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Editorial

Choice of treatment in *Clostridium difficile*-associated diarrhoea: Clinical practice guidelines (CPGs) or risk classifications[☆]



Elección del tratamiento en la diarrea asociada a *Clostridium difficile*: guías de práctica clínica (GPC) o clasificaciones de riesgo

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Clostridium difficile infection (CDI) is currently believed to be the primary cause of nosocomial diarrhoea in the developed world, and is becoming ever-more prevalent as an aetiological agent in community-acquired diarrhoea and healthcare-related infections.¹ Its pathogenic action can be attributed to the production of certain strains of toxin A and/or B in the presence of abnormal gut flora. This gives rise to gastrointestinal symptoms that can range from mild or moderate diarrhoea to pseudomembranous colitis, ileus and toxic megacolon.² This disease is particularly prevalent in certain epidemiological groups, such as hospitalised patients and the elderly, and is correlated with risk factors including the use of antibiotics and gastric acid suppressants, immunodeficiency or other gastrointestinal, neoplastic or cardiopulmonary comorbidities.³ CDI has sparked growing interest because of its association with healthcare and its impact on morbidity and mortality in immunosuppressed patients and the elderly.⁴

A growing number of studies on its prevalence, changes in clinical presentation and epidemiology have been published in recent years, with the identification of new risk factors. Although the frequency of CDI in Spain has not been sufficiently characterised, available data suggest that its prevalence is similar to neighbouring countries and is on the increase.⁵ In addition, the high and increasing use of broad-spectrum antibiotics in hospitals and in the domestic setting are factors that favour the growth of this disease. The emergence of the ribotype 027 strain has increased the incidence and severity of CDI in some countries. The recent emergence of the hypervirulent ribotype 027 strain in some Spanish hospitals led to significant, but controlled, outbreaks with a particular clinical and epidemiological profile.⁶ One in two episodes of CDI is not diagnosed in Spanish hospitals due to a lack of clinical suspicion or the use of insensitive diagnostic methods. In diagnostic microbiology, diagnostic algorithms are recommended based

on glutamate dehydrogenase detection and the molecular detection of the toxins' genes, with or without direct toxin detection. However, in stark contrast to the *underdiagnosis* of CDI, which has been identified in numerous targeted studies and which healthcare providers are becoming increasingly aware of,⁷ possible *overdiagnosis* of the infection has now been recognised due to the sensitivity and fine-tuning of microbiological detection techniques,⁸ particularly molecular tests, which can lead to confusion in certain cases where the appropriate clinical criteria are not applied.⁹

Recurrent CDI is one of the main complications associated with the infection, defined as the onset of a new CDI episode within eight weeks of a previous episode that was treated correctly and whose symptoms completely abated. About 85% of patients diagnosed with CDI respond adequately to antibiotic therapy, although around 20% of patients experience a recurrence of the disease in the following weeks. Recurrences have an enormous impact as they have been associated with increased mortality and higher costs.⁵ Recurrence is associated with the persistence of spores, an insufficient immune response and the loss of gut microbiota diversity.^{1,4} Recurrences, which account for 15–30% of all episodes, may be a new episode caused by the same strain (relapse), or a new infection caused by a different strain (reinfection). After suffering an initial recurrence, the likelihood of experiencing further relapses ranges from 35 to 50%. This risk of recurrence holds true for all subsequent recurrences.^{10–12} In up to 11% of cases, recurrences may manifest as a severe clinical condition associated with ileus or intestinal perforation. Patients who experience an initial recurrence are highly likely to suffer further recurrences (33–60%). Recurrences generally occur within the first month following treatment, although they can also manifest more than four months later.¹³ They are more common in patients over the age of 65 years and in patients who remain in hospital after the initial episode of CDI-associated diarrhoea. Other risk factors associated with the onset of recurrence are persistent abnormalities in gut flora (e.g. due to the continued administration of antibiotic therapy during and/or after the episode), the severity of the initial episode, inadequate immune response to *C. difficile* toxin A, having suffered previous episodes of the disease, interleukin-8 promoter polymorphisms or the continued concomitant administration of antacids. Recurrent CDI

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may be caused by the same initial *C. difficile* strain or by a new strain. Recurrences caused by the same strain tend to occur within 10–14 days of suspending targeted therapy against *C. difficile*, although cases up to four months later have also been reported. They are believed to be caused by the germination of *C. difficile* spores and not by the development of bacterial resistance to the antibiotic used. Reinfections tend to manifest later (about four weeks after suspending treatment) and are caused by the reexposure of patients with the same persistent risk factors that caused the initial episode and who remain hospitalised or within a healthcare setting. Early diagnosis of CDI episodes and their appropriate treatment is vital in order to improve the disease's prognosis and to take the appropriate measures to prevent transmission to other patients and to minimise the risk of recurrence.¹⁴

Although it is currently preferable to talk about management strategies, any drug used to treat CDI should look to meet or cover at least four objectives: Eliminate vegetative forms of *C. difficile*, block the production and activity of toxins, prevent or reduce sporulation and preserve or protect the normal microbiota or even promote its reconstitution. A formula that promotes or discourages the use of a particular treatment option can be constructed based on the success achieved in each of these aspects, the lack of relevant side effects and affordability.

The recommended treatment for CDI depends on the type of infection and patient characteristics. That is why CDI is classified into five therapeutic groups by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID)¹⁵ treatment guidelines, as well as by other similar guidelines issued by North American societies for other specialties: initial non-severe CDI, initial severe CDI, first recurrence of CDI (or high risk of recurrent disease), multiple recurrences and treatment of CDI when oral administration is not possible. According to these and other guidelines issued by scientific societies,¹⁶ oral vancomycin or fidaxomicin is the treatment of choice in the event of a first recurrence or when there is due cause to suspect that the patient could relapse or not respond well to metronidazole due to risk factors. The most effective treatment of second recurrences has been found to be faecal transplantation, after preparation with oral vancomycin for a number of days. Faecal transplantation (or faecal microbiota transplantation) involves the transfer of a sample of faeces from a healthy donor to the colon of the patient by colonoscopy, nasoduodenal tube or encapsulated faecal material. The recolonisation of the colon with the transplanted bacteria helps to eliminate toxigenic *C. difficile*, thereby preventing recurrence. A recent meta-analysis on more than 600 faecal transplantation patients found the long-term efficacy (≥ 90 days) of this treatment method to be 94.5%.¹⁷ A cost-effectiveness analysis of six strategies to treat CDI from the perspective of public insurer in the healthcare services of Ontario (Canada), and which used a decision analytic model to simulate the costs and lifetime health effects of each strategy, found faecal transplantation by colonoscopy to dominate all other strategies in the base case in a typical patient with up to three recurrences (18 weeks) (87% probability that it was the most beneficial strategy). The willingness-to-pay threshold was \$50,000/QALY (quality-adjusted life years) gained.¹⁸ However, in recurrent CDI, fidaxomicin was the most cost-effective option if faecal transplantation at a specific centre was unavailable, at an additional cost of \$25,968 per QALY gained, compared to metronidazole.

An alternative to transplantation is the administration of high-dose oral vancomycin in a gradual dose reduction regimen for four or more weeks, concluding with intermittent doses to eliminate both the vegetative and spore forms of *C. difficile* from the gut. The main drawback of this treatment, which has been used without always being fully evaluated, is that it may give rise to the onset of strains of vancomycin-resistant enterococci. For this reason, the introduction of new drugs against *C. difficile*, like fidaxomicin, which

has shown a greater recurrence rate reduction following treatment of an initial CDI episode than vancomycin, or even the design and testing of new administration strategies, such as extended-pulsed fidaxomicin, may achieve greater efficacy versus standard treatments. The recently-published results of the EXTEND study have shown that such strategies not only lead to a much higher sustained CDI cure rate, but also better recurrence prevention.¹⁹ In addition to the fidaxomicin pivotal and registration trials, results from “real-life” studies of fidaxomicin have also been very favourable in terms of reducing the number of recurrences in high-risk patients. In a recent study of the English National Health Service's aim to reduce the incidence of CDI to lower morbidity and mortality, robust real-world data were collected to understand the effectiveness of fidaxomicin in routine practice. The study, which collected data on CDI episodes occurring 12 months before and 12 months after the introduction of fidaxomicin from seven hospitals, concluded that the pattern of adoption of fidaxomicin appears to affect its impact on CDI outcome and clinical course, with maximum reduction in recurrence and all-cause mortality where it is used as first-line treatment.²⁰ It was also found to shorten the mean symptom resolution time from diagnosis and reduce the mean length of hospital stay, the number of readmissions and the ICU admission rate (although not at all hospitals). A reduction in *C. difficile* environmental contamination by hospitalised patients treated with fidaxomicin had already been demonstrated.²¹ The economic assessment of fidaxomicin for the treatment of CDI in special patient populations with cancer, concomitant antibiotic treatment or chronic kidney disease also found it to be a cost-effective treatment compared to vancomycin, according to the study's economic model and the premises considered.²²

Data from trials evaluating the use of a monoclonal antibody, bezlotoxumab, against *C. difficile* toxins, alongside patients' standard-of-care treatment for CDI episodes, have also recently been published.²³ Despite the implementation of an attractive combination therapy strategy (bezlotoxumab plus metronidazole, vancomycin or even fidaxomicin), with its additional associated costs, the rate of recurrence was still 17%, nowhere near the expectations established prior to the studies. Nevertheless, these results should be taken into account in the latest updates of CDI treatment recommendation guidelines. It should be remembered that the two main objectives of CDI treatment are, firstly, to cure the acute episode, and secondly, to reduce, delay or prevent recurrence.

In weighing up these two objectives and trying to achieve appropriate focus and scope in the treatment of CDI, clinicians who treat complicated or serious cases, or patients with a high risk of recurrence, should choose a strategy²⁴ that offers the best sustained clinical cure rate together with the lowest possible rate of recurrence, with the lowest acceptable ecological cost on faecal microbiota and the highest safety. In addition to microbiota restoration therapy, which involves the transplantation (or transfer) of faecal microbiota from healthy donors and whose efficacy has been demonstrated and proven, or the option of immunotherapy, which uses monoclonal antibodies that neutralise the toxins, the effectiveness of which has yet to be established,²⁵ a “pulse therapy” strategy could also be implemented, which involves administration of a treatment over time in an intermittent manner. With which drug? Rather than vancomycin, this should be administered with fidaxomicin as, according to information collected from clinical trials, cohort studies and “real-life” data, this is the most effective anti-*C. difficile* drug that is currently available to treat first recurrences and prevent future episodes.²⁶ This may enable us to improve disease management and further minimise CDI recurrences in high-risk patients²⁷ in whom the infection results in greater frailty, loss of autonomy, loss of individual and family quality of life, health system sustainability issues and high morbidity and mortality.

In order to choose the most appropriate drug or the most effective strategy or combination of strategies – as there is no reason why multiple-drug therapy should not be administered (see current treatment for tuberculosis or *Helicobacter pylori* infection, for example) – we need tools that can discriminate between treatments to help clinicians choose the best option. Clinical practice guidelines and their recommendations have traditionally been used for this purpose, despite the constant need to update them and include new evidence in an ever-changing digital world. This may have impacted on their versatility, their relevance to the present day, their application to the clinical and epidemiological setting and, ultimately, their suitability for reliably and safely guiding the various specialists responsible for CDI treatment. Far from offering actual help and practical advice, some guidelines have been known to cause greater confusion and perplexity through the endorsement of antagonistic, contradictory, anachronistic or even outdated recommendations.²⁸ Furthermore, one of the main limitations of guidelines is the variety of definitions of CDI and severity (or mildness) criteria proposed, as well as the wide-ranging risk of complications, risk factors for recurrence and, on occasions, CDI triggering factors, resulting in non-standardised guidelines that are completely diverse in content from one another. One potential technique introduced to mitigate these limitations has been the design and use of risk scores or classifications, many of which are intended to be used at the patient's bedside, which would have been designed in the evaluation of CDI severity criteria as regards the risk factors of recurrent CDI. They could be used both to discriminate between different CDI manifestations and as a predictive tool. It should be remembered that designing a good score is not easy and requires considerable clinical observation and specialist knowledge, particular expertise in selecting items and values, and significant mathematical and statistical support. The necessary derivation cohort should also be established, followed by the checking and “rolling-out” of the score in an appropriate validation cohort. This is to make it as easy as possible to apply it to our setting, our patients and to the “real world”. These predictive and discriminative tools could be used to guide the decision-making process, ensuring the best and most cost-effective drug or therapeutic strategy is chosen, at a time when both the financial crisis and healthcare costs influence the decisions taken by health managers and lead to the adoption of rather restrictive policies by medical facilities.

It is from this perspective and with this intention that the article by Vivancos-Gallego et al., on the use of a scoring system for prescribing fidaxomicin for CDI in the treatment of patients at a high risk of recurrence, is published in this edition of the EIMC (Infectious Diseases and Clinical Microbiology) journal.²⁹ Under the scoring system proposed by the authors, treatment with fidaxomicin was considered when patients with microbiologically-confirmed symptomatic CDI had a score ≥ 4 points. The variables considered were age (>65 years: 1 point; >80 years: 2 points), kidney failure ($\text{Cr} > 1.5 \text{ mg/dl}$: 1 point), modified Horn's index scores of 3 or 4 (1 point), prior episodes (1 episode: 1 point; 2 episodes: 3 points) and the need to continue antibiotic therapy (1 point). Despite the small number of patients (13) analysed in the series and the indication of recurrent CDI often in second or subsequent episodes, 71.4% of patients experienced no recurrences after treatment with fidaxomicin in the study period. The median age of patients enrolled was 80.5 years and one third were classified as severe episodes, although no cases of ribotype 027 were reported in the series. All these factors could have “stressed” the use of the scoring system and influenced the outcomes of treatment with fidaxomicin. The lack of any biomarkers (CRP) or additional analytical parameters (lactate, albumin, leucocyte count) among the evaluation variables of the episodes selected by the authors for their scoring system, as well as insufficient justification for their exclusion in the methodology, is striking, although it is likely that these

factors are related more to predicting severity and complications rather than the risk of recurrence. The outlined score is an interesting proposal although it has yet to be tested in complementary validation cohorts by the author's own research group or in other centres, as it could also not be guaranteed that the clinical decision-making tool was applied to the entire CDI cohort in this period or that everyone with a score ≥ 4 points was treated with fidaxomicin. More interesting still could be the experience published regarding the usefulness of fidaxomicin in first relapses (100% treatment success rate, 6/6), while the response rate fell drastically when used in subsequent relapses (55%; 5/9), notwithstanding the limited size of the series.

Although numerous other scores with different discriminatory and predictive parameters have been published in the literature, the purpose of this editorial is not to conduct an exhaustive comparison. Rather than to propose or endorse a specific scoring system, the real purpose of this article is to encourage the reasoned implementation of one or more of them. In the meantime, we eagerly await the chance to evaluate new more comprehensive, “refined” and precise predictive tools of CDI recurrence that calculate this risk more accurately, in order to facilitate a better, safer and above all more cost-effective choice of treatment for the patient and for the Spanish health system. Could this be the recently-published GEIH-CDI score – an authentic and Spanish clinical prediction tool to determine the risk of recurrence of CDI?³⁰

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