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A comprehensive approach for the patient with *Clostridium difficile* infection

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ABSTRACT

During the last decade there have been many changes and advances in the research on *Clostridium difficile* infection (CDI). We have improved diagnostic and therapeutic tools and, at the same time, we have learned that the CDI implies, especially in the most vulnerable patients, an important morbidity. CDI has traditionally been undervalued and it is widely dispersed in hospitals. Surely, there is inertness in its management and there are also broad areas of improvement. If we add to this the high cost of the new drugs and the practical difficulties to implement the faecal microbiota transplant, we realize that we may not be taking full advantage of all the opportunities to improve patient's outcomes. The implementation of policies that favour the supervision of all CDI cases by an expert in infectious diseases will contribute to a better global management of this important disease.

Key words: *Clostridium difficile*, recurrence, clinical prediction tools, management.

Valoración integral del paciente con infección por *Clostridium difficile*

RESUMEN

Durante la última década ha habido muchos cambios y avances en la investigación sobre la infección por Clostridium difficile (ICD). Han mejorado las herramientas diagnósticas y el tratamiento de la enfermedad al mismo tiempo que hemos aprendido que la ICD implica, especialmente en los pacientes más vulnerables, una importante morbilidad. La ICD ha sido tradicionalmente infravalorada y su atención médica está muy dispersa en los hospitales. Seguramente, hay una gran inercia en el manejo de esta enfermedad y, por ello, amplias áreas de mejora. Si a lo anterior sumamos el alto coste de los nuevos medicamentos y las dificultades prácticas para implementar el trasplante de microbiota fecal, es fácil concluir que no aprovechemos al máximo todas las oportunidades para mejorar los resultados clínicos que padecen ICD. La implementación de políticas que favorezcan la supervisión de todos los casos de ICD por parte de un experto en enfermedades infecciosas contribuirá a un mejor manejo global de esta importante enfermedad.

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The absence, for decades, of new drugs and advances in diagnostic techniques has kept *Clostridium difficile* infection (CDI) in a secondary plane of the infectious diseases. Traditionally, there was hardly more debate than the one involving the decision of using vancomycin or metronidazole to treat patients (and surprisingly for favouring the less efficacious drug). Moreover, recurrences of the disease were also accepted as unavoidable facts. In summary, the management of CDI has been very conservative and, in some way, too passive.

However, the scenario of the disease has changed radically in recent years due to three factors: we are witnessing an increase in the incidence derived from new hypervirulent strains [1], new faster and more sensitive diagnostic techniques have arrived [2] and, finally, we have very relevant new therapies that allow to modify the natural history of the disease [3-5]. These diagnostic and therapeutic novelties pose new challenges and confront microbiologists and infectious diseases specialists with new questions and complex decisions. How should the new more expensive diagnostic techniques be implemented in the laboratories? How to interpret the results of these more sensitive techniques? Which patients should be offered (or not) new treatments that are more effective but much more expensive?

Table 1 **Clinical prediction tools for CDI recurrence**

Author	Methods	Model	AUC	Accuracy	Applicability
Hu [11]	Prospective cohort (63 cases) External validation (89 cases)	Age >65, Antibiotics after CDI, Horn index.	0.83	77%	Low[1]
Eyre [12]	Retrospective cohort (1678 cases) No external validation	Age (60-69; 70-79;>80) Type of admission, previous MRSA, previous Gastroenterology ward admission, level of CRP, admission with CDI	ND	ND	Low
Hebert [13]	Retrospective cohort (829 cases) No external validation	Age, fluoroquinolones, ICU admission, cefalosporins, metronidazole or PBI after CDI	0.70	ND	Low[1]
Zilberberg.[14]	Retrospective cohort (4196 cases) Not external validation	Age, >2 hospital admissions 2 months before, community onset-health care associated, high risk antibiotics at DI onset, FQ at CDI onset, acid secretion suppression, ICU admission	0.64	ND	Low
D'Agostino [15]	Retrospective cohort (922 cases) Not external validation	Age >75, >10 stool, Creatinine >1.2 mg/dL, previous episode, not fidaxomicin	0.64	ND	High
LaBarbera [16]	Random forest -machine learning algorithm- (198 cases) No external validation	Not applicable	0.83	66%	Low
Viswesh [17]	Prospective cohort (340 cases). Not external validation	CDI at admission, nosocomial CDI, T^{a}>37.8 ^{o}C at admission, Leukocyte >15.000/ uL at admission, abdominal distension	0.72	ND	High
Cobo [18]	Prospective cohort (274 cases) External validation (185 cases)	Age (70-80; >80), previous CDI episode, free toxin+, diarrhoea day +5 of treatment	0,72	75%	High

[1]**Some variables are not available during the period of treatment (e.g. antibiotics after CDI)**

It is clear that we can currently improve the management of patients with CDI. In this article we will review three relevant aspects, such as the importance of correctly interpreting the tests to avoid overdiagnosis, how to identify patients with high risk of recurrence and how to better manage the disease globally in health institutions.

DECISION TO TREAT MATTERS MUCH MORE THAN ONE COULD THINK

The incorporation of techniques based on molecular biology for the diagnosis of CDI currently allows us to diagnose virtually all cases, since these techniques reach a sensitivity of almost 100% and may be available within a few hours from the collection of the sample. As recommended by scientific societies, most centres carry out diagnostic algorithms in two or three steps, which implies that some patients are eventually diagnosed by molecular techniques (NAAT), while the detection of free toxin is negative (NAAT+/ TOX-), and on the contrary in others the toxin is detected directly in the patient's stool (TOX+). At present we know there is evidence that there are differences between these two populations and, although there are still controversies, in general we can say that globally there are fewer severe cases and less symptomatic disease (and therefore more colonization) in the NAAT+/TOX- than in the TOX + [6,7].

Vancomycin is practically not absorbed and, therefore, adverse effects due to its administration are not expected. This idea, together with the assumption that its administration could eradicate *C.difficile* from the intestine of patients at risk, may lead many physicians to not raise many doubts about the treatment once it receives the result of the toxigenic *C.difficile* detection in the stool of their patients. There are at least two important harmful consequences of this attitude. First, several studies have shown that vancomycin (and also metronidazole) exerts a profound effect on the diversity of the human intestinal microbiota and, in fact, favours colonization by enterococci, by antibiotic resistant Enterobacteriaceae [8]. We also know that this colonization precedes many infections. Therefore, an unnecessary administration of vancomycin may be confronting new risks to frail patients. Secondly, the decision to treat implies the diagnosis of a CDI episode. This means

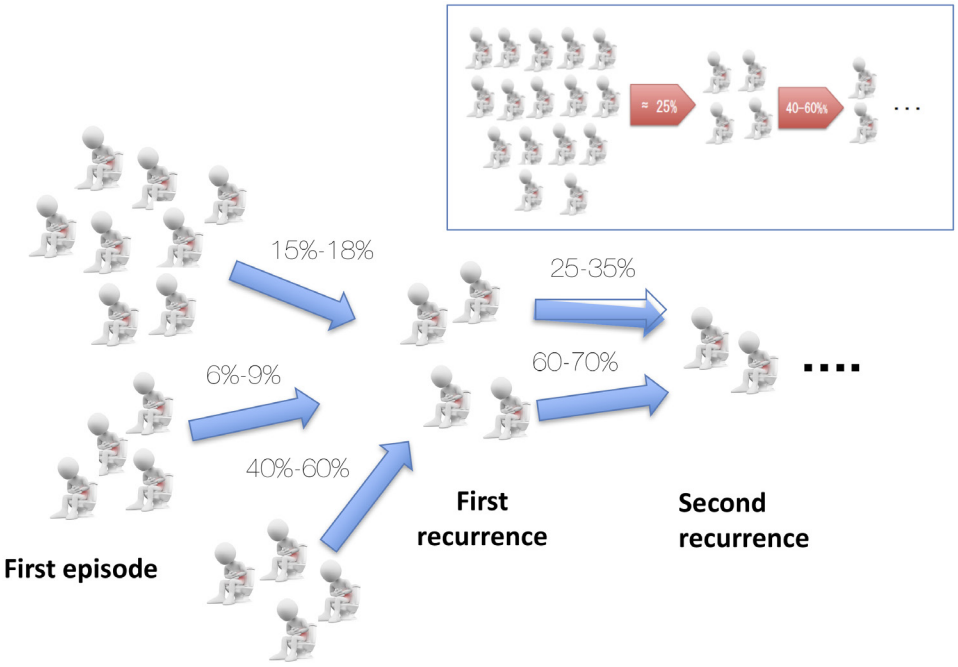

Figure 1 **The upper figure is true: globally the patients in the first episode present a lower risk than the patients in the second episode. However, this does not mean that all patients in the first episode (or in the second) have the same risk of recurrence. The knowledge of risk factors and predictive models can allow us to identify subpopulations of higher and lower risk.**

that if the patient were to be diagnosed (correctly or not) of a new episode, probably the use of expensive or sophisticated treatments would be unnecessarily considered. Indeed, in a recent study, a reference centre for faecal microbiota transplantation reported that after evaluating the cases referred by other physicians, they considered that 25% of the patients had been diagnosed incorrectly of recurrent CDI [9].

WHO ARE THE PATIENTS AT HIGH RISK OF RECURRENCE?

Until recently we could hardly modify the risk of recurrence of patients. At best, we could recommend them to avoid the use of antibiotics and proton pump inhibitors if they were not strictly necessary. However, today we have new antibiotics (fidaxomicin) and a monoclonal antibody (bezlotoxumab) that allow us to significantly reduce recurrences, changing the natural history of the disease. They would be used routinely in most cases if it were not for its high cost. An efficient use of these resources requires the ability to select patients with a high risk so that the number of patients needed to treat is substantially reduced.

Multiple investigations have shown several recurrence risk factors, some of which are repeated consistently [10]. These include the age over 65 years, continued use of PPIs or antibiotics, previous treatment with quinolones, kidney failure and history of previous episodes of CDI. But we should not forget others such as inflammatory bowel disease, having an enteral tube or severe immunosuppression. As all these factors can coexist and interact, the mere knowledge of the risk factors is not enough to establish, when evaluating a given patient, the specific risk of recurrence.

A more useful approach are clinical prediction tools, and even more recently the use of big data and machine learning systems (table1) [11-18]. Important limitations of these tools should be recognized. Only two of the models have been validated externally and not all the tools proposed are easy to apply in real practice. In addition, the accuracy of the models is not very high. However, they allow to discern subgroups of high and low risk reasonably well, and show us that the risk for patients in the first episode can vary widely and, in some cases, can be even higher than the risk established for patients in the second episode (figure 1)

As an example, in a recently published study we followed a prospective cohort of 274 patients of which 25% had recurrence. By means of multivariate analysis we were able to generate a clinical prediction rule with a precision of 0.75 and AUC 0.72. The included variables were age (with two different rang-

es), the history of a previous episode of CDI, having a positive toxin determination in faeces and a slow response defined by continuing diarrhea after 5 days of treatment [18]. Considering this model, for example, an 85-year-old patient in a severe first episode diagnosed with a positive toxin test and who shows a slow response, would have a risk of recurrent CDI greater than 50%, and in any case higher than a 68-year-old patient in his second episode diagnosed by PCR that shows a rapid response.

Not only risk assessment of recurrence but also an evaluation of potential consequences of CDI recurrence should be addressed. For example a recent report has shown that haematological patients on chemotherapy that present CDI recurrence suffer significantly more delays in the planned chemotherapy than patients without CDI recurrences [19].

Clinical guidelines usually arrange the recommendations for the treatment of CDI depending on the number of the episode and its severity. However, this approach could be excessively rigid for patients with a high risk of recurrence or with serious potential repercussions of it. In short, surely we should progress towards more individualized treatments.

CAN WE IMPROVE THE CARE OF PATIENTS WITH CDI?

CDI has been an undervalued disease for decades. One of the problems in its management – and it is not new for some nosocomial infections- lies in the wide distribution of the disease within the hospitals. We have calculated that the last 800 CDI cases in our institution have been attended by more than 25 different surgical and medical services and more than 100 different physicians. The potential consequences of such dispersion are variability in clinical management, lack of expertise to manage severe cases, lack of continuity in the medical care of patients with recurrent CDI, and difficult access to new drugs and therapies.

There exist some experiences showing benefits of "CDI stewardships" or CDI bundles [20] imitating other similar positive experiences such as the well-known effect of the supervision of *S. aureus* bacteremia by experts in infectious diseases.

In our opinion, supervision by an expert of all CDI cases diagnosed by the laboratory could improve the following points:

1) Avoiding treatments of merely colonized patients

2) Early detection of severe cases that require urgent evaluation by the surgeon

3) Favouring early access of patients at high risk of recurrence to new treatments

4) Serving as a reference physician for the management of patients with multiple recurrences, facilitating accessibility and rapid diagnosis

5) Supervising the inappropriate administration of antibiotics and PPIs to patients with recent diagnosis of CDI

Ideally, such a program should be coordinated with a reinforcement of infection control policies and education of health professionals on the mechanisms of transmission of CDI and the importance of judicious use of antibiotics.

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