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REVIEW ARTICLE

Treatment of *Clostridioides (Clostridium) difficile* infection

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ABSTRACT

Clostridioides (formerly: *Clostridium*) *difficile* infection (CDI) is a major cause of diarrhoea for inpatients as well as outpatients. Usually, CDI is healthcare-associated but the number of community-acquired infections is increasing. CDI is generally associated with changes in the normal intestinal microbiota caused by administration of antibiotics. Elderly and immunocompromised patients are at greater risk for CDI and CDI recurrence. Recently, the treatment options of CDI have undergone major changes: current recommendations speak against using metronidazole for primary CDI, fidaxomicin and bezlotoxumab have been added to the treatment armamentarium and microbial replacement therapies have emerged. Several other therapies are undergoing clinical trials. In this article, we review current treatment guidelines, present the most recent data on the options to treat CDI and glance towards future developments.

KEY MESSAGES

- The cornerstones for the treatment of CDI are vancomycin and fidaxomicin. Metronidazole should be used only in mild-to-moderate disease in younger patients who have no or only few risk factors for recurrence.
- In recurrent CDI, bezlotoxumab infusion (a monoclonal antibody against *C. difficile* toxin B) may be considered as an adjunctive therapeutic strategy in addition to the standard care provided to patients with several risk factors for recurrence.
- Faecal microbiota transplantation (FMT) should be offered to patients with frequently recurring CDI.

Abbreviations: ESCMID-CPG: European Society of Clinical Microbiology and Infectious Diseases – clinical practice guidelines; FMT: Faecal microbiota transplantation; IBD: Inflammatory bowel disease; IDSA/SHEA-CPG: Infectious Diseases Society of America/Society of Healthcare Epidemiology of America – clinical practice guidelines; RCT: Randomized controlled trial; rCDI: Recurrent *Clostridium difficile* infection; SOC: Standard of care

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Introduction

Clostridium difficile was identified in 1976 as the cause of "clindamycin colitis" in hamsters [1]. Later, it became evident that *C. difficile* toxins A and B are responsible for antibiotic-associated colitis and that virtually all antibiotics can expose to this type of colitis. Subsequently, after a global epidemic of ribotype 027, which produces substantially more toxins and thus contributes to a more severe form of the disease, the number of people being hospitalized for *Clostridioides* (formerly: *Clostridium*) *difficile* infection (CDI) tripled compared to the previous 10 years, according to a report by the Centres for Disease Control and Prevention [2].

Recurrent CDI (rCDI) is associated with a significantly higher risk of death within 6 months after completion of the initial CDI treatment compared with CDI patients who do not develop a recurrence (36 versus 26% mortality rate) [3]. The 6-month mortality rate, however, exaggerates the true mortality rate of CDI, since 90% of deaths occur in people aged >65 years. According to a Finnish study, the 30-day case fatality rate was 3.2% in community-acquired and 13.3% in hospital-acquired CDI [4].

Clostridioides difficile infection is usually associated with changes in the normal intestinal microbiota caused by antibiotics. However, over the last decade CDI is being diagnosed more often in individuals at low risk with no preceding use of antibiotics. *Clostridium difficile* is the eighth most frequently reported microorganism in healthcare-associated infections, and the incidence is rising in most countries.

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The incidence of community-acquired CDI may have recently increased to 30% of all CDI cases [5].

After a primary episode of CDI, roughly 25% of patients treated with metronidazole or vancomycin will have a rCDI in the next 3 months, usually in 2–3 weeks after the initial treatment regimen has been discontinued. After the first recurrence, the rate of rCDI increases to about 45% [6–8]. The cornerstones of CDI treatment have recently changed from metronidazole/vancomycin to vancomycin/fidaxomicin [9–11]. Fidaxomicin, a narrow-spectrum antibiotic with minimal systemic absorption, reduces the rate of rCDI to about 15–20%, even for patients with a history of rCDI [12–15]. However, also all of the above-mentioned antibiotics do alter the normal gut microbiome and decrease the resistance against *C. difficile* colonization [16]. The risk factors for rCDI are presented in Table 1 [15–23].

Thus far, faecal microbiota transplantation (FMT) has been shown to be the most effective treatment for rCDI [24,25]. However, FMT is not available everywhere, and all patients are not eligible for the procedure. Bezlotoxumab is a fully humanized monoclonal antibody against *C. difficile* toxin B and indicated for prevention of rCDI in at-risk patients [26]. Nevertheless, there is still need for other treatment options.

During the recent years, there have been major changes in the management of CDI: recommendations against using metronidazole for primary CDI, the addition of fidaxomicin and bezlotoxumab to the treatment armamentarium and emergence of microbial replacement therapies. Several other therapies are undergoing clinical trials. In this article, we present a review of different recent guidelines, the most recent data on new CDI treatment options and discuss future developments.

Classification of CDI

Before treatment of CDI is started, the severity of the episode must be graded. CDI is classified as mild-to-moderate, severe or fulminant (formerly severe-complicated) based on laboratory findings and clinical features [9,27]. The usual criteria for classification are: CDI is severe if the blood white blood cell count is $>15{,}000 \times 10^6$/l, or the serum creatinine rises >1.5-fold from baseline or is >1.5 mg/dl. CDI is fulminant if the patient is hypotensive, is in shock, has sepsis, needs intensive unit care, develops megacolon or gut perforation or needs colectomy due to CDI. The CDI is mild-to-moderate when the criteria for severe or fulminant disease are not met [10,28].

Table 1. Risk factors for recurrent *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI).

Age >65 years
Hospitalization
Compromised immunity (chemotherapy or other immunosuppressive treatment)
Severe CDI and/or infection with hypervirulent ribotypes of *C. difficile*
Prior CDI episode(s)
Inflammatory bowel disease (IBD)
Chronic kidney disease
Liver cirrhosis
Non-CDI antibiotic use during or 3 months after standard of care (SOC) of CDI
Use of proton pump inhibitors

Treatment of the first CDI episode

The most recent (2017) clinical practice guidelines by the Infectious Diseases Society of America/Society of Healthcare Epidemiology of America (IDSA/SHEA-CPG) recommend oral vancomycin as the first choice treatment for patients with their first, non-severe CDI episode, while the current (2013) clinical practice guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID-CPG) recommend, for the same indication, metronidazole as the first-line drug in non-severe CDI and vancomycin in severe CDI [9,10]. However, there is an additional recommendation in ESCMID-CPG stating that oral vancomycin is appropriate for the treatment of non-severe CDI in patients with an increased risk for recurrent disease. These risk factors are age >65 years, continued use of non-CDI antibiotics after diagnosis of CDI, and/or after CDI treatment, severe underlying disease and/or renal failure, history of previous CDI and concomitant use of proton pump inhibitors [9]. While this addition reduces the preference for metronidazole use, it does complicate the decision-making process which probably impairs adherence to the guidelines [29]. A strong argument for metronidazole is the much lower cost in comparison to vancomycin capsules. However, two randomized controlled study results published in 2014 showed superiority of vancomycin relative to metronidazole: according to pooled analysis of these trials clinical success occurred in 81% of the patients treated with vancomycin *versus* 73% with metronidazole. The corresponding figures in severe disease were 79 *versus* 66% [8]. Since then, the superiority of vancomycin over metronidazole has also been shown in a meta-analysis published in 2017 [30]. On the other hand, another large study that was published only after the IDSA/SHEA-CPG update, did not show any difference in the recurrence or mortality between patents with mild CDI treated with metronidazole or vancomycin. Nevertheless, the 30-day

mortality for all patients, including severe CDI, was significantly lower when vancomycin rather than metronidazole was used. The authors conclude that their findings further justify the use of vancomycin as initial therapy for severe CDI [31]. For mild to moderate CDI, the guidelines recommend vancomycin at a dose of 125 mg orally four times daily for 10 days.

The lack of "no treatment" controlled studies does not allow for conclusions regarding the need for antibiotic treatment in patients with mild CDI beyond withdrawal of the culprit antibiotic [30]. The role of probiotics for the treatment as well prevention of rCDI is completely unknown, because studies and meta-analyses on their use have serious limitations [11,32]. There are studies that have shown a positive effect of probiotics in the prevention of primary CDI. However, the studies differ largely with regard to doses and types of probiotics, *C. difficile* strains, doses and types of antibiotics and timing of therapy. Considering the pathophysiology of CDI, it appears that probiotics could contribute to CDI prevention or treatment. However, we still lack properly randomized studies addressing this problem [11]. In a systematic review including meta-regression analysis, Shen *et al.* found evidence that administration of probiotics close to the first dose of antibiotic reduces the risk of CDI by >50% in hospitalized adults. They analysed data from 19 published studies, comprising 6261 subjects. The incidence of CDI in the probiotic cohort was lower (1.6%, 54 of 3277) than among the controls (3.9%, 115 of 2984) ($p < .001$). Further research is needed especially on the optimal dose, species and formulation of probiotics. A cohort selection strategy including different risk factors (other than antibiotic usage) is needed in future randomized controlled trials [33].

Metronidazole is no longer recommended in most scenarios and the preferred initial treatment is ambiguous. This means that, in practice, the treatment decision is driven by cost [34]. The cheaper initial cost of metronidazole compared to vancomycin or fidaxomicin will probably remain as an important consideration in healthcare, regardless of clinical guidelines. This must be balanced against some important drawbacks of metronidazole. Some recent studies have demonstrated that metronidazole is clinically ineffective, has adverse effects, including allergic reactions, gastrointestinal irritation and neuropathy and causes interactions with ethanol and some common drugs (e.g. warfarin). This inevitably casts shadows on the use of metronidazole, even for treatment of a first episode of non-severe CDI. Therefore, we suggest that it should only be used as first-line therapy for patients younger than 65 years (since in patients aged >65 years the risk of rCDI is 5–10-fold) with no or very few risk factors for rCDI.

On the other hand, oral vancomycin generates a selective pressure on the intestinal microbiota and favours the emergence of enterococcal resistance [35]. However, a recent retrospective study showed that patients treated with oral vancomycin were no more likely to develop VRE infection within 3–6 months than patients treated with metronidazole. Nor was there any increase in the risk of VRE, according to surveillance sources, between patients treated with vancomycin compared to those treated with metronidazole. Obviously, more studies are needed to assess if a large-scale shift to oral vancomycin instead of metronidazole increases the selection pressure favouring VRE colonization [36].

According to a meta-analysis, oral fidaxomicin (standard dosing 200 mg two times daily for 10 days) may be considered as first-line therapy for CDI [37]. Further, Guery *et al.* showed in 2017 (EXTEND study) that extended-pulsed fidaxomicin treatment (days 1–5, 200 mg two times daily, followed by once daily on alternating days on days 7–25) is superior ($p = .03$) to vancomycin (125 mg oral capsules, four times daily on days 1–10) among elderly patients with a median age of 75 years and many of whom had had previous episodes of CDI. This fidaxomicin regimen resulted in sustained clinical cure of CDI: the recurrence rate 30 days after end of treatment was 4% among the patients treated with fidaxomicin versus 17% for vancomycin; at 90 days the respective numbers were 6 and 19% [38]. Subgroup analyses of the EXTEND study showed that an extended-pulsed fidaxomicin regimen is efficacious and well tolerated for the treatment for CDI regardless of patient age, presence or absence of cancer, infection with *C. difficile* PCR-ribotype 027, CDI severity and prior CDI episodes [39]. Clinical cure sustained for 90 days was significantly more common with extended-pulsed fidaxomicin than with vancomycin in patients infected with *C. difficile* PCR-ribotype 027. In the EXTEND study, the current 20-tablet fidaxomicin course was used, which does not increase the already high cost of this treatment. A cost-effectiveness study showed that this extended-pulsed fidaxomicin regimen is cost-effective compared with vancomycin for first-line treatment of CDI in patients aged 60 years and older [40]. Extended-pulsed dosing is crucial for improving prevention of rCDI, whether the first occurrence, first recurrence or multiple recurrences treated with either fidaxomicin or vancomycin, as shown for fidaxomicin by the EXTEND study,

experimental gut model studies and observational studies involving tapered and pulsed dosing to treat CDI [41].

Clinicians should bear in mind that there is no test of cure after the treatment of CDI, since nucleic acid amplification tests verifying the presence of a toxin-producing strain of *C. difficile* do not necessarily mean that the strain produces toxin at the time of testing. There may be a significant percentage of asymptomatic patients colonized by *C. difficile* where the normalized intestinal microbiota inhibits overgrowth of *C. difficile* preventing clinical recurrence.

Treatment of severe and fulminant CDI

The criteria of severe CDI are derived from data of fully immunocompetent hosts and may not be applicable to populations like stem cell transplantation recipients. The severity of CDI in cancer patients may be underestimated due to circumstances like neutropenia which may occur quite often [42]. Patients with haematologic malignancies have lower creatinine levels at the time when CDI is diagnosed than control patients. Therefore, CDI severity criteria based on white blood cell count and creatinine level may not be applicable to all patients [43].

Regarding the severity of CDI, a recent retrospective study comparing 213 fidaxomicin with 639 oral vancomycin courses showed no statistically significant differences for the primary outcome of combined clinical failure or recurrence and for the secondary outcomes of mortality at 30, 90 and 180 days [44].

There is only a single recommended treatment regimen in IDSA/SHEA-CPG for fulminant CDI: oral vancomycin (500 mg four times daily) plus intravenous metronidazole (500 mg three times daily). CDI may be fulminant and present with septic shock and a need for intensive care treatment. Patients who fail treatment may die from fulminant CDI; those who survive will often undergo colectomy and become subjected to the risk of mortality related to colectomy. Patients who survive colectomy are assumed to be cured permanently of the CDI [45]. The ESCMID guidelines recommend intravenous metronidazole to be combined with oral vancomycin (125–500 mg four times daily) or fidaxomicin for treating fulminant CDI. There are, however, limited data on the therapeutic role of intravenous metronidazole in fulminant CDI. The guidelines recommend early colectomy for fulminant CDI. A recent study [46] favours diverting loop ileostomy over total abdominal colectomy for the surgical management of patients with fulminant *C. difficile* colitis. There is one study and one case series where FMT has been used to treat severe CDI—the results were encouraging and cure rates around 90% [47,48].

If ileus is present, vancomycin should be administered per rectum (500 mg in 100 ml saline as an enema) four times a day for 10–14 days. If there is partial ileus, vancomycin should be administered both orally and rectally. Rectal vancomycin administration is associated with a risk of large bowel perforation, and should only be used to treat patients who do not respond to oral therapy—some patients may have a delayed response to treatment and if this is the case, treatment could be extended to 14 days [11].

Clinically, there is an overlap between CDI and inflammatory bowel disease (IBD). Therefore, all patients with a suspected IBD flare should be tested for *C. difficile* [27]. In the case of rCDI, FMT may be preferred, since there is emerging data on efficacy of FMT for treating IBD as well [27].

Other antibiotics that are not included in CDI treatment guidelines but show activity against *C. difficile* include oral teicoplanin and nitazoxanide, and intravenous tigecycline. There is a study ongoing on the use of bezlotoxumab in severe CDI (clinicaltrials.gov).

Treatment of rCDI

There is lack of high-quality data on the optimal management of the first CDI recurrence [27]. At present, vancomycin and fidaxomicin are the drugs of choice in treating rCDI. Efficacy data on rifaximin are limited. The use of metronidazole is limited to the intravenous formulation in fulminant disease and is otherwise not used in rCDI. If vancomycin was used to treat the first episode, fidaxomicin may be the logical choice for best treatment of the recurrence. Best results with fidaxomicin in preventing rCDI have been achieved with the extended-pulsed regimen (see above). If oral vancomycin is used, the regimen may be given pulsed-tapered (each dose 125 mg): first four times daily for 10–14 days, then twice daily for 1 week, then once daily for 1 week and then once every 2 or 3 days for 2–8 weeks [11]. FMT should be offered, if available, to patients who have many recurrences of CDI.

The MODIFY I and MODIFY II trials ran in 2011–2015 showed that bezlotoxumab given as adjunctive to standard of care (SOC) significantly reduces ($p < .001$) rCDI and has a favourable safety profile [49,50]. The rate of sustained cure (initial clinical cure without recurrent infection in 12 weeks) was 64% for those treated with bezlotoxumab infusion and

54% with placebo. Bezlotoxumab infusion (single infusion 10 mg/kg) as an adjunctive treatment to SOC given to patients with several risk factors provided the greatest reduction in CDI recurrence, which suggests that this patient population could be a potential target for the drug [51]. Subgroup analysis showed that from the patients with three or more risk factors for rCDI only 21% had a recurrence. The use of bezlotoxumab is associated with a significant risk of complication among patients with a history of heart failure. *Post hoc* analyses of MODIFY I and II trials demonstrated that treatment with bezlotoxumab, given concomitantly with antibacterial agents active against *C. difficile*, reduces CDI-associated rehospitalizations, especially among patients with high-risk prognostic factors [52].

We conducted a retrospective study of high-risk patients treated with bezlotoxumab in a real-world setting, and found that 73% of patients remained free of rCDI during follow-up for 3 months. The drug was also effective among immunocompromised patients and prevented recurrence of CDI in 71% of these patients, and, furthermore, prevented the recurrence of severe CDI in 63%. Therefore, the adjunctive use of bezlotoxumab may be considered already after the first or second recurrence to treat patients at high risk, i.e. three or more risk factors for recurrence. For patients who fulfil the criteria for FMT, bezlotoxumab may be an alternative [53].

Comparisons of different studies on the recurrence rate of CDI are presented in Table 2.

Faecal microbiota transplantation (FMT)

Disruption and reduced diversity of the gut microbiome is the underlying cause of primary and rCDI. This is primarily due to use of antibiotics, and, indeed, antibiotics used to treat active CDI will further disrupt the normal gut microbiota. After discontinuation of antibiotics used to treat CDI, the residual *C. difficile* spores may germinate in the presence of the disrupted microbiota, leading to rCDI. Restoration of the normal microbiota is the principle of FMT.

FMT has emerged as a safe and effective treatment for the management of rCDI; the overall efficacy rate is between 80 and 90% [54,55]. However, FMT has been associated with lower cure rates in randomized trials than in open-label and in observational studies [56]. The ESCMID panel agreed that FMT is best reserved for patients who have experienced at least two episodes of rCDI [9]. Other indications for FMT include treatment of refractory CDI and, possibly, even primary CDI [57]. The efficacy of FMT seems to be higher for recurrent than for refractory CDI [58].

Table 2. Recurrence rates for CDI in different studies.

Study/publication	Recurrence rate (%)	Recurrence rate (%) in severe CDI	Comments
Two RCTs, Johnson et al. [8]			
Metronidazole	27	34	
Vancomycin	19	21	
Meta-analysis, Nelson et al. [30]			Evidence of moderate quality suggests that vancomycin is superior to metronidazole and fidaxomicin is superior to vancomycin
Metronidazole			
Vancomycin			
Retrospective study, Stevens et al. [31]			Mortality lower with vancomycin than metronidazole
Fidaxomicin versus vancomycin			
Louie et al. [12], randomised, double-blind)	25		
Vancomycin	15		
Fidaxomicin			
Fidaxomicin versus vancomycin,			
Cornely et al. [13], randomised, double-blind	27		
Vancomycin	13		
Fidaxomicin			
Extended-pulsed fidaxomicin (EXTEND study),			Patients at risk for rCDI Median age 75 years
Guery et al. [38], randomised, open label			
Vancomycin	20		
Fidaxomicin	5		
Bezlotoxumab (MODIFY I & II)			Subgroup analysis [51]: patients with 3 or more risk factors for rCDI, recurrence rates (%)
Wilcox et al. [49]			
SOC + bezlotoxumab	36		21
SOC + placebo	46		46
Bezlotoxumab, Oksi et al. [53]			Patients at high risk for rCDI
High-risk patients without immunosuppression	27		
High-risk patients including immunosuppression	29		
High-risk patients with severe CDI		37	

For comparison of different fidaxomicin studies, the percentages were recalculated by Gerding [41] Lancet ID. RCT: randomized controlled trial; SOC: standard of care; rCDI: recurrent *Clostridium difficile* infection.

Faecal microbiota may be delivered to the upper gastrointestinal tract through a nasoenteric tube, by esophagogastroduodenoscopy or by ingestion of capsules, and to the lower gastrointestinal tract by colonoscopy, flexible sigmoidoscopy or enema. Systematic reviews and meta-analyses [54,59,60] show a trend towards better results with delivery through colonoscopy than through delivery to the upper GI tract. Basically, the route of delivery depends on institutional practice and expertize, patient preference and severity of illness. Although standardized mixtures of bacteria for FMT have been developed, there is no alternative to whole-stool FMT in clinical practice at present [61].

The long-term safety of FMT is unclear. The main risks are transfer of infectious pathogens from the donor to the recipient and development of autoimmunological disorders. Careful evaluation and selection of all candidate stool donors is therefore important, which is also pointed out in guidelines and a safety alert [62–64]. There are also patients whose comorbid situation is not suitable for the use of FMT, e.g. patients with haematologic illnesses characterized by neutropenia and patients who have undergone allogenic transplants. No significant adverse effects related to FMT have been reported. The most serious adverse events are related to the procedure and occur with the same frequency as when these procedures are performed for other indications than rCDI [65].

Primary prevention strategies

The most important strategies for preventing CDI are judicious antibiotic use and infection control practices, particularly during outbreaks [66]. Antimicrobial stewardship programmes and diagnostic stewardship (to test only patients with a high pre-test probability) should be universal. Testing of patients receiving laxatives should be minimized, since positive results of *C. difficile* toxin by PCR testing may be due to colonization. Since the use of proton pump inhibitors is a risk factor for CDI, clinicians should consider if treatment with a proton pump inhibitor could be discontinued in patients at risk for CDI.

Reduction of transmissions of CDI requires strict adherence to contact precautions, and patients with diarrhoea of unknown aetiology need to be placed on isolation. Alcohol-based hand rubs do not kill *C. difficile* spores and are less effective than soap and water—albeit rubs are more effective than soap and water for controlling vegetative bacteria [67,68]. Therefore, the recommendation is to first wash the hands with soap and water and then to disinfect them with alcohol-based hand rub [10].

Investigational drugs and therapies for CDI and vaccines for primary prophylaxis

Development of the drugs cadazolid and surotomycin was stopped, because they were not superior over vancomycin [28,69].

According to the results of a phase II trial of ridinilazole, a non-absorbable oral antibiotic, primary cure was comparable and sustained cure for 30 days was higher for ridinilazole than vancomycin due to a lower recurrence rate [70]. Two large multicentre phase III trials, Ri-CODIFY 1 and 2, are being planned, and are expected to be completed by 2021 (ClinicalTrials.gov identifiers: NCT03595553, NCT03595566) [28].

Nontoxigenic *C. difficile* spores protect against the colonization by toxigenic strains and reduce the risk for rCDI. A phase II trial found a very low (2%) recurrence rate within 6 weeks of treatment in patients colonized with nontoxigenic *C. difficile* spores [71]. Phase III trials are warranted to elucidate the role of this interesting treatment option for preventing CDI [28]. Another investigational study is being conducted on the use of biotherapeutics examines the effect of a preparation of 12 different anaerobic bacterial spores in oral capsules [68].

Several vaccines against *C. difficile* are being developed and are currently undergoing clinical trials (ClinicalTrials.gov identifiers: NCT01887912, NCT02316470, NCT02117570, NCT02561195). Vaccination could be an effective approach in select high-risk populations—if effective and safe, vaccination would decrease cost, morbidity and mortality [28].

Conclusion

The cornerstones for the treatment of CDI are vancomycin and fidaxomicin. Metronidazole should be used only in mild-to-moderate disease in younger patients with no or few risk factors for recurrence. In rCDI, bezlotoxumab infusions (monoclonal antibody against *C. difficile* toxin B) may be considered as an adjunctive treatment to SOC of patients with several risk factors for rCDI. FMT should be offered to patients with frequently recurring CDI.

Disclosure statement

J.O. has been a scientific advisor (review panel or advisory committee) to Astellas, Gilead Sciences Finland, GlaxoSmithKline, MSD Finland, and Unimedic Pharma AB,

received lecture honoraria from Gilead Sciences Finland, GlaxoSmithKline, MSD Finland and Pfizer, and received coverage for congress travel/accommodation expenses from Gilead, Grifols, Janssen, MSD and Pfizer. V-J.A. has received lecture honoraria from MSD, Astellas, Roche, Pfizer, BristolMyersSquibb and Unimedic Pharma AB. E.M. has been a scientific advisor (review panel or advisory committee) and received lecture honoraria from MSD Finland.

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