [including ceftriaxone] and penicillins)	Phase II
	• DAVI32 (DaVolterra; a medical device consisting of an activated-charcoal-based product in an enteric-coated pill)	Phase I

Note: Adapted from Drug Discovery Today, Volume 20, Ivarsson ME, Leroux J, Castagner B, Investigational new treatments for *Clostridium difficile* infection, Pages 602–608, Copyright 2015, with permission from Elsevier.³⁹

Abbreviations: n/a, not available; NTCD, nontoxicogenic *Clostridium difficile*.

be an urgent public health threat. CDI is closely associated with the use of antibiotics. As such, a key negative impact of CDI is the ability to continue to safely prescribe particular antibiotics, notably penicillins and cephalosporins, which have long been considered to be valuable classes for treating serious infections. Using an antibiotic inactivation approach can both potentially reduce the risk of collateral damage and CDI and allow the continued clinical use of valuable antibiotics. This approach could provide reassurance that, even in patients at increased risk of CDI, antibiotic therapy can be initiated and continued to achieve optimal clinical outcomes. The development of microbiome-friendly interventions could also be beneficial in preventing the establishment and selection of other multidrug-resistant organisms that exploit the niches created by antibiotic-induced collateral damage.

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