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Cutting edges in Clostridioides difficile infections

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Summary

Clostridioides difficile is the most common cause of hospital-acquired diarrhoea and one of the most important causes of hospital-acquired infections. It results in significant morbidity, mortality and economic burden - especially in the context of recurrent infections. After initial antibiotic therapy of a *C. difficile* infection, recurrence occurs in about 20% of all patients, which increases the risk of further recurrence to about 45%.

Traditional therapeutic options for treatment of *C. difficile* infection include metronidazole or vancomycin. Newer therapy options such as fidaxomicin, the administration of monoclonal antibodies or faecal microbiota transplantation demonstrate significant advantages over traditional therapies, particularly regarding the reduction of the recurrence rate.

This article highlights the main differences between the recommendations of the Swiss Society for Infectious Diseases on the management of *"Clostridioides difficile* infection" and the IDSA/SHEA reference guideline "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)" and discusses some important challenges in -treatment of *C. difficile*.

Introduction

In Europe, the incidence of *Clostridioides difficile* infection (CDI) is not well defined, as systematic surveillance is not established uniformly and underreporting is likely. Multinational studies estimate incidence rates of four to seven cases of CDI per 100,000 patient-days across Europe, with a wide variation across countries and healthcare facilities (range 0.0 to 36.3 and 0.7 to 28.7, respectively) [1, 2]. The incidence rate in participating Swiss hospitals was within the European average (mean rate of 4.8 per 10,000 patient-days) [1]. Older reports demonstrated lower incidence rates of 2.3 and 2.8 in Swiss hospitals [3–5], but a more recent point-prevalence study suggests a higher burden, reporting 5.7 to 11.4 cases per 10,000 patient-days, depending on the sampling period and testing methodology [6]. In Switzerland, reporting of CDI is not mandatory, and surveillance is limited mainly to acute care hospitals. Thus, national efforts aiming at improved surveillance and management of CDI are being initiated.

In 2019, a national expert panel developed clinical guidelines for the management of CDI in Switzerland. A series of guidelines of the Swiss Society for Infectious Diseases (SSI) are being developed as part of the national strategy against antimicrobial resistance (StAR). Guidelines are based on international guidelines whenever available. For *C. difficile*, the 2017 IDSA Clinical Practice Guidelines for *C. difficile* Infection in Adults and Children [7] were used as reference. Here we review the treatment recommendations made for *C. difficile* infection in the SSI guidelines. We highlight the main differences between the Infectious Diseases Society of America (IDSA) / Society for Healthcare Epidemiology of America (SHEA) reference guideline and the Swiss recommendations, particularly regarding the following:

1. The use of metronidazole for treatment of non-severe CDI
2. Prolonged vancomycin therapy (pulsed or tapering regimens)
3. Indications for the use of fidaxomicin
4. Indications for the use of bezlotoxumab

Trends in therapy of C. difficile infection

Most clinical expertise in CDI management is derived from treatment with metronidazole and vancomycin, early randomised controlled trials demonstrating equal efficacy of both drugs [8, 9]. Because of the lower price of metronidazole and concerns of selecting resistant intestinal microorganisms, in particular vancomycin-resistant enterococci (VRE), metronidazole was given preference over vancomycin as first-choice therapy for treatment of CDI in the following years and decades, as reflected in previous guidelines [10]. Subsequent studies could not prove a clear superiority of either of the two substances, and interpretation of existing evidence remains complex due to very heterogeneous study designs and large variation between settings, and diagnostic and antibiotic regimens compared. More recent studies on larger cohorts stratified by disease severity suggested superiority of vancomycin over metronidazole, particularly for the treatment of severe CDI [11, 12]. Pooled analyses further strengthen the benefits of vancomycin over metronidazole [13, 14], even for treatment of mild infections.

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Although initial treatment response is high for both drugs, treatment failures are possibly more prevalent in patients treated with metronidazole than with vancomycin. Systematic reviews including randomized controlled trials only, as well as meta-analyses with more liberal inclusion criteria, conclude that vancomycin is superior to metronidazole regarding symptomatic cure (metronidazole 72% and vancomycin 79% [13] or treatment failure (22.4% for metronidazole and 14.2% for vancomycin [14]). However, the effect regarding recurrence rates is less clear: one meta-analysis reported recurrence rates of 27.1% and 24.0% following CDI treatment with metronidazole and vancomycin, [14]. Nelson et al. concluded, that available data are insufficient to draw firm conclusions.

There may be a more immediate effect with vancomycin in terms of symptom duration (time to response 3.0 days for vancomycin and 4.6 days for metronidazole), and symptom persistence with metronidazole has been reported in some cases [15, 16]. However, few randomised controlled trials have focused on symptom duration, and existing data failed to show a relevant difference in time to symptom resolution for the two drugs [17]. Fidaxomicin appears to result in more rapid symptom control (median time to resolution of diarrhoea 3.0 days with standard dosage) and sustained suppression of toxin production of the remaining bacteria in the post-treatment period [18, 19].

Strong evidence regarding eradication of *C. difficile* is still lacking, mainly because the microbiological resolution has not been reported consistently in the newer and larger trials [13]. Vancomycin shows rapid killing of vegetative bacteria and a steep fall of toxin levels in gut models. With only minimal absorption when given orally, it achieves high antibiotic concentrations in stool, avoiding most of the common adverse reactions experienced with its intravenous application. Since vancomycin is only effective against vegetative bacteria, *C. difficile* spores remain a possible reservoir for relapses and reappearing toxin levels are frequently reported in post-treatment follow up [20, 21]. In vitro data demonstrate high activity of metronidazole against *C. difficile*, but its efficacy in vivo might be limited to patients with severe inflammation. In the absence of inflammation, metronidazole is readily absorbed during digestive passage and reaches only low activity levels in the colon [23–26].

The significance of metronidazole for treatment of CDI

The 2017 IDSA guidelines have made significant changes regarding the recommendation for metronidazole use. Previously considered the drug of choice for the initial episode of mild-to-moderate CDI, metronidazole is currently restricted to settings where access to vancomycin and fidaxomicin is limited [7, 10].

In Switzerland, metronidazole is still the most widely used antibiotic for initial treatment of CDI [27, 28] and the SSI guideline continues to promote the use of metronidazole for patients with non-severe CDI, presenting with a first episode. Vancomycin is a universal treatment option for all patients with a first episode or a first relapse of CDI. In severe, complicated infection or critically ill patients, vancomycin is the only antibiotic recommended and might be accompanied by intravenous metronidazole therapy.

Prolonged vancomycin therapy

The evidence base for the recommendation to administer vancomycin as a tapered or pulse regimen has been classified as low in the IDSA guideline, resulting in a weak recommendation for this treatment approach (as compared with the recommendations of fidaxomicin for treatment of a first recurrence and faecal microbiota transplantation for a second or subsequent recurrence, both based on moderate quality of evidence). Therefore, contrary to the IDSA recommendations, the SSI guidelines do not promote any treatment to be administered for more than 10 days. Approaches using vancomycin as a tapered or pulsed regimen following CDI treatment are intended to suppress the bacterial load of *C. difficile* while allowing restoration of the normal gut flora during antibiotic-free intervals. Microbiological studies, however, do not support this hypothesis and suggest, to the contrary, that exposure to vancomycin might even delay recovery and prolong the susceptible period in which colonisation resistance [19, 29] is reduced.

Considerations regarding vancomycin-resistant enterococci

Vancomycin is used restrictively in Switzerland, one of the concerns being its potential for promoting colonisation with vancomycin-resistant enterococci (VRE) during treatment for CDI. Such concerns seem reasonable, given the increase in selection pressure during vancomycin treatment and the shared reservoir. However, strong evidence for causality of increased VRE colonisation following vancomycin therapy is lacking. Since most patients received systemic antibiotics prior to developing *C. difficile* infection and therapy, this common risk factor may have already resulted in higher VRE colonis–ation rates prior to treatment, with only a small impact of the actual antibiotic chosen [30–33]. In accordance, studies of vancomycin used for eradication therapy of asymptomatic carriers showed hardly any new colonisation with VRE [34, 35]. Data suggest that fidaxomicin reduces new colonisation and inhibits overgrowth in patients with established colonisation. As fidaxomicin shows less disruption of the intestinal flora paired with in vitro activity against VRE, it might be the preferred agent in patients at high risk for VRE acquisition. A drawback, however, is the regularly observed increase in minimum inhibitory concentrations of VRE to fidaxomicin [19, 22, 36] – the benefit in terms of decreasing selection pressure potentially favouring VRE survival in the healthcare environment may outweigh such concerns by far.

Fidaxomicin

Fidaxomicin is a newer oral antibiotic and a promising therapeutic option for CDI. In clinical trials, it showed higher cure rates and lower recurrence rates compared with vancomycin, representing significant improvements in important clinical endpoints [38, 39]. This effect is believed to be two-fold. With its narrower activity spectrum, fidaxomicin induces less disruption of intestinal flora, thus facilitating recovery of the microbiome. Fidaxomicin demonstrates rapid killing of vegetative *C. difficile* and inhibits spore recovery and toxin production [19, 22, 40]. Consequently, its use is increasingly promoted as the preferred therapy option for patients with a high risk of recur-

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rence or in patients with multiple episodes of CDI, as reflected in the IDSA guidelines [7]. It is not approved for severe or complicated CDI and its use in first episodes of mild and moderate CDI is limited by significantly higher costs compared with standard therapy options. Therefore, the SSI guidelines encourage the use of fidaxomicin mainly for patients with heightened risk for recurrence and in situations beyond first episode of infection.

Alternative treatment options

There are only a few treatment options available to reduce recurrence, namely antibiotic therapy with vancomycin or fidaxomicin for patients at high risk of recurrence, vancomycin tapering in patients with multiple recurrences, and faecal microbiota transplantation (in addition to antibiotic therapy) [7, 17]. The efficacy of stool transplantation in preventing recurrences has been clearly demonstrated [41], but many questions remain unanswered regarding implementation, especially regarding safety aspects, long-term effects by alterations of the microbiome composition, preliminary examinations and selection of the donor, and regulation.

In cases with refractory illness and lacking a faecal microbiota donor, adjunctive therapy with bezlotoxumab should be considered. Bezlotoxumab is a monoclonal antibody with high affinity to *C. difficile* toxin B and has been available in Switzerland since late 2017 for the prevention *C. difficile* relapses. Toxin B is responsible for the inflammation and cell damage caused by *C. difficile* and thus for the induction of colitis [42]. Two randomised placebo-controlled trials have shown that a single dose of bezlotoxumab (10 mg/kg body weight) given concomitantly with standard therapy (vancomycin, metronidazole or fidaxomicin) for *C. difficile* reduced the recurrence rate by 38% over 12 weeks. Primary clinical response remained unchanged [43]. The latter may be due to the fact that bezlotoxumab was not administered at the beginning of antibiotic therapy but instead after a median of 3 days. The favourable effect of bezlotoxumab on the recurrence rate is likely to be due to its potential reduction of epithelial damage to the intestinal mucosa while promoting the restoration of normal microbial activity [44], although the exact mechanism of action is not known.

The most frequent adverse event during the 12 weeks of follow up was heart failure, most likely caused by volume overload rather than a direct cardiotoxic effect of the drug [43, 45].

Although current IDSA guidelines do not take a position on the use of bezlotoxumab [7], the SSI panel has decided to include a recommendation for its use as an adjunctive therapy in high-risk patients. At the time of revision, bezlotoxumab was not yet available for the American market. Upcoming guideline updates will likely include a statement on the use of monoclonal antibodies for the treatment of CDI, as the substance has received approval from the US Food and Drug Administration in the meantime.

Conflicts of interest

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