Non-antibiotic management for *Clostridium difficile* infection

Anshul Sood, Chetana Vaishnavi

Department of Gastroenterology,
Postgraduate Institute of Medical Education and Research, Chandigarh, India

ABSTRACT

Clostridium difficile infection (CDI) is a key cause of diarrheal illness due to outbreaks by the hypervirulent *C. difficile* NAP1/027 strain. The mainstay and time-honored antibiotic therapies for the management of CDI apart from killing *C. difficile*, also disturbs the standard healthy gut flora leading to dysbiosis. Mismanagement of antibiotics has led to a widespread increase in antibiotic resistance which has jeopardized the efficacy of antibiotics. This article has shed some light on the present-day vista of non-antibiotic approaches to combat CDI which include bacteriotherapy (fecal microbiota transplant, probiotics, non-toxigenic *C. difficile* spores), immunoglobulin therapy (monoclonal antibodies, polyclonal antibodies, bovine antibodies, whey protein concentrate, colostrum, *C. difficile* vaccine), photodynamic therapy and other miscellaneous therapies like the use of adsorbents, prebiotics and corticosteroids.

Keywords: Bacteriotherapy, immunoglobulin therapy, photodynamic therapy

INTRODUCTION

Clostridium difficile, generally acquired by the feco-oral route, is an important cause of gastrointestinal (GI) illness occurring as a complication of therapy by antibiotics, chemotherapeutics or other drugs that alter the gut microbiota in hospitalized patients.[1,2] The spectrum of *C. difficile* infection (CDI) ranges from mild diarrhea, infectious colitis or pseudomembranous colitis (PMC) and toxic megacolon. This illness is responsible for a high burden on the health-care management.

The two first line antibiotics – metronidazole and vancomycin– are most often used as antibiotics of choice for the treatment of CDI. Metronidazole is generally used for patients with initial episodes of mild to moderate CDI[3] whereas vancomycin is reserved for patients with serious illness as it hardly has any side effect and is not absorbed by the intestine.[4] However because of its high cost as also the risk of development of vancomycin-resistant enterococci, its routine use is discouraged.[2] Both the drugs have unacceptably high rates (15-35%) of recurrence of infection.[5,6] In May 2011, fidaxomicin, a new antibiotic, was approved for CDI by the US Food and Drug Administration (FDA).[7] All these three antibiotics are generally used to treat most patients with CDI. The leading risk factor linked with CDI development is prior antibiotic use.[2] Antibiotics disturb the normal healthy intestinal microflora causing dysbiosis and may thus provide an opportunity to *C. difficile* to cause CDI. Furthermore, the overuse and misuse of antibiotics has led to a widespread increase in antibiotic resistance which jeopardizes the efficacy of the antibiotics.

Due to the increase in CDI incidence, rise in the rate of recurrence, greater mortality and morbidity, appearance of hypervirulent *C. difficile* strains, and a widespread increase in antibiotic resistance, there is a strong need to prospect novel treatment paradigms and non-antibiotic ways to manage CDI. During the past few years, numerous non-antibiotic approaches have

Corresponding author: Prof. Chetana Vaishnavi
E-mail: chetanavaishnavi@gmail.com

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been developed for the management of CDI with each having its own pros and cons. This review is an attempt to streamline all the non-antibiotic strategies involved in the management of CDI.

Non-antibiotic management for CDI

Several non-antibiotic strategies are available and some have been put into practice to manage CDI. The important ones are listed below:

1. Probiotics, Prebiotics and Bacteriocins: Several different probiotics have been used oft and again to treat CDI. They are *Lactobacillus rhamnosus* GG, *L. acidophilus, Bacillus clausii, Enterococcus faecium* SF68, *Bifidobacterium longum*, *Clostridium butyricum*, *Saccharomyces boulardii* and even nontoxigenic *C. difficile.* CDI in mice was well resolved by the cocktail of six species including *Porphyromonadaceae*, *Lachnospiraceae*, *Lactobacillus*, *Coriobacteriaceae*, *Staphylococcus* and *Enterococcus* isolates.[8] *C. difficile* colonization resistance is an attribute of multiple microbial assemblies interacting in a context-dependent manner and not conferred by a single microorganism. Increased *C. difficile* colonization were reported with *Escherichia* and *Streptococcus* isolates whereas *Porphyro-monadaceae*, *Lachnospiraceae*, *Lactobacillus*, and *Alistipes* isolates were protective.[9] Colonization resistance in recurrent CDI was successfully restored by a more diverse consortium of bacterial species (n=33) including *Lactobacillus, Porphyro-monadaceae*, *Ruminococcaceae*, *Lachnospiraceae* and *Eubacteriaceae* isolates with diarrheal resolution by six months of treatment.[10] Enache *et al*[11] examined in four studies the combination of probiotic with either vancomycin or metronidazole for treatment of initial episode or recurrence of CDI in adults. It is believed that probiotics merely aid in restoring the microorganisms milieu within the intestine. Again it should be used with caution as in a case-series, use of *S. cerevisae* led to invasive fungemia.[11] Moreover the use of probiotics is not recommended in elderly, immunocompromised patients with increased colonic permeability due to CDI. Ollech *et al*[12] recently discussed the recommendations of probiotics, relying on evidence gathered from *in-vitro* laboratory and pre-clinical studies, and observed that probiotics are efficacious at preventing initial cases of CDI and also for its recurrences. However, because of inadequate substantiation, more research and large controlled clinical trials are required to use probiotic therapy by itself or in combination with antibiotic therapy for *C. difficile* colitis.

Oligofructose and inulin are prebiotics used as adjunct therapy to CDI which help to promote the growth of beneficial gut flora.[13] With combination of oligofructose with either vancomycin or metronidazole, fewer CDI relapse was reported by Lewis *et al.*[14]

Some gut bacteria can also produce bacteriocins that can act as bactericidal or bacteriostatic agent. Rea *et al*[15] reported one such *C. difficile* inhibiting bacteriocin "Thuricin CD" produced by *Bacillus thuringiensis* DPC 6431. This bacteriocin was shown to be effective against a large number of clinically significant *C. difficile* isolates, together with BI/NAP1/027-type strains while also having the least impact on the indigenous microbiota.[15] The same group of researchers later on in another experiment demonstrated that rectal administration of thuricin CD was more effective against *C. difficile* than oral gavage of the same due to lower bioavailability.[16] Another contractile R-type bacteriocin from *C. difficile* strain CD4 was genetically modified to diffocins (a.k.a. Avidocin-CDs) which was found to be effective against all 16 tested BI/NAP1/027 strains of *C. difficile* and also harmless to the host microbiota.[17]

2. Fecal microbiota transplantation: As CDI is an antibiotic-associated disease, treatment with antibiotic is best avoided, and replacement of the lost normal microflora with bacteria obtained from a healthy donor is required. Fecal microbiota transplantation (FMT) is another such method apart from probiotic therapy that serves the purpose. It involves the transplantation of stool from healthy individual to the patients' large intestine via enemas.[18] It has been efficaciously used to treat diarrhea for over 50 years even before *C. difficile* was documented as the chief cause of PMC. Eiseman *et al* [19] in their study reported four patients with PMC and after successful treatment with fecal enemas the authors showed vivid resolution of

diarrhea over 24-48 h post-treatment. Many methods have been used so far for stool delivery to patients which includes endoscopy/gastroscopy or *via* nasogastric tube for upper GI tract passage into the duodenum and *via* colonoscopy, rectal tube or enema for infusion into the lower GI tract.[20] Fresh stool samples are used for FMT preferably within six hours [21] but not later than 24 h.[22] The volume of stool taken should be 50 g suspended in about 500 ml of fluid.[23] Ideally 5–300 g of stool in volume ranging from 25 to 960 ml has been transplanted by investigators. Lower volume was used when delivered *via* the upper GI tract, but increased when delivered by colonoscopies to the lower GI tract.[20]

Castro *et al* [24] recently observed that antibiotics were not any longer needed after the transplantation of fecal microbiota. This was in accordance with the findings of Ganc *et al* [25] where a 60-year-old woman suffering with PMC received sequentially oral vancomycin and metronidazole followed by a course of intravenous (IV) meropenem and oral metronidazole. Despite this her diarrhea still continued, till she received FMT from two different donors. Recently, Asonuma *et al* [26] also reported successful FMT in a 49-year-old woman diagnosed with PMC and not responding to antibiotics. Diarrhea disappeared over three days of post-treatment and resolution of pseudomembranes was revealed after four days by colonoscopy and within the first year after discharge, recurrences were not reported.

FMT was used as a rational and relatively simple alternative approach to combat high recurrence rates of CDI.[18] Nood *et al* [27] reported 81% success rate for recurrent CDI treatment by duodenal infusion of donor stools compared to only 31% by vancomycin therapy.[28] A cure rate of 93% was achieved when stool was taken from two healthy donors and used for 27 patients in a study performed at McMaster University, Canada. In the remaining 7% the lack of retention of enema led to unsuccessful FMT.[29]

Human feces had been regulated as drug by the US FDA in May 2013.[30] In February 2014, a gastroenter-ologist and co-founder of the stool bank OpenBiome, a biological engineering Professor and a PhD candidate from Massachusetts Institute of Technology recommended that human stool should be regarded as a tissue and not as a drug for medical use.[30] Though very large unfavorable effects have not been reported with FMT so far, some risks and limitations do definitely exist *viz*. screening of suitable donor, threat of introducing opportunistic pathogens, patient preparation and various discomforts like short-lived abdominal uneasiness and bloating. By and large risks can be reduced by obtaining the stools from a donor of close physical association to the recipient, be it a spouse or another family member.[31] FMT is still considered successful for CDI and recurrent CDI on the basis of recent clinical trials.[32] Growing evidences show that FMT has hit the mark and is considered as a suitable method for restoration of microflora and competent non-antibiotic management of CDI. More investigations and clinical trials will help to establish the most efficient methods of gut microbiota restoration.

3. Non-toxigenic *Clostridium difficile* spores: *C. difficile* strains like M3 (VP20621) do not have genes for toxin production and thus are non-toxigenic *C. difficile* (NTCD). These strains are widespread in the hospital environment without evidence of CDI, thereby suggesting its asymptomatic carriage among patients. Oral administration of spores of a single NTCD-M3 has been found as an unconventional, alternative biotherapeutic approach to FMT. NTCD strains were selected for their high frequency of isolation from colonized patients and were identified using restriction endonuclease analysis typing.[33,34] A phase II, randomized, double-blind, placebo-controlled study was performed among 173 CDI patients with a successful treatment of oral vancomycin, metronidazole or both. Patients were given one of four random treatments comprising of oral liquid formulation of NTCD-M3, 10^4 spores/d for 7 days, 10^7 spores/d for 7 days or 10^7 spores/d for 14 days or placebo for 14 days. Among 168 patients, 157 completed the treatment. In 69% of patients receiving NTCD-M3, 63% fecal colonization was reported with 10^4 spores/d and 71% with 10^7 spores/d. Amongst patients receiving placebo 30% showed recurrence of CDI compared to only 11% of

patients receiving NTCD-M3; lowest recurrence was seen in 5% of patients receiving 10^7 spores/d for 7 days. CDI recurrence was seen in only 2% of patients who were colonized, but in 31% who were not colonized, but received NTCD-M3. The study shows that NTCD-M3 colonization in the GI tract considerably reduces CDI recurrence.[35] In another study, successful colonization of the same strains, in volunteers aged 60 years or older was reported when doses ranging from 10^4 to 10^8 spores per day were given for 14 days. To disturb the normal microbiota and stimulate CDI treatment, vancomycin was given for 5 days.[36] In an earlier study it was shown that colonization with NTCD was found to be effective against toxigenic CDI in hamsters also.[34] The mechanism by which NTCD colonization prevents CDI and its recurrence is unknown,[37] though it is assumed that NTCD strains exploits the same colonization niche as that of toxigenic strains to damage their inhabitation.[38]

4. Adsorbents: Cholestyramine and colestipol – the ion exchange resins – have been used time and again as an adjunct therapy to CDI as they attach to *C. difficile* toxins in the gut lumen before they bind to the intestinal epithelial cells to produce illness. Sequences of oligosaccharide bound to inert silica based support (Synsorb 90) work as a bait toxin receptor. Many successful cases have been reported with cholestyramine in pediatric and adult patients with numerous relapses and did not respond to conventional treatments.[39,40] Another high molecular weight styrene sulfonate polymer (tolevamer) binds non-covalently to *C. difficile* toxins to block their activity has also been used as CDI therapy.[41] The active ingredients of tolevamer are poly 4-styrenesulfonate containing either 100% sodium (tolevamer sodium) or a combination of 63% sodium and 37% potassium (tolevamer potassium-sodium) as counter ions.[42] In a multicenter phase II trial Louie *et al*[43] examined three and six gram doses of tolevamer for 14 days with vancomycin (500 mg x 10 days) in CDI patients. They observed that the six gram tolevamer dose was non-inferior to vancomycin for treatment of mild to moderate CDI. But hypokalemia was one of the side effects of tolevamer therapy. A phase III trial was conducted comparing vancomycin and metronidazole with a reformulated higher dose of tolevamer which included potassium.[44] This trial showed that tolevamer did not appear to be non-inferior to vancomycin, but recurrent CDI was not common with tolevamer indicating that flora sparing drugs could possibly reduce recurrences. Comparative studies made for tolevamer and cholestyramine revealed that tolevamer reduced fluid accumulation caused by toxin A in rat ileal loops and mortality in hamsters.[45] In rat models tolevamer was at least 80 folds more efficient at preventing accumulation of fluid due to toxin A and blocked intestinal permeability 16 times more efficiently than cholestyramine. Hamsters were protected from mortality due to CDI when treated with 80% tolevamer and 10% cholestyramine.[45]

DAV132 is a novel medicinal product which is adsorbent-based and has been reported recently for the treatment of CDI.[46] This enteric-coated formulated activated-charcoal based product delivers the adsorbent to the ileum and neutralizes the drug compounds and antibiotic residues in the proximal part of the intestine before the latter can make a significant change in the microbiota. Three clinical trials of DAV132 have been performed successfully.[47]

5. Immunoglobulin therapy

(i) Monoclonal antibodies: Lowy *et al*[48] in a phase II randomized, double-blind, placebo-controlled trial investigated the effects of monoclonal antibodies on the extent and severity of the initial occurrence of CDI as well as on the length of hospital stay. A single infusion (10 mg/kg body weight) of the human monoclonal antibodies comprising of CDA1 and CDB1 against both the *C. difficile* toxins was administered to 101 patients getting one of the two antibiotics *viz*. metronidazole or vancomycin and to 99 volunteers receiving a placebo. The collective infusion of these two monoclonal antibodies along with antibiotics drastically reduced the CDI recurrence. Humanized monoclonal antibodies (HuMAbs) were found effective against both toxin A (HuMAb CDA1) and toxin B (MDX-1388). HuMAb CDA1 was found safe and well-tolerated in doses between 0.3 and 20 mg/kg.[49] HuMAb CDA1 protected hamsters from mortality when used alone

and more effective results were seen when synergized with a combination therapy.[50]

Another set of HuMAbs – actoxumab and bezlotoxumab – that target toxin A and toxin B respectively, were found effective against several clinically relevant *C. difficile* strains and many BI/NAP1/027 and BK/NAP7/078 strain isolates, at antibody concentrations below the plasma levels as seen in humans.[51] A 73% reduction in the rates of CDI recurrence has been reported in phase II clinical trials when these monoclonal antibodies were given with either vancomycin or metronidazole.[48] These antibodies were found effective against *C. difficile* associated inflammatory response as well as damage to the gut wall, in murine CDI models together with mice challenged with a hypervirulent ribotype 027 strain.[52] Two phase III randomized controlled trials (MODIFY I and MODIFY II; MODIFY: Monoclonal Antibodies for *C. difficile* Therapy) demonstrated the effectiveness of standard care antibiotics in addition to either actoxumab, bezlotoxumab, both monoclonal antibodies together or placebo. Monoclonal antibody against toxin B was found as an effective adjunct against recurrent CDI in the study.[53] Bezlotoxumab alone was shown to work better than the combination of actoxumab and bezlotoxumab for prevention of CDI.[54]

(ii) Polyclonal antibodies: The presence of low serum antibody to *C. difficile* toxin A is a major risk factor for CDI.[55,56] Polyclonal ovine antibodies have been found effective against *C. difficile*. They react with an epitope each of N-terminal (1-957), mid-region (958-1831) or C-terminal (1832-2710) domain of toxin. Antibodies can be raised in sheep by introducing a *C. difficile* toxin and the toxicity of immunogen is reduced by recombinant or chemical method. Recombinant method discriminately turns off the active site of *C. difficile* toxin by deletion or mutation, like alteration of aspartates and/or other residues to alanine, or by modifying the DXD motif in the N-terminal domain of the toxin and chemically modifying by treatment with UDP-dialdehyde, glutaraldehyde, formaldehyde etc.[57]

In recent years IV immunoglobulins (IVIg) have been found beneficial in treating CDI patients.[58] Initially Leung *et al*[59] reported the use of IVIg (400 mg/kg once every three weeks) in five pediatric patients having recurrent CDI leading to complete resolution of symptoms. Abougergi *et al*[60] reported treatment with IVIg in severe CDI patients (n=21) having pancolitis or ileus. The total IVIg dose administered over a period of 1-3 days ranged from 200 mg/kg to 1250 mg/kg. Complete clinical resolution was observed in nine patients within 2-20 days. The remaining 12 patients did not survive during the hospital stay, showing that the advantage of the use of IVIg was based on the level of systemic involvement. It has been suggested that IVIg therapy should only be administered when the albumin status deteriorates. However additional studies are required to standardize the timing for administration of IVIg, the right dosage and the right selection of patients, before this kind of treatment can be fully accepted as one of the CDI management strategies. Oral immunoglobulin obtained from eggs of immunized leghorn hens were found to have neutralizing effects against toxins A and B in a hamster model.[61] Colonization factor-specific egg yolk antibodies (IgY) derived from chickens immunized with recombinant *C. difficile* colonization factors were found effective against *C. difficile* strain in hamsters and can be used as a treatment measure against acute and recurrent CDI in humans.[62]

(iii) Bovine antibodies and whey protein concentrate: Whey protein concentrate against *C. difficile* (anti-CD-WPC) is prepared from the milk of cows immunized against *C. difficile* to produce immunoglobulins (predominantly sIgA and smaller amounts of IgG and IgM). The immunoglobulin sIgA neutralizes *in vitro* the cytotoxicity of toxins and also protects hamsters against the otherwise lethal cecitis due to *C. difficile*.[63] Many studies have reported the efficacy of anti-CD-WPC against CDI.[63,64,28] In a double-blind randomized study, anti-CD-WPC was observed to be non-inferior to metronidazole in the prevention of CDI recurrences with a sustained recovery of 56% and 55% respectively.[28] Van *et al*[63] found that immune whey protein concentrate-40 when administered after a course of standard antibiotics helps in the prevention of relapse of CDI. In a prospective study

on 77 CDI patients, anti-CD WPC was found safe and effective against the illness.[64]

(iv) Colostrum: Human colostrum is efficiently active against *C. difficile.* It nullifies the *C. difficle* toxin activity and therefore protects the newborns from these toxins[65,66] "Immune milk" has also been developed from bovine colostrums.[67] Specific antigens and pathogens are used for the immunization of animals like cows to produce colostrum which has a large concentration of antibodies against specific pathogens.[3] Some animal models like cows, when vaccinated during gestation, produce hyperimmune bovine colostrum (HBC) that is rich in IgG. It has been shown that cows immunized against *C. difficile* resisted digestion and inactivation in the human intestine.[68] Patients were also able to inactivate the toxins A and B of *C. difficile* after oral consumption of the same bovine immunoglobulin concentrate.[68] Artiushin *et al*[69] also had shown that the colostrum blocks the cytopathic activity of *C. difficile* toxins. In their experiment, pregnant mares were immunized with recombinant binding domains of toxin A and toxin B of *C. difficile* and toxin neutralizing *antibodies were passed to the newborn in colostrums.* Anti-*C. difficile* HBC was found to prevent *in vitro* binding of *C. difficile* to enterocyte-like Caco-2 cells.[70] Sponseller *et al*[71] demonstrated that HBC does not alter the gut microbiota and mild or no diarrhea was developed in piglets that were treated with HBC either in liquid or lyophilized forms.

(v) *C. difficile* vaccine: A 50 times increase in serum antitoxin A production was reported by Aboudala *et al*[72] when a vaccine prepared from culture filtrate toxoids A and B were administered intramuscularly to 30 volunteers. Thus *C. difficile* toxoid vaccine was found to be safe and immunogenic in healthy volunteers. Souigioltzis *et al*[73] showed an increase in serum IgG to toxin A in 2/3 patients with recurrent CDI. No additional recurrence was observed when vancomycin treatment was discontinued. Suggesting that inoculation of *C. difficile* vaccine could help in the prevention and treatment of CDI. Another vaccine containing DNA which encodes the receptor binding domain (RBD) of *C. difficile* toxin A has been developed and found to be immunogenic *in vivo* and well-expressed *in vitro.*[74] Passive immunization with alpaca-derived polyclonal sera or immunization with toxoid was found effective against CDI in mouse.[75] Recombinant lipoprotein-based vaccine candidates eliciting antibodies by C-terminal receptor binding domain of TcdA (A-rRBD) were found to neutralize TcdA toxicity in Vero cell cytotoxicity assays in mice, rabbits and hamsters.[76] Insignificant protection (10-20%) against *C. difficile* spores was seen in hamsters but on formulation of rlipoA-RBD with B-rRBD protection was enhanced up to almost 100%. The authors believe that this could be an excellent vaccine candidate for future clinical trials and preclinical studies.[76] CDI vaccines currently in clinical development are "Sanofi Pasteur *C. difficile* toxoid vaccine" with antigen formalin-inactivated toxins A and B from VPI 10463 in phase III clinical trial, "Valneva Austria GmbH VLA84 *C. difficile* vaccine" with two other candidates in phase II clinical trial – recombinant fusion protein of toxin A and B binding regions and a genetically modified and chemically treated recombinant vaccine "Pfizer 3-dose *C. difficile* vaccine."[37]

6. Photodynamic therapy: The successful use of Photodynamic Antimicrobial Chemotherapy (PACT), a novel approach for CDI treatment has been reported in literature.[77,78] PACT comprises of locally applied visible light and photosensitiser which is a light sensitive dye[77,78] that targets microbial cells which produce reactive oxygen species containing free radicals and/or singlet oxygen. These dyes when combined with visible light in the presence of oxygen, eradicate the microorganisms. Target cells are inactivated by two oxidative mechanisms. Comprising electron/ hydrogen transfer reactions from the photo-sensitiser excited state and then the production of singlet oxygen from molecular oxygen by energy transfer from the long-lived triplet state.[79,80] Numerous photosensitizers have been studied for their use in photodynamic therapy. Nile blue derivative with a benzophenothiazinium dye structure known as EtNBS, a photosensitiser, was found to eliminate *C. difficile via* oxygen-independent photodynamic therapy without damaging the host intestine and methylene blue active in the presence of oxygen.[18] PACT was found to be an efficient method for killing most

hypervirulent *C. difficile* strains.[81] Sordi *et al*[82] reported 3/13 photosensitizers capable of killing 99.9% of *C. difficile* in both planktonic and biofilm state after exposure to red laser light (0.2 J/cm^2) with no harmful effects on model colon cells. *C. difficile* spore germination was induced by bile salt taurocholate, followed by PACT to demonstrate the applicability of PACT to eradicate *C. difficile* germinative spores. The efficacy of these photosensitizers is not restricted to certain genotypes since they were found effective against five extra recent *C. difficile* clinical isolates of different ribotypes. They found that non-cytotoxic photosensitizers were significantly more bactericidal against *C. difficile* both in aerobic and anaerobic conditions *in vitro* thereby making them as good candidates for *in vivo* investigations as well.

7. Corticosteroid treatment: The role of corticosteroid as therapy for CDI has been contentious. In a case report by Cavagnaro *et al*[83] a 5-year-old child with *C. difficile* associated bloody diarrhea and PMC, was unresponsive to standard *C. difficile* antibiotics despite two weeks of therapy. Upon treatment with IV methylprednisolone (1 mg/kg twice daily) resolution of diarrhea occurred within 24 hours.[83] The exact mechanism of action is not known. Corticosteroids obstruct phospholipase activity, which prevents arachidonic acid release from membranes, thereby decreasing eicosanoid production. The enhancement of colonic water and sodium absorption help in decreasing diarrhea.[84] Chang *et al*[85] observed that binding of the *C. difficile* toxin to human erythrocyte lysate was inhibited by number of sterols. Therefore it might have an effect on the binding of *C. difficile* to human colonic epithelial cells even though they are usually not used as therapy for *C. difficile* colitis.[85] These observations suggested corticosteroids as a useful therapy for *C. difficile* induced colitis which does not respond to standard treatment. Wojciechowski *et al*[86] in a retrospective study found that corticosteroids tend to reduce the incidence of CDI. However more studies are required to authenticate the efficacy of corticosteroids and to establish a clear association between the therapy and CDI.

CONCLUSION

Even though antibiotics are the key options for CDI, due to their several disadvantages, alternative strategies are required for CDI management. This review provides an overview and evidence of non-antibiotic therapies for the treatment of CDI. Since researchers are exploring all avenues to find better and more effective efficacies to combat *C. difficile* infections and various clinical trials are hitherto under way so modifications to the discussed treatment stratagem are likely.

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