How to: prophylactic interventions for prevention of Clostridioides difficile infection

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Narrative review

How to: prophylactic interventions for prevention of *Clostridioides difficile* infection

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ABSTRACT

Background: Clostridioides difficile infection (CDI) remains the leading cause of healthcare-associated diarrhoea, despite existing guidelines for infection control measures and antimicrobial stewardship. The high associated health and economic burden of CDI calls for novel strategies to prevent the development and spread of CDI in susceptible patients.
Objectives: We aim to review CDI prophylactic treatment strategies and their implementation in clinical practice.
Sources: We searched PubMed, Embase, Emcare, Web of Science, and the COCHRANE Library databases to identify prophylactic interventions aimed at prevention of CDI. The search was restricted to articles published in English since 2012.
Content: A toxin-based vaccine candidate is currently being investigated in a phase III clinical trial. However, a recent attempt to develop a toxin-based vaccine has failed. Conventional probiotics have not yet proved to be an effective strategy for prevention of CDI. New promising microbiota-based interventions that bind and inactivate concomitantly administered antibiotics, such as ribaxamase and DAV-132, have been developed. Prophylaxis of CDI with *C. difficile* antibiotics should not be performed routinely and should be considered only for secondary prophylaxis in very selected patients who are at the highest imminent risk for recurrent CDI (R-CDI) after a thorough evaluation. Faecal microbiota transplantation (FMT) has proved to be a very effective treatment for patients with multiple recurrences. Bezlotoxumab provides protection against R-CDI, mainly in patients with primary episodes and a high risk of relapse.
Implications: There are no proven effective, evidenced-based prophylaxis options for primary CDI. As for secondary prevention, FMT is considered the option of choice in patients with multiple recurrences. Bezlotoxumab can be added to standard treatment for patients at high risk for R-CDI. The most promising strategies are those aimed at reducing changes in intestinal microbiota and development of a new effective non-toxin-based vaccine. **Elena Reigadas, Clin Microbiol Infect 2021;27:1777**

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Background

Clostridioides difficile infection (CDI) is the leading cause of healthcare-associated diarrhoea; however, studies have also highlighted CDI as a cause of disease in the community setting [1,2]. CDI is associated with morbidity, mortality, and cost [3]. Recurrence of CDI (R-CDI) is challenging, with approximately 20% of CDI patients developing one or more recurrences [4], thus increasing morbidity and mortality even further [5].

Prevention of CDI is also challenging, as many risk factors are non-modifiable (e.g. age >65 years and the presence of other comorbidities) [6]. Prevention strategies focus mainly on control through improved hand hygiene, contact isolation, environmental decontamination, and antimicrobial stewardship programmes [7]. While effective in reducing the incidence of CDI [8], these strategies are not without their limitations. Consequently, novel prevention strategies are necessary.

In addition to prevention and antimicrobial stewardship strategies, prophylactic treatment interventions can be applied in individual patients. These can be divided into primary prophylaxis for prevention of CDI in a risk population and secondary prophylaxis to prevent R-CDI. The aim of this article is to review existing and developing CDI prophylactic treatment strategies and their implementation in clinical practice.

Sources

We conducted a literature search for prophylactic strategies for CDI. PubMed, Embase, Emcare, Web of Science and COCHRANE Library databases were searched. The search was restricted to articles published in English since 2012. Meeting abstracts were excluded. Study eligibility was assessed in a two-step selection process. Two independent reviewers per search screened Title and Abstracts for possible eligible articles. Full-text articles were retrieved for detailed assessment of suitability, risk of bias and data extraction. Cross-references of interest meeting the inclusions could be manually added to the included studies.

Active immunization

Considerable work has been carried out in the field of vaccine development, yet no vaccine is currently available. Discouraging results were reported from a recent phase III multicentre *C. difficile* toxoid (TcdA and TcdB) vaccine trial (NCT01887912, Sanofi Pasteur, 9302 participants in 23 countries) [9]. Subjects included were adults ≥50 years old considered to be at increased risk of CDI (patients with at least two hospital stays each of >24 h that had received systemic antibiotics in the previous year or those anticipated to be admitted for ≥72 h for elective surgery within 60 days of enrolment). The candidate vaccine was unable to reduce the incidence of symptomatic CDI in the first efficacy analysis (34/6173 versus 16/3085 cases of CDI in the vaccine and placebo groups, respectively), and the trial was terminated because of futility. Clinical development of the vaccine candidate was halted [9].

A phase III, placebo-controlled, randomized, observer-blinded study (NCT03090191, Pfizer) evaluating the efficacy, safety, and tolerability of a toxin-based *C. difficile* vaccine is being conducted in adults aged ≥50 years at risk of developing CDI (subjects who have received systemic antibiotics in the previous 12 weeks or with an increased risk of future contact with healthcare systems). The study is active, although it is no longer recruiting after the enrolment of 17 526 participants, who are to be followed up for 3 years after vaccination. No results have been reported to date.

Other candidates are in less advanced stages of clinical evaluation. VLA84, a recombinant fusion protein comprising fragments of the receptor-binding domains of TcdA and TcdB, has completed phase II (NCT02316470) and is currently phase III-ready; the developer is looking for partners. An investigational *C. difficile* vaccine based on the F2 antigen is being evaluated in a phase I study (NCT04026009) estimated to be completed in July 2021.

Passive immunization

Regarding passive immunization, bezlotoxumab—a human monoclonal antibody against *C. difficile* toxin B—was recently approved for the prevention of R-CDI in combination with antibiotics for treatment of CDI [10]. The efficacy of bezlotoxumab was assessed in two randomized controlled trials including patients with first-episode CDI or R-CDI receiving standard-of-care antibiotic therapy (metronidazole, vancomycin or fidaxomicin). In both trials (MODIFY I/MODIFY II), the proportion of patients developing R-CDI was lower in the bezlotoxumab arm than in the placebo arm (17% versus 28%; 95%CI −15.9 to −4.3; $p < 0.001$/16% versus 26%; 95%CI, −15.5 to −4.3; $p < 0.001$ respectively), with a 10% reduced risk of recurrences. A post hoc analysis showed that the greatest reduction in risk (25%) was observed in patients with at least three concomitant risk factors (age ≥65 years, history of CDI, compromised immunity, severe CDI, and ribotype 027/078/244) [11]. Bezlotoxumab had a safety profile similar to that of placebo, although heart failure was more common in patients with a history of congestive heart failure than in the placebo group (12.7% versus 4.8%), as was mortality in this subgroup (19.5% versus 12.5%) [10]. While the efficacy of bezlotoxumab for primary prevention of CDI has not yet been assessed, it would undoubtedly be an expensive option. Passive immunity would not be a suitable cost-effective strategy for primary prevention since it provides immediate but short-lived protection [10].

Vaccination of cows with *C. difficile* antigens to produce polyclonal antibodies for prevention of CDI in humans constitutes another possible approach. In preclinical studies, oral administration of anti-C. difficile whey protein isolates proved to be protective for both primary treatment of CDI and prevention of its recurrence [12]. The preliminary results of a prospective, randomized study for treatment of CDI indicated that whey was as effective as metronidazole; however, the study was terminated early after sponsor bankruptcy [13]. Several oral antibody therapies to prevent CDI are in preclinical development (OraCAb) [14] or in phase I (IMM-529, Immunon NCT03065374).

Microbiota-targeted therapy: dysbiosis restoration

Faecal microbiota transplantation (FMT), live biotherapeutic products (LBPs), and probiotics have been proposed as methods to restore gut microbiota and inhibit pathogenic bacterial colonization. In general terms, FMT transfers a whole set of intestinal microbiota, while LBPs are less diverse, containing a more reduced number of different bacterial species; this is even more so in the case of conventional probiotics that generally contain one or only a few different microorganisms.

FMT has proven to be very effective for preventing R-CDI [15–17] in patients with multiple R-CDI (defined as more than three episodes), with most studies reporting overall cure rates >90% [18]. FMT programmes have advanced significantly and include the use of frozen faecal matter, the introduction of stool banks, and the development of more convenient formulations such as lyophilized capsules [19,20]. However, the use of FMT is still not widespread in clinical practice, probably owing to the lack of dedicated centres,

difficulties with donor recruitment, regulatory issues, and safety concerns.

There are several FMT-derived products that are currently under investigation for R-CDI prevention. Rebiotix product RBX2660 consists of a suspension of healthy donor microbiota formulated as an enema. It has completed enrolment for its phase III trial (NCT03244644) for R-CDI prevention. A lyophilized capsule presentation, RBX7455, recently completed investigator-sponsored phase I trial for the prevention of R-CDI (NCT02981316). CP101 is an investigational Full-Spectrum Microbiota® (FSM®) therapy delivered in an oral capsule that has completed enrolment in PRISM3, its multicentre, placebo-controlled phase II clinical trial (NCT03110133).

The use of FMT for primary prevention has not been assessed. A trial investigating the use of FMT capsules as prophylaxis during antibiotic treatment in patients with a history of CDI recently closed enrolment (NCT03621657 https://doi.org/10.1016/j.conctc.2020.100576).

LBPs are defined as biological products that contain live organisms, such as bacteria, and are used for the prevention, treatment, and cure of a disease or condition of human beings. LBPs are under investigation for secondary prevention of CDI in phase II and phase III studies, and include SER-109 (Seres Therapeutics, Boston; NCT03183128) and VE303 (Vedanta Biosciences, Boston; NCT03788434).

The efficacy of probiotics for prevention of CDI is controversial, although international guidelines agree that there is insufficient evidence to recommend probiotics for prevention of CDI [15,16]. Systematic reviews and meta-analyses on probiotics include very heterogeneous studies that report conflicting results or have been unable to draw solid conclusions on the real efficacy of probiotic-based prophylaxis or on how it should be administered [21]. Interestingly, a recent meta-analysis showed probiotics to be efficacious, albeit with a moderate quality of evidence, when administered to patients with a high baseline risk (>5%) [22]. However, these results were not confirmed in subsequent randomized clinical trials [23] and other large-scale studies including 'real-life' patients [24]. When analysing data specifically on probiotics for primary prevention, most randomized studies do not show statistically significant differences [25], with the result that no clear recommendations can be made regarding specific species, strains, or doses [26]. Of all the probiotics studied for preventing CDI in a hospital setting, *Saccharomyces boulardii* and *Lactobacillus* species are the most frequently reported to have positive effects [22,27], although bloodstream infection is a serious adverse event [28,29]. Therefore, the use of probiotics should be assessed carefully, especially in immunosuppressed or critically ill patients.

Non-toxigenic spores (NTCD-M3) were efficacious for the prevention of R-CDI in a randomized placebo-controlled clinical trial [31]. Their role in primary prevention has been explored only in animal models, and the results of these studies showed that colonization by non-toxigenic *C. difficile* could be an effective prevention strategy during antibiotic therapy [32,33]. Clinical trials for the continued development of NTCD-M3 for primary and secondary prevention of CDI are required [34].

Modification of bacterial strains was recently explored for use in prevention of CDI. In this sense, *Saccharomyces boulardii* has been engineered to secrete an antibody that potently neutralizes *C. difficile* toxins A and B [35]. This oral yeast immunotherapy has been studied in mouse models and protect against primary and recurrent CDI [35]. Other strains with direct anti-*C. difficile* effects that are currently being investigated include *Enterococcus thailandicus* strain d5B, which has probiotic properties and strong bactericidal effects against *C. difficile* strains [36].

Lactobacillus rhamnosus GG (LGG) and *Streptococcus thermophilus* ST-21 have been manipulated with lemon exosome-like nanoparticles (LELNs) [37]. In this study, LELNs protected mice against CDI by enhancing the viability of the probiotic, and LELN probiotics induced metabolomic changes that play a key role in protection of the host from infection [38].

Other potentially applicable non-antibiotic strategies include bile salts, which could act as CDI growth inhibitors [30]. However, further studies are needed to demonstrate their efficacy and feasibility for treatment.

Microbiota-targeted therapy: dysbiosis prevention

A novel strategy for the prevention of CDI is the co-administration of poorly absorbed β-lactamase enzymes when administering antibiotics to degrade these in the gastrointestinal tract. In this sense, SYN-004 (ribaxamase) is a first-in-class oral class A serine enzyme designed to protect the colonic microbiota from the disruption caused by commonly used intravenous β-lactam antibiotics. A phase IIb trial found that the use of ribaxamase (SYN-004) reduced the incidence of CDI in patients receiving ceftriaxone without affecting antibiotic efficacy [39]. The CDI rate was 2/206 in the ribaxamase group and 7/206 patients in the placebo (risk reduction 2.4%, 95%CI −0·6 to 5.9; one-sided p 0.045). The clinical development of ribaxamase is ongoing. Related products that are also being developed have potential additional advantages such as co-administration with oral β-lactam antibiotics (SYN 007) and other β-lactam antibiotics, including carbapenems (SYN 006) [40,41].

DAV-132, a novel colon-targeted adsorbent, recently successfully completed a phase II study (NCT03710694) evaluating its efficacy in hospitalized patients at high risk for CDI and who received fluoroquinolones for the treatment of acute infections or for prophylaxis of febrile neutropenia. DAV-132 could potentially protect the gut microbiome against antibiotics from several distinct and therapeutically important classes such as β-lactams of all categories (penicillins, cephalosporins, and carbapenems), fluoroquinolones, and lincosamides.

Antibiotic prophylaxis

Prophylactic use of antibiotics can only be justified when there are relevant clinical benefits. Primary prophylaxis with antibiotics for prevention of CDI is problematic because of its impact on the microbiome, with an associated increased risk for R-CDI and selection of antimicrobial resistance [51,52]. One of the most recently published national guidelines discussed using oral vancomycin prophylaxis (OVP) for selected cases that are at high risk for recurrent CDI and have been scheduled for treatment with systemic antimicrobials [42]. A list of published articles on the clinical practice of antibiotic prophylaxis for CDI is presented in Table 1.

A recent meta-analysis by Babar et al. examined a total of 2174 patients from nine studies (2016–2019) to assess the efficacy and safety of OVP [43]. The authors showed that OVP was associated with an overall reduction in CDI rates (OR 0.245, 95%CI 0.13–0.48), with reduced rates for both primary and secondary CDI in at-risk patients. OVP was associated with a significant reduction in CDI rates in immunocompetent and immunosuppressed patients [43]. Most of the studies included were retrospective, and therefore attrition bias may have led to a reduction in the observed outcomes and an overestimation of the effect of antibiotic prophylaxis.

To date the only randomized controlled trial on OVP with published data indicated that OVP protects against healthcare-facility-onset CDI in targeted patients receiving systemic antibiotics [44]. In the OVP group ($n = 50$) no patients developed CDI, while six (12%)

Table 1
Antibiotic prophylaxis for *Clostridiodes difficile* infection

Article	Study Design	Subjects	Intervention	Control	Outcome
Carignan A et al. Am J Gastroenterol 2016; 111(12):1834–40	Retrospective cohort ($n = 551$)	Patients ≥18 years with primary or R-CDI who subsequently received a course of antibiotics for other reasons	Vancomycin 125 mg q.i.d. ($n = 227$)	No prophylaxis ($n = 324$)	Adjusted hazard ratio: R-CDI: 0.47 (95%CI 0.32–0.69, p < 0.0001) Primary CDI: 0.91 (95%CI 0.57–1.45, p 0.68)
Van Hise et al. Clin Infect Dis 2016; 63(5):651–3	Retrospective cohort ($n = 203$)	Patients ≥18 years with CDI and subsequent hospitalization receiving systemic antibiotics	Vancomycin 125 mg PO b.i.d. ($n = 29$) Vancomycin 250 mg b.i.d. ($n = 42$)	No prophylaxis ($n = 132$)	CDI rate: 4.2% versus 26.6% (p < 0.001)
Ganetsky A et al. Clin Infect Dis 2019; 68(12):2003–9	Retrospective cohort ($n = 145$)	Patients ≥18 years with allogeneic HSCT admitted as inpatients	Vancomycin 125 mg PO b.i.d. ($n = 90$)	No prophylaxis ($n = 55$)	CDI rate: 0% versus 20% (p < 0.001)
Knight EM et al. J Pharm Pract 23 2019; 897190019825994.	Retrospective cohort ($n = 636$)	Patients ≥18 years undergoing lung transplantation	Vancomycin PO 2–4 times daily ($n = 82$) Median dose: 125 mg PO b.i.d.	No prophylaxis ($n = 554$)	CDI rate: 1% versus 6% (p 0.059)
Morrisette T et al. Biol Blood Marrow Transplant 2019; 25(10):2091–7	Retrospective cohort ($n = 760$)	Patients ≥18 years with primary CDI or R-CDI who subsequently received broad-spectrum antibiotics	Vancomycin PO (dose not specified) ($n = 193$)	No prophylaxis ($n = 567$)	R-CDI: 9.8% versus 9.4% at 90 days (adjusted OR 0.63 (95% CI 0.35–1.14)) R-CDI: 11.4% versus 9.5% at 180 days (adjusted OR 0.72 (95%CI 0.41–1.29))
Splinter LE et al. Ann Pharmacother 2018; 52(2):113–9	Retrospective cohort ($n = 36$)	Patients ≥18 years with a kidney transplant with healthcare-onset CDI who received broad-spectrum antibiotics	Vancomycin 125 mg PO b.i.d. > 48 h ($n = 12$)	No prophylaxis ($n = 24$)	R-CDI: 0% versus 8% (p 0.54)
Caroff DA et al. Infect Control Hosp Epidemiol 2019; 40(6):662–7	Retrospective cohort ($n = 91$)	Patients ≥18 years with a primary or R-CDI who received broad-spectrum antibiotics	Vancomycin 125 mg PO q.i.d. ($n = 10$) Vancomycin 250 mg PO q.i.d. ($n = 22$)	No prophylaxis ($n = 59$)	R-CDI: 6.3% versus 28.8% (OR 0.16, 95%CI 0.04–0.77, p 0.01)
Bajrovic V et al. J Heart Lung Transplant 2019; 38(8):874–6	Retrospective cohort ($n = 50$)	Patients ≥18 years with HSCT or haematological malignancy with primary CDI receiving broad-spectrum antibiotics	Vancomycin 125 mg PO b.i.d. ($n = 21$)	No prophylaxis ($n = 29$)	R-CDI: 5% versus 35% (p 0.016)
Allegretti et al. Dig Dis Sci 2019; 64(6):1668-71	Retrospective cohort ($n = 404$)	Patients who achieved cure with FMT for R-CDI at 8 weeks and presented afterwards with diarrhoea	Anti-CDI antibiotics ($n = 34$)	Received non-CDI antibiotics and did not receive anti-CDI antibiotics ($n = 77$)	CDI rate: 26.5% versus 11.7% (p 0.2)
				No antibiotics of any class ($n = 293$)	CDI rate: 26.5% versus 5.1%
Papic et al. Infect Dis 2018; 50(6):483-6	Retrospective cohort ($n = 244$)	Patients >65 years hospitalized for >72 h receiving systemic antibiotics	Vancomycin dosed at 125 mg once daily PO ($n = 71$)	No prophylaxis ($n = 173$)	CDI rate: 0% versus 10.4% (p 0.0022)
Johnson et al. Clin Infect Dis 2020; 71(5):1133–9	Prospective cohort, randomized, prospective, open-label study ($n = 100$)	Patients receiving systemic antibiotics	Vancomycin dosed at 125 mg once daily PO ($n = 50$)	No prophylaxis ($n = 50$)	0% healthcare-facility-onset CDI 0% in oral vancomycin prophylaxis versus 12% in the no-prophylaxis group (p 0.03)
Mullane et al. Clin Infect Dis 2019; 68(2):196–203	Randomized controlled trial ($n = 600$)	Patients ≥18 years undergoing HSCT and planned fluoroquinolone prophylaxis	Fidaxomicin 200 mg q.d. ($n = 301$)	Placebo ($n = 299$)	CDI rate: 4.3% versus 10.7% (p 0.0014) Composite outcome d: 28.6% versus 30.8% (p 0.278)
Tobar-Marcillo et al. Gastroenterol Hepatol Engl 2018; 41(6):362–8	Randomized open-label study ($n = 96$)	Inpatients aged 55–75 years receiving at least one broad-spectrum antibiotic	Metronidazole 500 mg t.i.d. for 7 days ($n = 41$)	Observation ($n = 55$)	CDI rate: 0% versus 9.1% (OR 0.91, 95%CI 0.84–0.99, p 0.069)

CDI, *Clostridioides difficile* infection; R-CDI, recurrent *C. difficile* infection; HSCT, haematopoietic stem cell transplantation; FMT, faecal microbiota transplantation; OR, odds ratio.

developed CDI in the no-prophylaxis group ($n = 50$) (p 0.03) [44]. However, this study is limited by its small number of patients and short follow-up.

Concern over enteral vancomycin has grown owing to the emergence of vancomycin-resistant *Enterococcus* (VRE), which has been associated mainly with long-term use or recurrent exposures [45,46]. Some of the studies evaluating the efficacy of OVP also examined the risk for VRE [44,47–49] and reported that OVP was not associated with an increased risk for VRE. However, assessments are limited by their short follow-up period and their focus on

infection rather than on colonization. This shortcoming should be better addressed in further prospective randomized controlled studies on the long-term effects of prolonged courses of OVP. Moreover, previous studies showed that prolonged vancomycin use, especially at high dosages, may be associated with the risk of subsequent *Candida* or bloodstream infection caused by enteric bacteria [50]. Translocation from the gut appears to be the major underlying mechanism, and vancomycin appears to be associated with intestinal damage and selection of pathogenic intestinal microorganisms [51,52]. Therefore, concerns regarding widespread prophylactic use of oral vancomycin remain unresolved.

Recently, a phase IV study evaluating the role of oral vancomycin in the prevention of R-CDI (NCT03200093) has terminated; however, no results have yet been communicated. Four ongoing prospective clinical trials (NCT02996487, NCT04000555, NCT03462459, NCT03466502) are evaluating the role of oral vancomycin in the prevention of CDI in patients receiving systemic antibiotic therapy. These studies will presumably overcome some of the limitations of the previous studies.

Data on antibiotic prophylaxis with antibiotics other than vancomycin are scarce. The randomized placebo-controlled trial by Mullane et al. examined the efficacy and safety of fidaxomicin (200 mg once daily) as prophylaxis against CDI in patients undergoing allogenic or autologous haematopoietic stem cell transplantation (HSCT) and receiving fluoroquinolone as prophylaxis during neutropenia [53]. In this study ($n = 611$), the incidence of confirmed CDI at 30 days after treatment was significantly lower in the fidaxomicin group than in the placebo group (4.3 versus 10.7%, respectively; p 0.0014). Similarly, the incidence of confirmed CDI was lower at 60 days after treatment and up to study day 70 [53].

As for metronidazole, a prospective, randomized, open-label study ($n = 96$) showed that none of the patients in the intervention group (oral metronidazole 500 mg/8 h for 7 days) versus 9.1% in the observation group developed CDI (OR 0.91 (0.84-0.99), p 0.069). However, this difference did not result in a statistically significant reduction in CDI rates. Also important is the finding of metronidazole resistance in *C. difficile* and increasing reports of resistance in other anaerobes [54,55].

How to: prophylactic interventions

As mentioned above, there is no vaccine for CDI, although this may change in the coming years given the various clinical trials in progress and ongoing research. The recent failure of one of the vaccine candidates means that it is essential to improve reformulations. In this sense, antigens other than toxins should be taken into consideration, such as those targeting colonization and sporulation. One of the greatest challenges of an effective CDI vaccine is that the main target population comprises elderly people, in whom immunosenescence can cause impaired recognition of antigens [56]. Therefore, the development of an effective vaccine needs to elicit an immune response with a considerable duration of protection in elderly and immunocompromised patients who are at particularly high risk for CDI. Also challenging is the implementation of a viable and cost-effective vaccination programme.

Passive immunization strategies could be implemented for secondary prevention of CDI in patients deemed at high risk of recurrence. Given that bezlotoxumab was only recently introduced, it has not yet been incorporated into international guidelines. Bezlotoxumab showed more benefit when used in patients with three or more of the following risk factors for R-CDI: age $\geq$65 years, history of CDI in the previous 6 months, immunosuppression, severe CDI, and strains associated with poor outcomes (ribotypes 027/078/244) [11]. The drug is administered as a single intravenous dose of 10 mg/kg over 60 minutes during the course of oral antibiotic therapy. It can be administered early or $\geq$5 days after the initiation of standard treatment, with no differences in effectiveness [10,57]. Bezlotoxumab does not require the dose to be adjusted in renal or hepatic impairment. In patients with a history of congestive heart failure, it should only be used when the benefit outweighs the risk. Use of bezlotoxumab is limited, probably because of its high cost, although it could prove cost-effective in an appropriately selected population.

The use of FMT for multiple recurrences is accepted by most international guidelines. European treatment guidelines recommend (A-1) faecal transplantation for multiple R-CDI [15]. The Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) guidelines [16] also include a strong recommendation for the use of FMT in second and subsequent episodes of R-CDI. FMT should be implemented by an experienced multidisciplinary team after a thorough risk assessment for each candidate and FMT product. Donor screening programmes should follow international recommendations and comply with local regulations [20,58].

Regarding probiotics, we conclude that there is no clear evidence to support the use of the currently available probiotics in the prevention of primary or secondary CDI. In fact, administration of probiotics should be evaluated carefully, especially in immunosuppressed or critically ill patients [28]. LBPs made from bacterial communities with proven efficacy against *C. difficile* might be a more rational and promising approach for primary prevention of CDI. However, with the exception of FMT, most microbiota-based strategies are still in the early stages of development. More research is needed for a better understanding of the interactions between the microbiome, the metabolome, and *C. difficile* so that effective targeted therapies using microbiome signatures can be developed for the prevention of CDI.

We do not advocate routine administration of antibiotic prophylaxis for CDI. Prophylaxis with antibiotics for the prevention of CDI is problematic because of its negative impact on the microbiome and potential selection of antimicrobial resistance. It will be interesting to study non-antibiotics with efficacy as primary prophylaxis in *C. difficile*, such as auranofin, an FDA-approved oral antirheumatic drug that inhibits vegetative cell growth in *C. difficile* as well as toxin production and spore production *in vitro* [59].

Antibiotic prophylaxis may be considered in very specific cases only, and then only after evaluation by a multidisciplinary group of the potential benefits over risks. Such specific cases would include the elderly patient with a history of recurrent CDI who has to reinitiate systemic antibiotics known to have triggered a previous CDI episode, or the immunosuppressed patient with a previous history of CDI who needs to undergo a treatment/procedure that has previously led to R-CDI. Fidaxomicin and vancomycin have both proved to be effective in reducing CDI in high-risk patients [43,53]. While there is more existing literature on vancomycin, fidaxomicin is a narrow-spectrum antibiotic that is known to cause fewer alterations to gut microbiota than vancomycin [60]. Therefore, while fidaxomicin seems to be a more suitable prophylactic option for preserving the intestinal microbiota, its high cost means that it is not feasible in all countries. Based on available data [43,44,53], reasonable dosage options for prophylaxis seem to be 200 mg once daily for fidaxomicin and 125 mg once daily for vancomycin for the duration of the antibiotic course or the treatment/procedure that poses the risk for CDI. However, the strength of evidence supporting this strategy is currently limited owing to study design, sample size, and lack of prolonged and systematic follow-up. Further studies are needed to identify the optimal dosing strategy and evaluate efficacy outcomes and long-term safety, especially the acquisition and selection of multidrug-resistant microorganisms.

Conclusion

In conclusion, there are currently no effective prophylactic options for primary prevention of CDI that allow for widespread use. Conventional probiotics have not yet clearly been proven as an effective strategy for primary prevention of CDI, and antibiotics should not be routinely administered for prophylaxis of CDI. FMT has proven to be very effective for the prevention of R-CDI. Bezlotoxumab provides protection against R-CDI, although more real-world experience with this drug is needed. Secondary prophylaxis of CDI with antibiotics can be considered only after thorough evaluation by specialists in very selected patients who are at the highest imminent risk for R-CDI. In the future, we anticipate increased use of microbiome-targeted therapies, improvements in administration of FMT, development of improved multistrain probiotics, selective antibiotics, and further introduction of passive and active immunization in clinical practice.

Author contributions

We describe contributions to the paper using the CRediT taxonomy. Writing—original draft: ER, JVP, MF, FF, MV, EK and EB. Writing—review and editing: ER, JVP, MF, FF, MV, EK and EB. Conceptualization: EK, ER, JVP and EB. Investigation: ER, JVP, EK and EB. Funding acquisition: ER.

Transparency declaration

MJGTV has given talks for Astellas Pharma, Basilea, Gilead Sciences, Merck/MSD, Organobalance, Pfizer, EUMEDICA, DiaLog Service, and Akademie für Infektionsmedizin, Landesärztekammer Hessen and has received grants from 3M, Astellas Pharma, Biontech, DaVolterra, Evonik, Gilead Sciences, Glycom, Immunic, MaaT Pharma, Merck/MSD, Organobalance, Seres Therapeutics, and Takeda Pharmaceutical. MJGTV is also a consultant to Alb Fils Kliniken GmbH, Arderypharm, Astellas Pharma, DaVolterra, Farmak International Holding GmbH, Ferring, Immunic AG, MaaT Pharma, Merck/MSD, and SocraTec R&D GmbH. EK has received unrestricted grant support from Vendata Biosciences (Boston) and MSD. The other authors declare that they have no conflicts of interest. This study was supported by the Fondo de Investigaciones Sanitarias (FIS), Research Projects number PI16/00490 and PI20/01381, and by the European Regional Development Fund (FEDER) “A way of making Europe”.

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