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Management of *Clostridioides difficile* infection in adults and challenges in clinical practice: review and comparison of current IDSA/SHEA, ESCMID and ASID guidelines

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Clostridioides difficile infection (CDI) remains a significant clinical challenge both in the management of severe and severe-complicated disease and the prevention of recurrence. Guidelines released by the Infectious Diseases Society of America and Society for Healthcare Epidemiology of America (IDSA/SHEA) and ESCMID had some consensus as well as some discrepancies in disease severity classification and treatment recommendations. We review and compare the key clinical strategies from updated IDSA/SHEA, ESCMID and current Australasian guidelines for CDI management in adults and discuss relevant issues for clinicians, particularly in the management of severe-complicated infection.

Updated IDSA/SHEA and ESCMID guidelines now reflect the increased efficacy of fidaxomicin in preventing recurrence and have both promoted fidaxomicin to first-line therapy with an initial CDI episode in both non-severe and severe disease and endorsed the role of bezlotoxumab in the prevention of recurrent infection. Vancomycin remains acceptable therapy and metronidazole is not preferred. For severe-complicated infection the IDSA/SHEA recommends high-dose oral ± rectal vancomycin and IV metronidazole, whilst in an important development, ESCMID has endorsed fidaxomicin and tigecycline as part of combination anti-CDI therapy, for the first time. The role of faecal microbiota transplantation (FMT) in second CDI recurrence is now clearer, but timing and mode of FMT in severe-complicated refractory disease still requires further study.

Introduction

Despite key advances in therapeutic strategies, *Clostridioides difficile* infection (CDI) remains challenging for clinicians worldwide, not only in the management of infrequent cases of fulminant colitis, which carry a high risk of mortality,[1] but particularly with respect to the prevention of recurrent infection.[2–4] However, heterogeneity in definitions used for severe CDI has been a confounding factor when assessing treatment guideline recommendations and trial outcomes.[3–5] There is no international consensus on strict timing of parameter measurement with respect to treatment commencement. Updated ESCMID guidelines have included new severity definitions, which are now more harmonized with the IDSA/SHEA recommendations.[4] The Australasian Society for Infectious Diseases (ASID) guidelines are older[6] and the criteria for severe disease are more reflective of prior ESCMID definitions.[7] ESCMID has also included specific recommendations regarding prophylaxis for prevention of CDI, for the first time in international guidelines.[4]

Treatment of non-severe CDI

Consensus between IDSA/SHEA and ESCMID regarding optimal treatment of initial and first recurrence of non-severe CDI has now been reached.[3,4] Non-severe CDI is defined in IDSA/SHEA guidelines as a case with a WBC count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL,[3] whilst ESCMID specifies the same WBC count breakpoint, but in addition suggests that the temperature at presentation should be ≤38.5°C and the rise in serum creatinine be ≤50% above baseline with absence of imaging features of severity (Table 1).

The role of oral metronidazole, vancomycin and fidaxomicin in IDSA, ESCMID and ASID

Oral metronidazole was recommended for initial CDI in mild/moderate disease in 2014 ESCMID guidelines,[7] but in contrast, 2017 IDSA/SHEA guidelines advised metronidazole only for patients with an initial episode of non-severe CDI in settings where

Table 1. Severity classification of *C. difficile* infection in the three guidelines

	IDSA/SHEA 2021	ESCMID 2021	ASID 2016
Non-severe	WBC count of ≤15 000 cells/mL and a serum creatinine level <1.5 mg/dL.	WBC count of ≤15 000 cells/mL and a serum creatinine level ≤50% above baseline, and core body temperature at presentation ≤38.5°C. No imaging features of severity.	Absence of all features consistent with severe CDI.
Severe	One of the following factors at presentation: WBC count of >15 000 cells/mL or a serum creatinine level ≥1.5 mg/dL.	One of the following factors at presentation: WBC count of >15 000 cells/mL or a rise in serum creatinine level >50% above baseline or core body temperature >38.5°C. Additional supporting factors, when available, are distension of the large intestine, pericolonic fat stranding or colonic wall thickening (including low-attenuation mural thickening) at imaging.	Any of the following features if no other explanation can be provided: WBC count of >15 000 cells/mL or a rise in serum creatinine level >50% above baseline or core body temperature >38.5°C. Rigors, haemodynamic instability, peritonitis or evidence of bowel perforation, ileus or toxic megacolon, elevated lactate level, albumin level <25 mg/L, large intestine distension, colonic wall thickening, fat stranding, unexplained ascites (imaging) or pseudomembranous colitis on colonoscopy.
Severe-complicated 'fulminant'	Presence of hypotension or shock, ileus or megacolon.	Presence of one of the following factors that needs to be attributed to CDI: Hypotension, septic shock, elevated serum lactate, ileus, toxic megacolon, bowel perforation or any fulminant course of disease (i.e. rapid deterioration of the patient).	An episode of CDI complicated by: Toxic megacolon, admission to intensive care for severe sepsis, requirement for surgery or death due to CDI.

vancomycin or fidaxomicin were unavailable.[8] The recent IDSA/SHEA update suggests fidaxomicin preferentially over vancomycin for initial CDI,[3] and new ESCMID guidelines concur with this recommendation, with vancomycin being acceptable for a first episode and metronidazole only if other agents are unavailable.[4] The older ASID guidelines still recommend metronidazole for a first episode of non-severe CDI[6] (Table 2).

Whilst oral metronidazole, vancomycin and fidaxomicin can all be associated with treatment failure and relapse after primary infection, fidaxomicin has been demonstrated to be superior in preventing recurrence.[9–14] Treatment of CDI with either metronidazole or vancomycin is associated with recurrence in 20%–30% of patients,[15] which then provides a 50%–60% likelihood of further recurrence.[2,16] The theoretical advantage of oral vancomycin versus metronidazole is that it achieves high concentrations in the stool, well above the MIC required for its action (MIC_{90} for *C. difficile* is 1–2 mg/L), is not absorbed systemically and achieves predictably high levels in the colon throughout the entire course of administration, whilst oral metronidazole levels in stool are low and decrease to undetectable levels as colonic inflammation resolves.[17] There are no conclusive data regarding the relationship between MICs and clinical outcome for these two antibiotics.[18]

Focusing on comparisons between oral metronidazole and oral vancomycin in four randomized clinical trials, two unblinded studies found no key differences in outcomes.[9,10] However, two subsequent randomized placebo-controlled trials demonstrated that vancomycin was superior to metronidazole.[11,12] In both trials, vancomycin trended toward superiority in the mild/moderate disease subgroups. In the first study, clinical cure rate for all patients with vancomycin was 97% versus 84% ($P<0.006$) with metronidazole.[11] In the second trial, clinical cure rate with vancomycin was better in every disease category, but the difference was most pronounced in patients with severe disease, being 66.3% with metronidazole versus 78.5% with vancomycin.[12] A multivariate analysis by Johnson *et al*. found vancomycin to be superior overall, independent of disease severity.

A 2017 Cochrane meta-analysis including 22 trials mostly consisting of patients with non-severe disease, provided moderate-quality evidence suggesting that vancomycin is superior to oral metronidazole in all cases.[19] However, Fabre *et al*.[20] in 2018 contested the change to the IDSA/SHEA guidelines for vancomycin for non-severe disease. In response, McDonald *et al*.[21] commented that a large retrospective multicentre propensity score-matched study of >10 000 patients demonstrated that 30 day mortality for all patients treated with vancomycin versus metronidazole was significantly lower, although most of the reduced mortality was seen in patients with severe CDI. However, a more recent cohort study suggested younger age (<65 years) may predict better response to oral metronidazole in mild cases without the presence of severe underlying comorbidities or hypoalbuminaemia.[22]

Emphasis on differing efficacy between these two agents being more clearly delineated in those with risk factors for severe disease was the basis for use of oral metronidazole for a first non-severe CDI episode in earlier ESCMID and ASID guidelines.[6,7] In

Table 2. Treatment recommendations for *C. difficile* in the three guidelines

Category	IDSA/SHEA 2021	ESCMID 2021	ASID 2016
Initial episode, non-severe	Fidaxomicin STD preferred[a] OR vancomycin 125 mg PO 6 hourly for 10 days (alternative). If above agents are unavailable: metronidazole, 500 mg PO 8 hourly for 10–14 days.	Fidaxomicin STD preferred[a] OR vancomycin 125 mg PO 6 hourly for 10 days (alternative). If above agents are unavailable: metronidazole, 500 mg PO 8 hourly for 10 days. If high risk of recurrence, especially elderly hospitalized, consider EPFX[b] or adjunctive bezlotoxumab if fidaxomicin is unavailable.	Metronidazole 400 mg PO 8 hourly for 10 days.
First recurrence non-severe	Fidaxomicin STD[a] or EPFX[b] OR vancomycin tapered and pulsed regimen alternative[c] OR vancomycin 125 mg PO 6 hourly for 10 days alternative and adjunctive bezlotoxumab if prior episode within 6 months.	Fidaxomicin STD[a] if fidaxomicin not used for initial episode of CDI OR Fidaxomicin STD[a] or vancomycin 125 mg PO 6 hourly for 10 days with adjunctive bezlotoxumab OR vancomycin tapered and pulsed regimen[c] is acceptable alternative if other options are unavailable.	Vancomycin 125 mg PO 6 hourly for 10 days.
Second or subsequent recurrence non-severe	Fidaxomicin STD[a] or EPFX[b] OR vancomycin tapered and pulsed regimen[c] OR vancomycin 125 mg PO 6 hourly for 10 days followed by rifaximin 400 mg PO 8 hourly for 20 days and adjunctive bezlotoxumab if prior episode within 6 months. FMT: appropriate antibiotic treatment for at least two recurrences (i.e. three CDI episodes) should be tried prior to offering FMT.	FMT: after pretreatment with fidaxomicin STD[a] OR vancomycin 125 mg PO 6 hourly for 10 days OR Fidaxomicin STD[a] or Vancomycin 125 mg PO 6 hourly for 10 days with adjunctive bezlotoxumab OR vancomycin tapered and pulsed regimen[c] is acceptable alternative if other options are unavailable.	Vancomycin 125 mg PO 6 hourly for 14 days ± vancomycin taper OR fidaxomicin STD[a] OR FMT if available OR vancomycin 125 mg PO 6 hourly for 10 days followed by rifaximin 400 mg PO 8 hourly for 20 days.
Severe	Fidaxomicin STD[a] OR vancomycin 125 mg PO 6 hourly for 10 days and adjunctive bezlotoxumab for primary CDI if other risk factors for recurrence (age ≥65 years, immunocompromised host) or if episode in prior 6 months.	Fidaxomicin STD[a] OR vancomycin 125 mg PO 6 hourly for 10 days.	Vancomycin 125 mg PO 6 hourly for 10 days. If unable to tolerate oral therapy, use vancomycin via nasogastric tube plus metronidazole 500 mg IV 8 hourly ± vancomycin per rectum.
Severe-complicated 'fulminant'	Vancomycin 500 mg 6 hourly PO or by nasogastric tube and metronidazole 500 mg IV 8 hourly AND consider vancomycin per rectum if ileus present.	Fidaxomicin STD[a] OR vancomycin 125 mg PO 6 hourly for 10 days and consider IV tigecycline 100 mg load, then 50 mg 12 hourly. Consult a surgeon.	Vancomycin up to 500 mg 6 hourly PO or by nasogastric tube ± vancomycin per rectum plus metronidazole 500 mg IV 8 hourly. Consult a surgeon.
Severe-complicated 'fulminant' refractory	No commentary in focused update.	Refer for surgery OR consider rescue FMT if ineligible for surgery.	Consider tigecycline monotherapy OR consider rescue FMT AND consider role of surgery.

Vancomycin per rectum: 500 mg in 100 mL of normal saline per rectum 6 hourly as a retention enema. Bezlotoxumab adjunctive therapy: bezlotoxumab 10 mg/kg given IV once during administration of standard-of-care antibiotics.
STD, standard.
[a]Fidaxomicin STD regimen: 200 mg PO 12 hourly for 10 days.
[b]Fidaxomicin extended-pulsed regimen: 200 mg PO 12 hourly for 5 days followed by 200 mg PO every other day for 20 days.
[c]Tapered/pulsed vancomycin regimen example: 125 mg four times daily for 10–14 days, two times daily for 7 days, once daily for 7 days, and then every 2–3 days for 2–8 weeks.

addition, concern persists with vancomycin selecting acquired glycopeptide resistance in enterococci through selective pressure on the intestinal microbiota. Most patients have already been pretreated with other antimicrobials, which makes the relative contributions of each agent to dysbiosis hard to quantify. Both agents cause significant disruption of the intestinal microflora and there is not clear consensus that one promotes overgrowth of VRE more than the other.[23,24] A recent retrospective study, including 15 776 patients, demonstrated that those treated with oral vancomycin were no more likely to develop VRE infection within 3–6 months than with metronidazole.[25] A pragmatic difficulty with utilizing treatment such as oral metronidazole for primary non-severe CDI is that the severity staging of an episode is a dynamic target. This can inadvertently result in patients receiving inferior therapy to try and achieve clinical cure. Patel *et al.*[26] reported that 90 day mortality attributable to CDI was 21.7% in those undertreated using prior IDSA/SHEA guidelines versus 8.9% in those appropriately treated ($P=0.03$) and 8.2% in those either appropriately treated or overtreated ($P=0.015$).

Fidaxomicin and extended-pulsed fidaxomicin

Fidaxomicin performed favourably against vancomycin in clinical trials of CDI,[13,14] but widespread use worldwide has been inhibited due to high cost. Fidaxomicin is a non-absorbable, narrow-spectrum, macrocyclic antibacterial that has minimal systemic absorption.[27] It has higher *in vitro* activity against *C. difficile* than vancomycin, with a more prolonged post-antibiotic effect and reduces sporulation and toxin production whilst demonstrating greater preservation of the intestinal microbiota than vancomycin *in vitro* and *in vivo*.[27,28] Of note, fidaxomicin-treated hospital inpatients were less likely to contaminate their environment (25/68; 36.8%) than patients treated with metronidazole and/or vancomycin (38/66; 57.6%) ($P=0.02$).[29]

Two prospective randomized controlled trials demonstrated non-inferiority of fidaxomicin versus vancomycin for clinical cure of CDI, and a significantly lower recurrence rate.[13,14] Also, fidaxomicin-treated patients were less likely to have acquisition and overgrowth of VRE and *Candida* species.[30] A subgroup analysis of 128 in the per-protocol population from both studies demonstrated recurrence within 28 days occurred in 35.5% of vancomycin and 19.7% of fidaxomicin-treated patients, respectively, who had recent CDI prior to study enrolment.[15] These data informed the 2017 IDSA/SHEA recommendation for using fidaxomicin for recurrent CDI.[8] Two subsequent retrospective studies from England[31] and the USA[32] demonstrated decreased CDI recurrence and re-hospitalizations following hospital policy changes to utilize fidaxomicin as early first-line monotherapy.

The EXTEND trial of extended-pulsed fidaxomicin (EPFX) in 362 hospitalized patients aged ≥60 years with confirmed primary or recurrent CDI reported the lowest observed recurrence rates in a randomized controlled trial of antibiotic treatment for CDI, for patients who had a clinical response at the test of cure visit, at 4% 30 days post treatment and 6% at Day 90.[33] Two economic analyses found EPFX more cost-effective than vancomycin for first-line treatment of CDI in older patients.[34,35] Consequently, recent IDSA/SHEA guidelines suggested EPFX or standard-dose fidaxomicin for recurrent CDI and commented that further study comparing the two fidaxomicin regimens is required.[3] ESCMID has suggested an extended (off-label) approach may be considered for treatment of the population studied in the trial, i.e. older patients who are at risk for CDI recurrence.[4]

Authors who reviewed the 2017 IDSA/SHEA guidelines and performed Markov modelling to investigate cost-effectiveness of differing treatment regimens concluded that metronidazole is suboptimal for non-severe CDI as it is less beneficial than alternative strategies, with the preferred treatment regimen being fidaxomicin for primary non-severe CDI, fidaxomicin for first recurrence and consideration of faecal microbiota transplantation (FMT) for subsequent recurrence.[36] This strategy is now reflected in both updated IDSA/SHEA and ESCMID guidelines[3,4] (Table 2).

Treatment of severe CDI

There is consensus that oral metronidazole is not appropriate for the treatment of severe CDI, based on evidence from randomized controlled trials and a retrospective multicentre propensity score-matched study of >10 000 patients.[11,12,21] IDSA/SHEA define severe CDI as the presence of a WBC count of >15 000 cells/mL or a serum creatinine level ≥1.5 mg/dL. ESCMID uses similar criteria or fever >38.5°C or distension of the large intestine, pericolonic fat stranding or colonic wall thickening (including low-attenuation mural thickening) at imaging (Table 1).

ASID guidelines suggest oral vancomycin 125 mg 6 hourly for 10 days for severe disease, whilst fidaxomicin is not recommended.[6] Louie *et al.*[14] found fidaxomicin was non-inferior to vancomycin in achieving clinical cure in patients with severe disease and this has now been endorsed by ESCMID, IDSA/SHEA guidelines and international commentary.[3,4,18] However, there are no data on the efficacy of fidaxomicin in severe life-threatening disease.

Treatment of severe-complicated CDI

Both the IDSA/SHEA and ESCMID criteria define severe-complicated or 'fulminant' CDI as the presence of hypotension or shock, ileus or toxic megacolon. In addition, ESCMID includes patients with an elevated serum lactate, bowel perforation or any fulminant course of the disease in this category (Table 1). Notably, the 2021 IDSA/SHEA advice excludes fidaxomicin for fulminant disease and recommends adding IV metronidazole 500 mg 8 hourly, higher-dose vancomycin (500 mg 6 hourly) orally (PO) or via nasogastric tube, and potentially rectal vancomycin via rectal tube as retention enemas 6 hourly, particularly in the presence of ileus. 2016 ASID guidelines were similar, but had also suggested the option of consideration of tigecycline monotherapy or rescue FMT, whilst having surgical consultation.[3,6] ESCMID now differs in allowing fidaxomicin treatment, not routinely recommending IV metronidazole and suggesting the addition of IV tigecycline (Table 2).

There are surprisingly few studies supporting the usage of higher-dose vancomycin, rectal administration of vancomycin and the combination with IV metronidazole. The 125 mg dose of vancomycin achieves 500–1000 times the MIC_{90}, which should be adequate for clinical efficacy. However, Cunha *et al.*,[37] in a retrospective study of 160 patients, demonstrated a 97% response rate to vancomycin 500 mg PO 6 hourly in patients failing

to achieve rapid clinical improvement after 72 h with conventional vancomycin dosing. Rectal vancomycin has shown efficacy in small case series, but has the potential disadvantage of a small risk of colonic perforation.[38,39] A retrospective review of 47 patients with *C. difficile* colitis treated with adjunct intracolonic vancomycin was published by Kim *et al*. in 2013.[40] Thirty-three of 47 patients (70%) with severe CDI responded with complete resolution without surgery, whilst 21% died. In a more recent case–control study of 24 ICU patients, vancomycin per rectum did not reduce the need for colectomy or decrease mortality.[41] All authors agree prospective studies of efficacy are needed.

The recommendation for combined oral vancomycin and IV metronidazole in severe-complicated disease derives from expert opinion and a single-centre, retrospective, observational, comparative study performed in 88 critically ill patients with CDI from the USA in 2015.[42] The combination therapy group received IV metronidazole within 48 h after initiating vancomycin, for at least 72 h, with a median duration of 12.5 days (range 3–33). Mortality was 36.4% and 15.9% in the monotherapy and combination therapy groups, respectively ($P=0.03$). In the setting of gut dysmotility in critically ill patients, therapeutic metronidazole concentrations at the site of colonic inflammation may still occur with IV therapy, and explain the potential benefit. There has been no prospective randomized controlled trial evaluating efficacy of the combination regimen versus vancomycin alone in severe-complicated disease, which is likely a function of the medical and ethical complexities involved. ESCMID noted that a large retrospective analysis ($n=2114$) found no association between dual therapy and 90 day mortality, colectomy and CDI recurrence in patients with non-severe ($n=727$), severe ($n=861$) and fulminant CDI ($n=526$).[4,43]

Severe-complicated, refractory CDI

Refractory CDI is CDI not responding to recommended CDI antibiotic treatment, i.e. no response after 3–5 days of therapy.[4] The options for patients on vancomycin and IV metronidazole combination medical therapy who are still deteriorating include addition of tigecycline, surgery or rescue FMT. The timing and choice of these interventions has largely rested with treating clinicians. The role of medical therapy beyond vancomycin and IV metronidazole, particularly for difficult groups of patients excluded from FMT studies, has been contentious. As mentioned, in an important development, ESCMID has now endorsed the addition of tigecycline to other anti-CDI therapy when a patient is progressing to severe-complicated CDI, which is consistent with our practice using combination therapy in non-pregnant adults.[4,44] The IDSA focused update did not comment on tigecycline. It is important that such patients also have a concurrent surgical referral for careful observation;[8] however, total colectomy should be avoided if possible, especially without the presence of toxic megacolon. There has been no randomized controlled trial evaluating tigecycline combination therapy versus surgery, and whilst ESCMID now recommends that total abdominal colectomy might be prevented by partial colectomy or loop ileostomy, the mortality benefit for any of these procedures versus maximal medical therapy is unclear.[45–47] A new clinical strategy, therefore, is maximal medical therapy with tigecycline and then proceeding to surgery or rescue FMT if there is clinical failure or drug toxicity.

Tigecycline is a broad-spectrum glycylcycline that suppresses *C. difficile* toxin production and sporulation.[48] IV administration circumvents limitations observed with oral and rectal vancomycin therapy and provides broad-spectrum cover for intra-abdominal sepsis. The advantage of tigecycline is that the delay and procedural decisions relating to FMT are avoided; however, the major disadvantage is potential liver function derangement, coagulopathy or pancreatitis, limiting the duration of therapy.[44,49] Close monitoring of patients is required, with early discontinuation of tigecycline therapy if adverse effects develop. A duration >14 days is a risk factor for tigecycline-induced coagulopathy and often only shorter courses are needed for salvage of patients with fulminant CDI.

Small series and cohort studies evaluated clinical outcomes in patients treated with tigecycline monotherapy or combination therapy including oral vancomycin and IV metronidazole, but these studies are not easily comparable because the severity criteria are different.[50,51] We found tigecycline beneficial as part of early combination therapy in a retrospective analysis of 13 patients with severe or severe-complicated CDI where clinical cure was documented in 77.0% and mortality was 8% in patients to whom adjunctive tigecycline was administered earlier than recommended in current guidelines.[44] Results from other studies have been mixed and there has been no prospective randomized controlled trial.[52,53] A Phase 2 study ceased due to slow accrual.[54] However, a recent meta-analysis based on 186 patients (four studies) showed a clinical cure rate of 79% (95% CI 73.0%–84.5%).[50] Of note, the pooled clinical cure rate was higher than that after single FMT in the recent meta-analysis.[55] Tigecycline monotherapy is controversial and avoided at our institution. Szabo *et al*.[56] originally reported in a retrospective study of 90 patients with severe CDI that those treated with tigecycline had significantly better outcomes versus patients treated with standard therapy with oral vancomycin plus IV metronidazole (clinical cure 75.6% in the tigecycline group versus 53.3% in the standard therapy group, $P=0.02$). However, the same investigators subsequently reported that tigecycline monotherapy in 110 patients with severe CDI resulted in the primary outcome of treatment failure in 37.3%.[57] Patients with failure frequently had chronic cardiac and pulmonary comorbidities, peritonitis, higher C-reactive protein (CRP) levels, ICU admittance rates and need for total parenteral nutrition and vasopressors. The timing of drug commencement is important, and this issue requires further clarification in prospective studies. The ESCMID 2014 and ASID 2016 guidelines suggesting salvage tigecycline monotherapy have now been superseded by the new ESCMID recommendation, as discussed.[6,7]

FMT shows promise in severe-complicated refractory CDI, but has complexities in immunosuppressed patients and requires donor screening, which is difficult in precipitant circumstances.[58,59] Unknown donor stool banking facilitates urgent delivery but is not widely accessible.[60] It has not been endorsed by IDSA/SHEA in this context, but ESCMID recently ratified consideration of FMT where surgery is not feasible.[3,4] Australasian guidelines endorse consideration of FMT if there is a failure of medical therapy.[6]

A 2017 review considered 23 case reports and series reporting FMT for severe or complicated CDI and concluded this approach was appropriate in patients with severe-complicated, refractory CDI to avoid surgery.[58] In 2020, Guery *et al*.[5] concurred that

FMT was a reasonable option to treat severe-complicated CDI. Fischer *et al.*[59] demonstrated the need for a second FMT for cure in complicated cases and success with continuation of oral vancomycin in patients with pseudomembranes. The same author then described an 87% cure rate at 1 month for severe-complicated, refractory CDI in an observational cohort study of 38 patients.[61] A recent series from Taiwan of 39 patients treated with colonoscopic FMT for recurrent, refractory or complicated CDI had a success rate of 89.7%.[62] A recent randomized controlled trial of 56 patients reiterated that multiple transplants may be required for clinical cure.[63] Notably, this trial included patients who only received monotherapy with vancomycin or fidaxomicin before being defined as refractory and excluded patients with toxic megacolon, septic shock and those undergoing ongoing treatment for malignancy or receiving concomitant systemic antimicrobials. This was the only randomized controlled trial included in a recent meta-analysis including 676 patients who underwent FMT for severe or fulminant CDI.[55] The overall rate of clinical cure in the meta-analysis after single FMT was 61.3% (95% CI 43.2%–78.0%) with 10.9% (95% CI 0.2%–30.2%) of patients experiencing major adverse events. The pooled colectomy rate after FMT was 8.2% (95% CI 0.1%–23.7%) with a pooled all-cause mortality rate after FMT of 15.6% (95% CI 7.8%–25.0%).[55]

Prevention of relapse and treatment of recurrent CDI

Bezlotoxumab

A single infusion of bezlotoxumab, the human monoclonal antibody against toxin B, significantly decreased recurrence in patients receiving standard antibiotic treatment for primary or recurrent CDI versus placebo, after initial clinical cure at 12 weeks, in two double-blind, randomized, placebo-controlled Phase 3 trials.[64] Concerns around high cost, potential for infusion reactions and heart failure in some patients have been limitations to standard use. Its use is cautioned in patients with congestive heart failure (CHF) as more deaths were seen in this group (19.5% versus 12.5% placebo). Of note, only 4% of patients received fidaxomicin in the bezlotoxumab trials, so this combination is not well defined. Kampouri *et al.*[3] recently commented that the recurrence rate after bezlotoxumab is comparable to the rate observed with the classic administration of fidaxomicin.[18] The 2021 IDSA/SHEA guidelines suggest using bezlotoxumab as a co-intervention along with standard antibiotics in primary infection only if the patient is at high risk for recurrence and has severe CDI, whereas ESCMID suggests it is relevant for high-risk patients only if fidaxomicin is not available (Table 2). Both societies agree with its use in all patients who then present with a second episode of CDI within 6 months[3,4] and warn that in patients with a history of CHF, bezlotoxumab should be reserved for when the benefit outweighs the risk. Bezlotoxumab has not yet been endorsed in Australian guidelines, but recommendations may be updated in view of international commentary.

Other antimicrobial strategies

ESCMID and IDSA/SHEA guidelines advise that vancomycin in a tapered and pulsed regimen can be considered for the first or subsequent CDI recurrence[3,4] as an acceptable alternative to standard-dose fidaxomicin or EPFX. Prolonged oral vancomycin 125 mg daily has also been effective to prevent relapse in the elderly, where FMT was impractical.[65] Rifaximin after completion of standard antibiotic therapy decreased recurrence rate at 12 weeks from 29.5% to 15.9% in a randomized placebo-controlled trial.[66] Rifaximin is endorsed for patients with more than one recurrence (weak recommendation, low quality of evidence) in both 2017 and 2021 IDSA/SHEA guidelines,[3,8] but was not given strong support by ESCMID, who have listed FMT post standard-of-care antibiotic treatment as preferred for second recurrence (Table 2).

Faecal microbiota transplantation

Kampouri *et al.*[18] recently suggested study of FMT at the first recurrence. However, IDSA/SHEA recently restricted FMT to third and subsequent recurrence, noting two FDA alerts documenting transmission of pathogenic *Escherichia coli* from donors to recipients, with resultant morbidity and mortality, and new concerns regarding potential transmission of severe acute respiratory syndrome coronavirus 2.[3] There is symmetry between ESCMID and Australasian guidelines regarding FMT for second recurrence.[4,6]

Initial randomized controlled trials of FMT in patients with recurrent CDI demonstrated superiority over vancomycin therapy, with either duodenal infusion or rectal administration.[67,68] Overall, results suggest that a single administration by the nasoenteric route, enema, capsule or endoscopic administration via the upper or lower GI tract has between a 65% and 95% success rate of cure.[69–71] A systematic search of 14 studies with data from 305 patients suggested that the lower route was more effective.[72] A prospective cohort study of 180 patients demonstrated that frozen capsulized FMT was effective, where at 8 weeks, CDI resolved in 82% of patients after one treatment, rising to a 91% cure rate with two treatments.[71] In multiply recurrent CDI, a recent randomized controlled trial of 64 consecutive adults in Denmark demonstrated that FMT was superior to fidaxomicin or vancomycin for 10 days in achieving clinical resolution and a negative *C. difficile* toxin test at 8 weeks, with the primary outcome achieved in 71%, 33% and 19% of patients respectively.[73]

There are ethical implications of the metabolic and immunological consequences of transplantation of the human microbiome and there is a risk of rare complications such as aspiration with the upper route and colonic perforation with the lower route, although the lower route has been established as safer.[72,74] Longer-term follow-up has suggested weight gain in recipients and the temporal emergence of new medical conditions, plus modulation of insulin sensitivity and response to cancer therapeutics.[75,76] More targeted approaches to manipulate the gut microbiota are being trialled and may be safer in the long term.[18]

Probiotics

Probiotics have been studied for *C. difficile* in both a prophylactic and adjunctive setting, but have not been endorsed in updated CDI guidelines.[3,4,6–8] In 2017, IDSA/SHEA noted there were insufficient data to recommend probiotics for primary prevention of CDI,[8,77,78] and that whilst *Saccharomyces boulardii* and *Lactobacillus* species had shown promise for the prevention of

CDI recurrence, neither had yet produced significant and reproducible efficacy in controlled clinical trials.[79–81] Previously, a Cochrane review of probiotics for the prevention of *C. difficile*-associated diarrhoea in adults and children had concluded that short-term use appears to be safe and effective when used along with antibiotics in patients who are not immunocompromised or severely debilitated, and that patients should be informed of the potential benefits and harms of probiotics.[78] The conclusion, however, recently from ESCMID was that adverse effects may be significant and probiotics may actually delay microbiome reconstitution after antibiotic treatment.[4]

There are limited data regarding adjunctive probiotic therapy for a first episode or first recurrence of non-severe CDI and the nature and timing of administration has varied in the available studies. The first randomized, double-blind trial in patients with either initial or recurrent CDI found adjuvant *S. boulardii* reduced the rate of recurrence from 44.8% to 26.3% in patients receiving standard antibiotics.[80] A subsequent study utilizing patients from a national double-blind, placebo-controlled trial of treatment of adult patients with recurrent CDI in the USA found that *S. boulardii* (started on Day 7 of treatment with vancomycin and continued for 28 days) significantly reduced recurrence when combined with high-dose vancomycin only (2 g/day).[79] Barker *et al.*[82] described that 4 weeks of daily combination probiotic treatment (*Lactobacillus acidophilus*, *Lactobacillus paracasei*, *Bifidobacterium lactis*) in 31 non-severely immunocompromised patients with first-episode CDI treated with standard antibiotics was associated with significant improvement in diarrhoea outcomes, but the difference in recurrence rate versus placebo was not significant.

Concerns with the use of probiotics have also emerged due to reports of bacteraemia and fungaemia and lack of guidelines around exclusion criteria.[83,84] A recent meta-analysis that considered the use of probiotics for primary prevention of CDI commented on evaluation of non-pregnant, non-ICU, immunocompetent patients without prosthetic heart valves and found efficacy when probiotics were given within 2 days of the first antibiotic dose, with no reported episodes of bacteraemia of fungaemia.[85] Further prospective studies of the efficacy and safety of adjuvant probiotic therapy, particularly with fidaxomicin, are required.

Other considerations for prophylaxis for prevention of CDI

In addition to updated guidance advising against the routine use of probiotics for prevention of CDI, for the first time in international guidelines, ESCMID has specifically addressed the role of anti-CDI antibiotic prophylaxis for patients on systemic antibiotic treatment. A review of the evidence, including seven retrospective observational studies and one open-label randomized controlled trial of oral vancomycin in high-risk populations, plus one randomized placebo-controlled trial of fidaxomicin prophylaxis in stem cell transplantation patients receiving fluoroquinolone prophylaxis, led to a recommendation against the use of routine prophylaxis with this strategy.[4] However, it was advised that for very selected patients who have a history of multiply recurrent CDI precipitated by systemic antibiotic use, prophylaxis with microbiota-sparing anti-CDI antibiotics has a role, after careful consideration of the risk and benefits, and Infectious Diseases or Microbiology specialist consultation.[4] In addition, ESCMID concluded that other novel approaches may emerge. A Phase 3 *C. difficile* toxoid vaccine trial was unfortunately terminated because of futility;[86] however, a novel poorly absorbed β-lactamase (ribaxamase, SYN004) had promising results from a Phase 2b trial and remains in clinical development.[4,87]

Conclusions

It has been a period of major evolution in the international CDI guidelines with respect to the increased role of both fidaxomicin and bezlotoxumab at a time when the delivery of FMT for recurrent infection has become more complex due to the COVID-19 pandemic. Oral vancomycin retains an important role in therapy, whereas oral metronidazole is recommended only for use in settings where other agents are unavailable. The impact of these changes remains to be seen, but they may reduce the magnitude of the clinical problem in the USA and Europe and are likely to influence new Australasian guidelines. The ESCMID endorsement of tigecycline combination therapy is an important addition to medical therapy for severe-complicated CDI and further study of the role of FMT in this setting may also be beneficial.

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References

1 Carlson TJ, Gonzales-Luna AJ, Garey KW. Fulminant *Clostridioides difficile* infection: a review of treatment options for a life-threatening infection. *Semin Respir Crit Care Med* 2022; **43**: 28–38. https://doi.org/10.1055/s-0041-1740973

2 Shields K, Araujo-Castillo RV, Theethira TG *et al.* Recurrent *Clostridium difficile* infection: from colonization to cure. *Anaerobe* 2015; **34**: 59–73. https://doi.org/10.1016/j.anaerobe.2015.04.012

3 Johnson S, Lavergne V, Skinner AM *et al.* Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 focused update guidelines on management of *Clostridioides difficile* infection in adults. *Clin Infect Dis* 2021; **73**: e1029–e44. https://doi.org/10.1093/cid/ciab549

4 van Prehn J, Reigadas E, Vogelzang EH *et al.* European Society of Clinical Microbiology and Infectious Diseases: 2021 update on the treatment guidance document for *Clostridioides difficile* infection in adults. *Clin Microbiol Infect* 2021; **27** Suppl 2: S1–S21. https://doi.org/10.1016/j.cmi.2021.09.038

5 Guery B, Barbut F, Tschudin-Sutter S. Diagnostic and therapy of severe *Clostridioides difficile* infections in the ICU. *Curr Opin Crit Care* 2020; **26**: 450–58. https://doi.org/10.1097/MCC.0000000000000753

6 Trubiano JA, Cheng AC, Korman TM *et al.* Australasian Society of Infectious Diseases updated guidelines for the management of *Clostridium difficile* infection in adults and children in Australia and New

Zealand. *Intern Med J* 2016; **46**: 479–93. https://doi.org/10.1111/imj.13027

7 Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for *Clostridium difficile* infection. *Clin Microbiol Infect*. 2014; **20** Suppl 2: 1–26. https://doi.org/10.1111/1469-0691.12418

8 McDonald LC, Gerding DN, Johnson S *et al*. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis* 2018; **66**: 987–94. https://doi.org/10.1093/cid/ciy149

9 Teasley DG, Gerding DN, Olson MM *et al*. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium-difficile*-associated diarrhoea and colitis. *Lancet* 1983; **2**: 1043–6. https://doi.org/10.1016/S0140-6736(83)91036-X

10 Wenisch C, Parschalk B, Hasenhundl M *et al*. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. *Clin Infect Dis* 1996; **22**: 813–8. https://doi.org/10.1093/clinids/22.5.813

11 Zar FA, Bakkanagari SR, Moorthi KM *et al*. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007; **45**: 302–7. https://doi.org/10.1086/519265

12 Johnson S, Louie TJ, Gerding DN *et al*. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis* 2014; **59**: 345–54. https://doi.org/10.1093/cid/ciu313

13 Cornely OA, Crook DW, Esposito R *et al*. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis* 2012; **12**: 281–9. https://doi.org/10.1016/S1473-3099(11)70374-7

14 Louie TJ, Miller MA, Mullane KM *et al*. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. *N Engl J Med* 2011; **364**: 422–31. https://doi.org/10.1056/NEJMoa0910812

15 Cornely OA, Miller MA, Louie TJ *et al*. Treatment of first recurrence of *Clostridium difficile* infection: fidaxomicin versus vancomycin. *Clin Infect Dis* 2012; **55** Suppl 2: S154–61. https://doi.org/10.1093/cid/cis462

16 Johnson S. Recurrent *Clostridium difficile* infection: a review of risk factors, treatments, and outcomes. *J Infect* 2009; **58**: 403–10. https://doi.org/10.1016/j.jinf.2009.03.010

17 Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. *Gut* 1986; **27**: 1169–72. https://doi.org/10.1136/gut.27.10.1169

18 Kampouri E, Croxatto A, Prod'hom G *et al*. *Clostridioides difficile* infection, still a long way to go. *J Clin Med* 2021; **10**: 389. https://doi.org/10.3390/jcm10030389

19 Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for *Clostridium difficile*-associated diarrhoea in adults. *Cochrane Database Syst Rev* 2017; CD004610. https://doi.org/10.1002/14651858.CD004610.pub5

20 Fabre V, Dzintars K, Avdic E *et al*. Role of metronidazole in mild *Clostridium difficile* infections. *Clin Infect Dis* 2018; **67**: 1956–58. https://doi.org/10.1093/cid/ciy474

21 Stevens VW, Nelson RE, Schwab-Daugherty EM *et al*. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with *Clostridium difficile* infection. *JAMA Intern Med* 2017; **177**: 546–53. https://doi.org/10.1001/jamainternmed.2016.9045

22 Appaneal HJ, Caffrey AR, LaPlante KL. What is the role for metronidazole in the treatment of *Clostridium difficile* infection? Results from a National Cohort Study of Veterans with initial mild disease. *Clin Infect Dis* 2019; **69**: 1288–95. https://doi.org/10.1093/cid/ciy1077

23 Al-Nassir WN, Sethi AK, Li Y *et al*. Both oral metronidazole and oral vancomycin promote persistent overgrowth of vancomycin-resistant enterococci during treatment of *Clostridium difficile*-associated disease. *Antimicrob Agents Chemother* 2008; **52**: 2403–6. https://doi.org/10.1128/AAC.00090-08

24 Salgado CD, Giannetta ET, Farr BM. Failure to develop vancomycin-resistant *Enterococcus* with oral vancomycin treatment of *Clostridium difficile*. *Infect Control Hosp Epidemiol* 2004; **25**: 413–7. https://doi.org/10.1086/502415

25 Stevens VW, Khader K, Echevarria K *et al*. Use of oral vancomycin for *Clostridioides difficile* infection and the risk of vancomycin-resistant enterococci. *Clin Infect Dis* 2020; **71**: 645–51. https://doi.org/10.1093/cid/ciz871

26 Patel I, Wungjiranirun M, Theethira T *et al*. Lack of adherence to SHEA-IDSA treatment guidelines for *Clostridium difficile* infection is associated with increased mortality. *J Antimicrob Chemother* 2017; **72**: 574–81. https://doi.org/10.1093/jac/dkw423

27 Louie TJ, Cannon K, Byrne B *et al*. Fidaxomicin preserves the intestinal microbiome during and after treatment of *Clostridium difficile* infection (CDI) and reduces both toxin reexpression and recurrence of CDI. *Clin Infect Dis* 2012; **55** Suppl 2: S132–42. https://doi.org/10.1093/cid/cis338

28 Babakhani F, Gomez A, Robert N *et al*. Postantibiotic effect of fidaxomicin and its major metabolite, OP-1118, against *Clostridium difficile*. *Antimicrob Agents Chemother* 2011; **55**: 4427–9. https://doi.org/10.1128/AAC.00104-11

29 Biswas JS, Patel A, Otter JA *et al*. Contamination of the hospital environment from potential *Clostridium difficile* excretors without active infection. *Infect Control Hosp Epidemiol* 2015; **36**: 975–7. https://doi.org/10.1017/ice.2015.79

30 Nerandzic MM, Mullane K, Miller MA *et al*. Reduced acquisition and overgrowth of vancomycin-resistant enterococci and *Candida* species in patients treated with fidaxomicin versus vancomycin for *Clostridium difficile* infection. *Clin Infect Dis* 2012; **55** Suppl 2: S121–6. https://doi.org/10.1093/cid/cis440

31 Goldenberg SD, Brown S, Edwards L *et al*. The impact of the introduction of fidaxomicin on the management of *Clostridium difficile* infection in seven NHS secondary care hospitals in England: a series of local service evaluations. *Eur J Clin Microbiol Infect Dis* 2016; **35**: 251–9. https://doi.org/10.1007/s10096-015-2538-z

32 Gallagher JC, Reilly JP, Navalkele B *et al*. Clinical and economic benefits of fidaxomicin compared to vancomycin for *Clostridium difficile* infection. *Antimicrob Agents Chemother* 2015; **59**: 7007–10. https://doi.org/10.1128/AAC.00939-15

33 Guery B, Menichetti F, Anttila VJ *et al*. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. *Lancet Infect Dis* 2018; **18**: 296–307. https://doi.org/10.1016/S1473-3099(17)30751-X

34 Cornely OA, Watt M, McCrea C *et al*. Extended-pulsed fidaxomicin versus vancomycin for *Clostridium difficile* infection in patients aged ≥60 years (EXTEND): analysis of cost-effectiveness. *J Antimicrob Chemother* 2018; **73**: 2529–39. https://doi.org/10.1093/jac/dky184

35 Rubio-Terres C, Aguado JM, Almirante B *et al*. Extended-pulsed fidaxomicin versus vancomycin in patients 60 years and older with *Clostridium difficile* infection: cost-effectiveness analysis in Spain. *Eur J Clin Microbiol Infect Dis* 2019; **38**: 1105–11. https://doi.org/10.1007/s10096-019-03503-4

36 Rajasingham R, Enns EA, Khoruts A *et al*. Cost-effectiveness of treatment regimens for *Clostridioides difficile* infection: an evaluation of the

2018 Infectious Diseases Society of America guidelines. *Clin Infect Dis* 2020; **70**: 754–62. https://doi.org/10.1093/cid/ciz318

37 Cunha BA, Sessa J, Blum S. Enhanced efficacy of high dose oral vancomycin therapy in *Clostridium difficile* diarrhea for hospitalized adults not responsive to conventional oral vancomycin therapy: antibiotic stewardship implications. *J Clin Med* 2018; **7**: 75. https://doi.org/10.3390/jcm7040075

38 Apisarnthanarak A, Razavi B, Mundy LM. Adjunctive intracolonic vancomycin for severe *Clostridium difficile* colitis: case series and review of the literature. *Clin Infect Dis* 2002; **35**: 690–6. https://doi.org/10.1086/342334

39 Shetler K, Nieuwenhuis R, Wren SM *et al*. Decompressive colonoscopy with intracolonic vancomycin administration for the treatment of severe pseudomembranous colitis. *Surg Endosc* 2001; **15**: 653–9. https://doi.org/10.1007/s004640080104

40 Kim PK, Huh HC, Cohen HW *et al*. Intracolonic vancomycin for severe *Clostridium difficile* colitis. *Surg Infect (Larchmt)* 2013; **14**: 532–9. https://doi.org/10.1089/sur.2012.158

41 Malamood M, Nellis E, Ehrlich AC *et al*. Vancomycin enemas as adjunctive therapy for *Clostridium difficile* infection. *J Clin Med Res* 2015; **7**: 422–7. https://doi.org/10.14740/jocmr2117w

42 Rokas KE, Johnson JW, Beardsley JR *et al*. The addition of intravenous metronidazole to oral vancomycin is associated with improved mortality in critically ill patients with *Clostridium difficile* infection. *Clin Infect Dis* 2015; **61**: 934–41. https://doi.org/10.1093/cid/civ409

43 Wang Y, Schluger A, Li J *et al*. Does addition of intravenous metronidazole to oral vancomycin improve outcomes in *Clostridioides difficile* infection? *Clin Infect Dis* 2020; **71**: 2414–20. https://doi.org/10.1093/cid/ciz1115

44 Bishop EJ, Tiruvoipati R, Metcalfe J *et al*. The outcome of patients with severe and severe-complicated *Clostridium difficile* infection treated with tigecycline combination therapy: a retrospective observational study. *Intern Med J* 2018; **48**: 651–60. https://doi.org/10.1111/imj.13742

45 Hall BR, Leinicke JA, Armijo PR *et al*. No survival advantage exists for patients undergoing loop ileostomy for *Clostridium difficile* colitis. *Am J Surg* 2019; **217**: 34–9. https://doi.org/10.1016/j.amjsurg.2018.09.023

46 Juo YY, Sanaiha Y, Jabaji Z *et al*. Trends in diverting loop ileostomy vs total abdominal colectomy as surgical management for *Clostridium difficile* colitis. *JAMA Surg* 2019; **154**: 899–906. https://doi.org/10.1001/jamasurg.2019.2141

47 Ferrada P, Callcut R, Zielinski MD *et al*. Loop ileostomy versus total colectomy as surgical treatment for *Clostridium difficile*-associated disease: an Eastern Association for the Surgery of Trauma multicenter trial. *J Trauma Acute Care Surg* 2017; **83**: 36–40. https://doi.org/10.1097/TA.0000000000001498

48 Aldape MJ, Heeney DD, Bryant AE *et al*. Tigecycline suppresses toxin A and B production and sporulation in *Clostridium difficile*. *J Antimicrob Chemother* 2015; **70**: 153–9. https://doi.org/10.1093/jac/dku325

49 Cui N, Cai H, Li Z *et al*. Tigecycline-induced coagulopathy: a literature review. *Int J Clin Pharm* 2019; **41**: 1408–13. https://doi.org/10.1007/s11096-019-00912-5

50 Kechagias KS, Chorepsima S, Triarides NA *et al*. Tigecycline for the treatment of patients with *Clostridium difficile* infection: an update of the clinical evidence. *Eur J Clin Microbiol Infect Dis* 2020; **39**: 1053–8. https://doi.org/10.1007/s10096-019-03756-z

51 LaSalvia MT, Branch-Elliman W, Snyder GM *et al*. Does adjunctive tigecycline improve outcomes in severe-complicated, nonoperative *Clostridium difficile* infection? *Open Forum Infect Dis* 2017; **4**: ofw264. https://doi.org/10.1093/ofid/ofw264

52 Brinda BJ, Pasikhova Y, Quilitz RE *et al*. Use of tigecycline for the management of *Clostridium difficile* colitis in oncology patients and case series of breakthrough infections. *J Hosp Infect* 2017; **95**: 426–32. https://doi.org/10.1016/j.jhin.2016.12.018

53 Manea E, Sojo-Dorado J, Jipa RE *et al*. The role of tigecycline in the management of *Clostridium difficile* infection: a retrospective cohort study. *Clin Microbiol Infect* 2018; **24**: 180–4. https://doi.org/10.1016/j.cmi.2017.06.005

54 Kelly CR, Fischer M, Allegretti JR *et al*. ACG clinical guidelines: prevention, diagnosis, and treatment of *Clostridioides difficile* infections. *Am J Gastroenterol* 2021; **116**: 1124–47. https://doi.org/10.14309/ajg.0000000000001278

55 Tixier EN, Verheyen E, Luo Y *et al*. Systematic review with meta-analysis: fecal microbiota transplantation for severe or fulminant *Clostridioides difficile*. *Dig Dis Sci* 2021; **67**: 978–88. https://doi.org/10.1007/s10620-021-06908-4

56 Gergely Szabo B, Kadar B, Szidonia Lenart K *et al*. Use of intravenous tigecycline in patients with severe *Clostridium difficile* infection: a retrospective observational cohort study. *Clin Microbiol Infect* 2016; **22**: 990–5. https://doi.org/10.1016/j.cmi.2016.08.017

57 Szabo BG, Duma L, Lenart KS *et al*. Characteristics and predictors of treatment failure with intravenous tigecycline monotherapy among adult patients with severe *Clostridioides* (*Clostridium*) *difficile* infection: a single-centre observational cohort study. *Diagn Microbiol Infect Dis* 2021; **99**: 115231. https://doi.org/10.1016/j.diagmicrobio.2020.115231

58 van Beurden YH, Nieuwdorp M, van de Berg P *et al*. Current challenges in the treatment of severe *Clostridium difficile* infection: early treatment potential of fecal microbiota transplantation. *Therap Adv Gastroenterol* 2017; **10**: 373–81. https://doi.org/10.1177/1756283X17690480

59 Fischer M, Sipe BW, Rogers NA *et al*. Faecal microbiota transplantation plus selected use of vancomycin for severe-complicated *Clostridium difficile* infection: description of a protocol with high success rate. *Aliment Pharmacol Ther* 2015; **42**: 470–6. https://doi.org/10.1111/apt.13290

60 Cammarota G, Ianiro G, Kelly CR *et al*. International consensus conference on stool banking for faecal microbiota transplantation in clinical practice. *Gut* 2019; **68**: 2111–21. https://doi.org/10.1136/gutjnl-2019-319548

61 Fischer M, Sipe B, Cheng YW *et al*. Fecal microbiota transplant in severe and severe-complicated *Clostridium difficile*: a promising treatment approach. *Gut Microbes* 2017; **8**: 289–302. https://doi.org/10.1080/19490976.2016.1273998

62 Yeh YM, Cheng HT, Le PH *et al*. Implementation of fecal microbiota transplantation in a medical center for recurrent or refractory *Clostridioides difficile* infection and report of preliminary outcome. *Biomed J* 2022; **45**: 504–11. https://doi.org/10.1016/j.bj.2021.06.001

63 Ianiro G, Masucci L, Quaranta G *et al*. Randomised clinical trial: faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory *Clostridium difficile* infection-single versus multiple infusions. *Aliment Pharmacol Ther* 2018; **48**: 152–9. https://doi.org/10.1111/apt.14816

64 Wilcox MH, Gerding DN, Poxton IR *et al*. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection. *N Engl J Med* 2017; **376**: 305–17. https://doi.org/10.1056/NEJMoa1602615

65 Zhang K, Beckett P, Abouanaser S *et al*. Prolonged oral vancomycin for secondary prophylaxis of relapsing *Clostridium difficile* infection. *BMC Infect Dis* 2019; **19**: 51. https://doi.org/10.1186/s12879-019-3676-1

66 Major G, Bradshaw L, Boota N *et al*. Follow-on rifaximin for the prevention of recurrence following standard treatment of infection with *Clostridium difficile* (RAPID): a randomised placebo controlled trial. *Gut* 2019; **68**: 1224–31. https://doi.org/10.1136/gutjnl-2018-316794

67 van Nood E, Vrieze A, Nieuwdorp M *et al*. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; **368**: 407–15. https://doi.org/10.1056/NEJMoa1205037

68 Cammarota G, Masucci L, Ianiro G *et al*. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection. *Aliment Pharmacol Ther* 2015; **41**: 835–43. https://doi.org/10.1111/apt.13144

69 Mamo Y, Woodworth MH, Wang T *et al*. Durability and long-term clinical outcomes of fecal microbiota transplant treatment in patients with recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2018; **66**: 1705–11. https://doi.org/10.1093/cid/cix1097

70 Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. *Clin Infect Dis* 2011; **53**: 994–1002. https://doi.org/10.1093/cid/cir632

71 Youngster I, Mahabamunuge J, Systrom HK *et al*. Oral, frozen fecal microbiota transplant (FMT) capsules for recurrent *Clostridium difficile* infection. *BMC Med* 2016; **14**: 134. https://doi.org/10.1186/s12916-016-0680-9

72 Furuya-Kanamori L, Doi SA, Paterson DL *et al*. Upper versus lower gastrointestinal delivery for transplantation of fecal microbiota in recurrent or refractory *Clostridium difficile* infection: a collaborative analysis of individual patient data from 14 studies. *J Clin Gastroenterol* 2017; **51**: 145–50. https://doi.org/10.1097/MCG.0000000000000511

73 Hvas CL, Dahl Jorgensen SM *et al*. Fecal microbiota transplantation is superior to fidaxomicin for treatment of recurrent *Clostridium difficile* infection. *Gastroenterology* 2019; **156**: 1324–32.e3. https://doi.org/10.1053/j.gastro.2018.12.019

74 Leffler DA, Lamont JT. *Clostridium difficile* infection. *N Engl J Med* 2015; **372**: 1539–48. https://doi.org/10.1056/NEJMra1403772

75 de Groot P, Scheithauer T, Bakker GJ *et al*. Donor metabolic characteristics drive effects of faecal microbiota transplantation on recipient insulin sensitivity, energy expenditure and intestinal transit time. *Gut* 2020; **69**: 502–12. https://doi.org/10.1136/gutjnl-2019-318320

76 Chen D, Wu J, Jin D *et al*. Fecal microbiota transplantation in cancer management: current status and perspectives. *Int J Cancer* 2019; **145**: 2021–31. https://doi.org/10.1002/ijc.32003

77 Allen SJ, Wareham K, Wang D *et al*. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2013; **382**: 1249–57. https://doi.org/10.1016/S0140-6736(13)61218-0

78 Goldenberg JZ, Yap C, Lytvyn L *et al*. Probiotics for the prevention of *Clostridium difficile*-associated diarrhea in adults and children. *Cochrane Database Syst Rev* 2017; CD006095. https://doi.org/10.1002/14651858.CD006095.pub4

79 Surawicz CM, McFarland LV, Greenberg RN *et al*. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*. *Clin Infect Dis* 2000; **31**: 1012–7. https://doi.org/10.1086/318130

80 McFarland LV, Surawicz CM, Greenberg RN *et al*. A randomized placebo-controlled trial of *Saccharomyces boulardii* in combination with standard antibiotics for *Clostridium difficile* disease. *JAMA* 1994; **271**: 1913–8. https://doi.org/10.1001/jama.1994.03510480037031

81 Wullt M, Hagslätt ML, Odenholt I. *Lactobacillus plantarum* 299v for the treatment of recurrent *Clostridium difficile*-associated diarrhoea: a double-blind, placebo-controlled trial. *Scand J Infect Dis* 2003; **35**: 365–7. https://doi.org/10.1080/00365540310010985

82 Barker AK, Duster M, Valentine S *et al*. A randomized controlled trial of probiotics for *Clostridium difficile* infection in adults (PICO). *J Antimicrob Chemother* 2017; **72**: 3177–80. https://doi.org/10.1093/jac/dkx254

83 Munoz P, Bouza E, Cuenca-Estrella M *et al*. *Saccharomyces cerevisiae* fungemia: an emerging infectious disease. *Clin Infect Dis* 2005; **40**: 1625–34. https://doi.org/10.1086/429916

84 Appel-da-Silva MC, Narvaez GA, Perez LRR *et al*. *Saccharomyces cerevisiae* var. *boulardii* fungemia following probiotic treatment. *Med Mycol Case Rep* 2017; **18**: 15–7. https://doi.org/10.1016/j.mmcr.2017.07.007

85 Shen NT, Maw A, Tmanova LL *et al*. Timely use of probiotics in hospitalized adults prevents *Clostridium difficile* infection: a systematic review with meta-regression analysis. *Gastroenterology* 2017; **152**: 1889-–900.e9. https://doi.org/10.1053/j.gastro.2017.02.003

86 de Bruyn G, Gordon DL, Steiner T *et al*. Safety, immunogenicity, and efficacy of a *Clostridioides difficile* toxoid vaccine candidate: a phase 3 multicentre, observer-blind, randomised, controlled trial. *Lancet Infect Dis* 2021; **21**: 252–62. https://doi.org/10.1016/S1473-3099(20)30331-5

87 Kokai-Kun JF, Roberts T, Coughlin O *et al*. Use of ribaxamase (SYN-004), a β-lactamase, to prevent *Clostridium difficile* infection in β-lactam-treated patients: a double-blind, phase 2b, randomised placebo-controlled trial. *Lancet Infect Dis* 2019; **19**: 487–96. https://doi.org/10.1016/S1473-3099(18)30731-X