Diagnostic and therapy of severe *Clostridioides difficile* infections in the ICU

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Purpose of review
The purpose of the review is to provide all the recent data focusing on the diagnostic and treatment of *Clostridioides difficile* infection in patients admitted in the ICU.

Recent findings
In the ICU, diagnosis remains complicated with a large number of alternative diagnosis. The treatment classically relies on vancomycin but fidaxomicin and fecal microbiota transplantation are now potential solutions in selected indications.

Summary
Data on ICU-related CDI remain limited and conflicting. To date, there is no unique and simple way to obtain a diagnosis for CDI, the combination of clinical signs and a two-step testing algorithm remains the recommended gold-standard. Two molecules can be proposed for first line treatment: vancomycin and fidaxomicin. Although metronidazole may still be discussed as a treatment option for mild CDI in low-risk patients, its use for ICU-patients does not seem reasonable. Several reports suggest that fecal microbiota transplantation could be discussed, as it is well tolerated and associated with a high rate of clinical cure. CDI is a dynamic and active area of research with new diagnostic techniques, molecules, and management concepts likely changing our approach to this old disease in the near future.

Keywords
Clostridioides difficile, fecal microbiota transplantation, fidaxomicin, ICU, vancomycin

INTRODUCTION

Over the last decade, *Clostridioides difficile* infection (CDI) has become one of the most important infections worldwide and the most common healthcare-associated infection in North America. CDI is associated with a wide spectrum of presentations ranging from mild infection to fulminant colitis. Prevention of recurrences is the key issue for CDI management, yet in ICU patients, clinical cure is the priority where, as for the most severe cases, the vital prognosis is at stake. Defining severity of CDI is challenging as several classification systems have been proposed, and severity provides the basis for the choice of treatment. In this review, we will focus on the epidemiology, the diagnosis, and the treatment of CDI in the ICU.

EPIDEMIOLOGY OF *CLOSTRIDIOIDES DIFFICILE* IN THE ICU

CDI effects approximately 14.7/10 000 persons in the United States [1] and a growing number of patients in Europe (4.1/10 000 persons in 2008 and 7/10 000 persons in 2012–2013) [2,3]. In line, numbers of CDI are increasing in Asia and have, for instance been estimated at 7.4/10 000 persons in Japan [4]. In a recently published systematic review on the global burden of CDI, including 229 publications with data from 41 countries, the overall rate of healthcare facility-associated CDI was estimated at 2.24 [95% confidence interval (CI) 1.66–3.03] per

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Curr Opin Crit Care 2020, 26:450–458
DOI:10.1097/MCC.0000000000000753

KEY POINTS

- No single currently available commercial test can serve as a stand-alone test for diagnosing CDI.
- To optimize the diagnosis of CDI, two-step algorithms are currently recommended.
- Metronidazole is not an option in the ICU but can be administered intravenously associated to vancomycin in fulminant episodes.
- FMT could be a reasonable option to treat severe-complicated CDI but further studies are needed.

1000 admission annually and 3.54 (95% CI 3.19–3.92) per 10 000 patient-days annually [5] with rates being generally higher in North America and among the elderly. Estimated rates for CDI with onset on the ICU were notably higher at 11.08 per 1000 admissions annually (95% CI 7.19–17.08). On the basis of a systematic review and meta-analysis including 80 835 ICU patients from 22 studies, CDI may affect 2% (95% CI 1–2%) of all ICU patients and *C. difficile* was identified as the causative pathogen in 11% (95% CI 6–17%) of patients presenting with diarrhea [6]. Pooled prevalence was highest in North America (2%, 95% CI 1–4%), followed by Asia (3%, 95% CI 1–2%), and Europe (1%, 95% CI 1–2%). In conclusion, the literature points to a higher burden of CDI in ICU patients as compared with general cohorts of hospitalized patients. Data on mortality of CDI in ICU patients is conflicting, with some studies pointing to an increased risk of death and others rejecting it [7–9]. Yet, in a meta-analysis, overall pooled hospital mortality of patients with CDI differed significantly from mortality of ICU patients without CDI (32%, 95% CI 26–39% as compared with 24%, 95% CI 14–36%) and was not explained by differences in the morbidity score (Acute Physiology and Chronic Health Evaluation II) on ICU admission, suggesting significant attributable mortality [6]. Conflicting data on attributable mortality may be related to varying distributions of different ribotypes of *C. difficile* [10]. On the basis of reports of a greater potential for toxin production and multidrug resistance profiles [11,12], most of the evidence regarding increased virulence of specific ribotypes derives from settings in which such strains emerged rapidly, often resulting in outbreaks. In endemic settings, the association of disease severity has not been confirmed [13].

ICU patients are at increased risk for developing CDI because of an accumulation of predisposing factors [14] and most importantly, antibiotics [15], with up to 60% of ICU patients having concomitant infections [16]. Furthermore, colonization with toxigenic *C. difficile* on admission has been identified as an independent predictor of CDI in ICU patients [17]. This later association possibly points to the increasing importance of community-related, rather than healthcare-related acquisition of *C. difficile* [18]. Incidence of community-acquired CDI has almost doubled over the last decade [19] and has been estimated to account for 14.5% of all confirmed CDI cases among 5260 admitted to the ICU, the remainder being hospital-acquired (17.4%) or ICU-acquired [9]. Relating thereto, length of hospital and ICU stay have been associated with an increased risk for developing CDI [6]. Although surveillance studies commonly report categorization of CDI in respect to the onset and association of disease (i.e. community vs. healthcare) based on standardized criteria, such categorizations are of limited value to investigate sources of *C. difficile* acquisition. Both loss of colonization resistance and nosocomial transmission by direct or indirect contact or selection pressure exerted by prolonged administration of antimicrobials in the setting of community-acquired colonization may result in healthcare-associated CDI [20]. Thus, monitoring hospital-onset CDI cases followed by typing of strains in the context of the occurrence of clusters with an epidemiological link is needed to detect outbreaks and identifying gaps in infection prevention and control measures [21]. An ever-increasing body of evidence, however, supports antibiotic stewardship measures being the most important strategy to reduce CDI rates, impacting both loss of colonization resistance and selection pressure [22,23].

CLOSTRIDIOIDES DIFFICILE INFECTION DIAGNOSIS

The diagnosis of *C. difficile* infection (CDI) has gained more attention since the emergence and spread of hypervirulent strains, such as ribotype 027, which have contributed to the increased morbidity and mortality of infection worldwide. Nevertheless, in 2012, the multicenter EUCLID study showed that 23% of CDI were still not diagnosed in Europe because of an absence of clinical suspicion [2].

According to European and North American guidelines, a CDI case is defined by the following criteria [24,25▪]:

(1) Clinical signs of infection (diarrhea, ileus, toxic megacolon) and a stool test positive for toxins or toxigenic *C. difficile*, without evidence of another cause of diarrhea

(2) Presence of pseudomembranes during rectosigmoid or colonoscopic examination or histopathologic findings revealing pseudomembranous colitis.

The endoscopic diagnosis of CDI is usually specific (although other pathogens can be sometimes implicated in pseudomembranous colitis [26]) but not very sensitive. A negative result does not exclude CDI as pseudomembranes can be absent at the early stage of the disease or during mild forms of antibiotic-associated diarrhea. Most of the time, the CDI diagnosis relies on laboratory tests.

Many tests detecting different targets are currently available for the diagnosis of CDI [27▪]. They usually fall into two major categories: those that detect free toxins (toxin A and/or toxin B) in fecal samples [enzyme immunoassays (EIAs) and stool cytotoxicity test (CTA)] and those that detect the organism [toxigenic culture, glutamate dehydrogenase (GDH), and nucleic acid amplification tests (NAATs)].

CTA is a reference method for detecting free toxins in the stools. This method consists in inoculating a stool filtrate on a cell culture and observing a specific cytopathic effect (CPE). CPE is characterized by cell rounding and results from the disruption of the actin cytoskeleton by toxins. Although this technique is highly sensitive (in the order of the toxin picogram), it has been abandoned progressively due the long turn-around time to get the result and the need of having cell culture facilities.

EIA tests include microwell immuno-enzymatic (ELISA) and immunochromatographic techniques. They detect both toxins A and B, with or without differentiation. They are easy-to-use and more rapid but their sensitivity ranges from 29 to 86% compared with CTA, which prevents their use as a standalone method for CDI diagnosis [24,25▪]. More recently, ultrasensitive assays detecting free toxins A and B has been developed by several companies using the single molecule array technology (SIMOA). The SIMOA tests have a higher sensitivity than currently available toxin EIA and have the potential in the future to improve and simplify the CDI diagnosis [28–30].

NAAT are based on real-time PCR, isothermal loop amplification or microarray technologies. They detect a wide variety of targets and have the advantage of being very fast and sensitive (average sensitivity of 96% compared with toxigenic culture) [31]. However, the presence of a toxigenic strain does not imply that the patient is infected as approximately 3% of the general population are asymptomatic carriers of a *C. difficile* toxigenic strain.

Toxigenic culture is a two-step method where *C. difficile* strains are first isolated on a selective medium and then the isolates are tested for their ability to produce toxins *in vitro*. Although the time to obtain a result is too long for routine diagnosis (2 days or more), Toxigenic culture is very sensitive, and isolation of the strain is essential for determining its susceptibility to antimicrobials. This method is generally used as a gold standard when evaluating new NAAT assays.

GDH is a metabolic enzyme produced by all *C. difficile* strains (including toxigenic or nontoxigenic strains). It can be detected by ELISA or immunochromatographic tests. These tests display an excellent negative predictive value (NPV) [32] so that a negative result can rule out the diagnosis of CDI. However, a positive test must be confirmed by a more specific test detecting free toxins in stools.

No single currently available commercial test can serve as a stand-alone test for diagnosing CDI. Indeed, EIA methods detecting free toxins in stools are very specific but often lack sensitivity, which can lead to an underdiagnosis of CDI. Conversely, tests, such as NAAT and toxigenic culture, detecting the presence of toxigenic strains (irrespective of the presence of free toxins in stools) are more sensitive but less specific, which can lead to an overdiagnosis of CDI. Therefore, to optimize the diagnosis of CDI, two-step algorithms are currently recommended [24,25▪]. The first test must display a high NPV to reliably exclude patients without CDI. If positive, a second test with a high positive-predictive value (PPV) should be used. If positive, the patient is considered as truly infected. Feces samples without free toxins but with positive NAAT results need clinical evaluation to discern CDI from asymptomatic carriage.

Recent publications suggest that the bacterial load of *C. difficile* (evaluated by the cycle threshold of NAAT as a surrogate marker) is generally higher in patients with CDI compared with carriers and might serve as predictor of toxin presence [33,34].

To optimize the diagnosis of CDI, some general rules should be implemented to reduce inappropriate testing. First, it is important to take stool samples prior to initiation of CDI treatment. Any empirical treatment for CDI can lead to false negative test results [35]. Second, a test-of-cure should not be carried out at the end of the treatment. Actually, 30–40% of patients who are considered clinically cured are still positive for *C. difficile* toxins or culture at the end of the treatment [36]. Third, many guidelines recommend to implement criteria for stool selection to avoid detection of asymptomatic carriers. Only diarrheic stools (defined as stool taking the shape of the container) should be accepted by the laboratory. According to the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines, if clinical and laboratory personnel agree to not

submit stool specimens of patients receiving laxatives and to submit only stool samples from patients with an unexplained clinical diarrhea (≥3 unformed stools in 24 h), then NAAT can be used as a stand-alone test.

DEFINITION OF SEVERITY

The definition of severity of CDI is not yet consensual varying among the scientific societies [25▪,37,38] and clinical trials [39–41]. As treatment decisions are based on severity, these definitions are of great importance. A 3-year cohort study performed on 233 CDI patients showed that the frequency of severe CDI ranged from 11.6 to 59.2% depending on the definition [42]. In the latest IDSA/SHEA guidelines, only leucocyte number and renal function define severity [25▪], the previous article showed that serum albumin could also be an important factor to define severity, although this factor has been shown to be independently linked to mortality in septic patients without CDI [43]. Finally, the characteristics of the patient are also important to correctly assess the severity, for example, we have shown that for hematological patients, IDSA/SHEA-criteria could underestimate the severity and the potential risk of unfavorable outcome [44]. Using leucocytes and renal definitions, as recommended by the IDSA/SHEA [25▪], seems a reasonable approach combining measures easy to obtain in all patients and supported by a large number of studies. In the next section of this manuscript, we will therefore consider severity according to this definition.

TREATMENT OF *CLOSTRIDIOIDES DIFFICILE* INFECTION IN THE ICU

Treatment of CDI includes two distinct profiles of patients, CDI developing in the ICU and CDI requiring ICU admission. Although the entire spectrum of disease manifestations can be present in CDI developing during an ICU stay, severe and complicated forms lead to ICU admission. In 2018, the IDSA and SHEA provided an update of the clinical practice guidelines for CDI [25▪]. Episodes are classified as nonsevere, severe (defined by leukocytosis or serum creatinine), or fulminant (hypotension, shock, ileus, megacolon).

ORAL ANTIBIOTIC TREATMENT IN THE ICU

Mild-to-severe episode

According to the IDSA/SHEA guidelines, initial nonsevere episodes can be treated with vancomycin or fidaxomicin; metronidazole is an alternate if these two agents are not available [25▪]. Metronidazole is not an option for severe episodes but can be administered intravenously associated to vancomycin in fulminant episodes. To shortly address the issue of vancomycin and metronidazole in the ICU, a limited number of studies are available. A meta-analysis of randomized controlled trials extracted only five studies, in the subgroup analysis on severity, the clinical effects of vancomycin were higher than in metronidazole in severe cases [45]. Interestingly, these data are related to only two of the five considered trials [39,46]. A retrospective, propensity-matched cohort study evaluated a total of 47 471 patients treated by vancomycin or metronidazole [47]. In the subcohort of 3130 patients with severe disease, vancomycin significantly reduced the risk of all-cause 30-day mortality.

Fidaxomicin was introduced for treatment of CDI and compared with vancomycin with two pivotal publications [40,41]. In both of these multicentric, double-blind, randomized noninferiority trials, no difference was observed in the subgroup of severe patients analyzing clinical cure as well as sustained clinical response, suggesting this molecule could be an alternative in severe patients. In proven CDI, a study compared 20 ICU patients with 30 patients treated in medical wards and showed that the response to fidaxomicin was comparable between these two groups [48]. A retrospective multicentric cohort study with propensity score-matched analysis in severe CDI compared 213 patients treated with fidaxomicin to 639 patients treated with oral vancomycin [49]. No difference was found on the primary outcome, which combined clinical failure and recurrence. A comparative efficacy of treatments analysis was performed using a network meta-analysis, including 24 trials with a total of 5361 patients [50]. In severe infections, vancomycin and fidaxomicin resulted in comparable outcomes. Thus, it seems reasonable to propose either vancomycin or fidaxomicin as first line drugs for ICU patients (Fig. 1).

Complicated episode

The IDSA/SHEA guidelines recommend the administration of topical vancomycin with intravenous metronidazole. The evidence supporting this recommendation is not very high. Experimental data failed to show a difference [51], and a systematic review and meta-analysis also failed to show superiority of the combination treatment, but, because of the low number of studies performed, the combination treatment was not tested in each severity group [52]. A single-centre retrospective observational study compared critically ill patients receiving oral

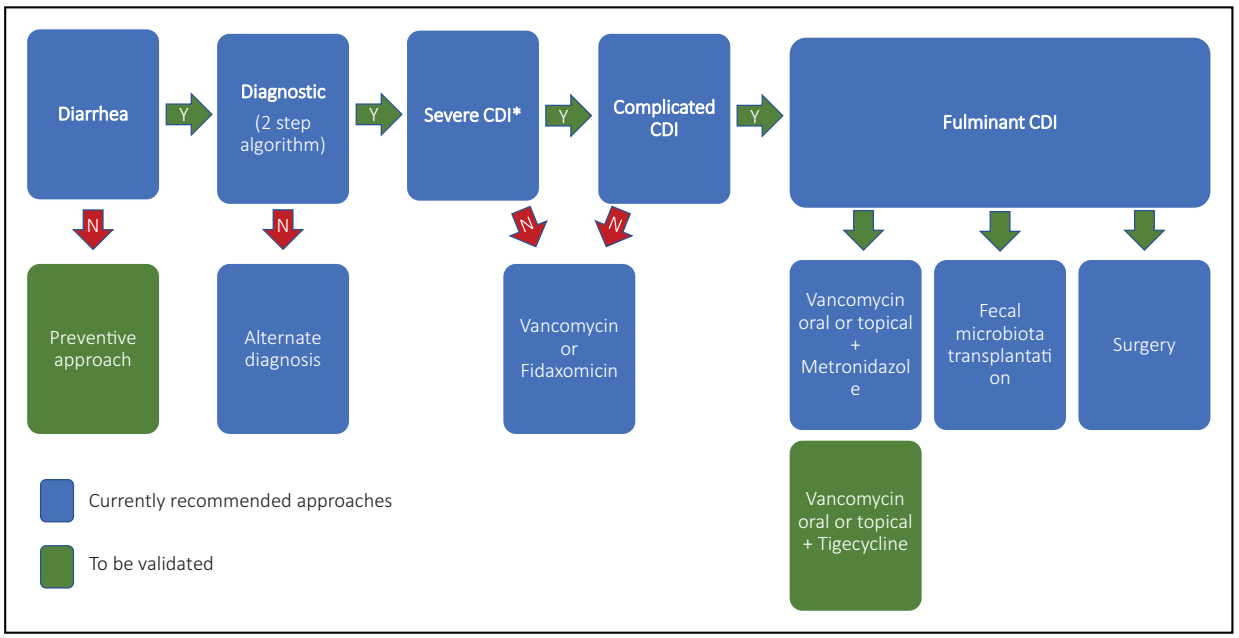

FIGURE 1. Algorithm for the treatment and prevention of *Clostridioides difficile* in the ICU. Y, yes; N, no. *Severe *Clostridioides difficile* (CDI) is defined according the 2018 Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of America (SHEA) guideline [25▪].

vancomycin to patients receiving oral vancomycin combined with intravenous metronidazole [53]. Eighty-eight patients were included, mortality was 36.4 and 15.9% in the monotherapy and combination therapy groups, respectively ($P = 0.03$). Even though the patients were not clearly classified according to the IDSA/SHEA guidelines into severity groups, this study suggests that a combined treatment is associated with a better outcome in ICU patients. Moreover, although renal function was comparable between the two groups, leucocyte counts were significantly higher in the combination group (13.8 vs. 20.2 cells/μl, $P = 0.004$), suggesting more severe CDI, and thus reinforcing better outcome for combined treatment. We do not have currently any data on the use of fidaxomicin in complicated forms, and this drug is not approved in this indication. Intravenous immunoglobulin has also been proposed in CDI but the clinical data remain very limited [54–56]

INTRACOLONIC ANTIBIOTIC TREATMENT IN THE ICU

In complicated forms of CDI, including the presence of ileus or megacolon, where oral drug administration is not possible, administration of adjunctive intracolonic vancomycin has largely been proposed [25▪] to be delivered by an endoscopic procedure [57]. A retrospective chart review of 696 patients showed that the group with intracolonic vancomycin had higher rates of toxic megacolon, ICU admission and colectomy but maintained a similar mortality suggesting a potential protecting effect of locally administrated vancomycin [58]. A single-centre retrospective study included 47 patients treated with intracolonic vancomycin [59]. Overall, 70% (33/47) of the patients responded to adjunct of intracolonic vancomycin with complete resolution of symptoms without surgery. Another retrospective case–control study identified 24 ICU patients with adjunctive per rectum vancomycin [60] found different results and showed that this approach neither reduced the need for colectomy nor mortality. Overall, the level of evidence remains low and well conducted trials are still needed to clearly evaluate the potential advantage of locally delivering vancomycin in this subgroup of patients.

ALTERNATE ANTIBIOTIC TREATMENT IN THE ICU

Tigecycline is broad spectrum protein synthesis inhibitor with a strong antimicrobial activity against *C. difficile* [61]. Several case report or small series have reported a potential effect of tigecycline in addition to the therapeutic regimen in severe and complicated CDI [62–66]. On a larger population, a single-centre retrospective cohort study compared 62 patients who received both tigecycline and vancomycin to 204 patients receiving only vancomycin [67]. In the propensity score-based analysis, the odds

ratio of favorable outcome was 0.92 (95% CI 0.60–1.44; $P = 0.74$) leading to the conclusion that adding tigecycline to standard therapy did not change rates of clinical cure. A well designed protocol is still needed to conclude on the potential effect of this molecule in severe and/or complicated forms of CDI but there is no strong rationale to propose this molecule as first-line treatment in complicated forms (Fig. 1).

FECAL MICROBIOTA TRANSPLANTATION IN THE ICU

FMT has been largely proposed by international guidelines [25▪,37] for treatment of recurrent CDI following the pivotal trial of Van Nood *et al.* [68]. In the ICU, several reports suggest that FMT can also be a treatment option [69–72], even for severe-complicated CDI including toxic megacolon [73,74], or CDI in immunosuppressed patients [75]. A small series of 29 patients with severe and severe/complicated CDI showed that FMT reached an overall treatment response in, respectively, 100% (10/10) and 89% (17/19) for each group [76]. In the long-term, a multicenter follow-up study analyzed 17 patients with severe and/or complicated forms treated with FMT [77]. FMT was well tolerated in this cohort with a primary cure rate of 88.2%. A cohort of 57 patients with severe and severe complicated CDI was treated with FMT, 91% (52/57) experienced clinical cure at 1 month with 100% for severe ($n = 19$) and 87% for severe complicated ($n = 33$) [78]. There was no serious adverse event. These data suggest that FMT could be a reasonable option to treat severe-complicated CDI (Fig. 1).

SURGERY

Colon-sparing diverting ileostomy with colonic lavage has been proposed as an alternative to colectomy in the treatment of severe complicated CDI [79]. In this study with a historical control group that underwent colectomy, 42 patients were treated using this surgical approach. This strategy resulted in reduced mortality compared with the historical population (19 vs. 50%) and preservation of the colon was achieved in 39/42 patients (93%). Interestingly, a retrospective review of patients treated surgically for severe complicated CDI compared 30-day mortality, 1-year mortality, and colon preservation in 10 patients with loop ileostomy and colonic lavage vs. 13 patients with total abdominal colectomy [80]. There was no difference in mortality in both time points, but loop ileostomy allowed preservation of the colon in all six surviving patients (Fig. 1).

PREVENTION OF *CLOSTRIDIOIDES DIFFICILE* INFECTION IN THE ICU

The ICU is associated with the exposition to large numbers of risks factors for CDI and it could be interesting to test a preventive approach for these patients exposed to large spectrum antibiotics, proton pump inhibitors, and other potential inductors of dysbiosis.

PASSIVE AND ACTIVE IMMUNIZATION

(1) Passive immunization: a randomized, double-blind, placebo-controlled study evaluated two monoclonal antibodies targeting *C. difficile* toxin A and B in 200 patients initially treated with metronidazole or vancomycin [81]. The rate of recurrence significantly decreased from 25 to 7% for patients treated with the antibodies. A phase 3 trial, involving 2655 patients with primary or recurrent CDI, showed that bezlotoxumab reduced the recurrence of infection from 28 to 17% [82].
(2) Active immunization: three vaccines are currently in phase 2 and 3 clinical trials. A formalin-inactivated toxoid-based vaccine is currently the most advanced [83,84]. Several phase 3 trials have been initiated (NCT00772343, NCT03090191). VLA84 is a recombinant fusion protein with epitopes of toxin A and B [85]. A DNA vaccine [86,87] has been recently proposed with interesting results in animal models.

Although these preventive approaches are quite attractive, a cost–benefit analysis has to be performed for Bezlotoxumab in the ICU, and for vaccines, data on target populations benefiting most are lacking. Immunotherapy has also been proposed but remains at the experimental level [88].

DRUGS

Rifaximin and other microbiota-based drugs have been proposed to prevent CDI [89–91] but there is no data available for ICU patients.

CONCLUSION

CDI in the ICU remains challenging at all levels, diarrhea is frequently encountered and can be multifactorial, CDI being one of the most important potential causes. The laboratory diagnosis does not rely on one test but must be combined with clinical data to optimize both positive and negative predictive values of the test performed. This approach remains the gold standard for diagnosis. In ICU patients, the use of metronidazole questionable

and both vancomycin and fidaxomicin should be proposed for first-line treatment. For severe-complicated forms, the combination of topical vancomycin and systemic metronidazole is still proposed, with many reports suggesting that FMT as an excellent, well tolerated, and efficient treatment option, potentially reducing the need for surgery. There is no data to promote an optimal preventive approach (i.e. immunization or preventive treatment) in the ICU. The figure proposes an algorithm for the management of CDI in the ICU.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

B.G. is a member of MSD Advisory Boards for C. difficile, of a Pfizer Antiinfectives Advisory Board. F.B. received Grants from Astellas, Anios, MSD, Biomérieux, Quidel, Cubist, Biosynex, GenePoc, Personal fees from Astellas, Pfizer, MSD, Danone, and Nonfinancial support from Astellas, Pfizer, Anios, MSD. S.T.S. is a member of the Astellas and MSD Advisory Boards for C. difficile, of the Pfizer Antiinfectives Advisory Board and the Menarini Scientific Advisory Board. She reports grants from the Swiss National Science Foundation NRP72 (407240_167060), the Gottfried und Julia Bangerter-Rhyner Stiftung, the Fonds zur Förderung von Lehre und Forschung der Freiwilligen Akademischen Gesellschaft Basel, and the Jubiläumsstiftung from Swiss Life.

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Very nice review of the pitfalls of diagnosis and the good practice to obtain a reliable conclusion.

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