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Current strategies for infectious diseases management

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Treatment of *Clostridioides difficile* infection: from guidelines to clinical practice

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ABSTRACT

The *Clostridioides difficile* Infection (CDI) treatment guidelines were published in 2021; however, the incorporation of these recommendations into clinical practice was rather irregular and inconsistent. The differences in the implementation of these new guidelines were due, in part, to the variety in the different professionals who provided patient care, as well as to the issues involved in either their accessibility or availability or both. The main requirements for implementation include appropriate reflection on patient stratification, drug positioning, accessibility to drugs, as well as the organization of structured clinical pathways that can facilitate the functionality and evaluation of the management of CDI.

Keywords: *Clostridioides difficile* treatment, guidelines, clinical pathway.

INTRODUCTION

After the new evidence related to the *Clostridioides difficile* Infection (CDI) treatment was reported, the main guidelines and recommendations were updated by several scientific societies, including those in America, Europe and Spain (IDSA, ESCMID, ACG and SEQ) in 2021.

The clinical outcomes in different pathologies showed clear optimization when the guidelines were strictly followed, although implementation into regular clinical practice was not always simple or feasible; further, from one center to another, wide variations were noted in terms of the percentage of adherence or follow-up of the recommendations.

In the course of this infection, two major challenges were encountered, the first of which was optimization of the therapeutic objective. Often, in clinical practice, the treatment goal is to clinically resolve the episode, and when the recurrence frequency of this infection is known to be 15-25%, the aim must be to attain sustained cure or cure with no recurrence. Several times, this goal is not achieved, most often because of insufficient follow-up over time and sometimes because the recurrences are not well tracked. The second challenge was that the treatment of this infection was developed from a comparatively stagnant state over the last 20 years. It now includes in its arsenal, new therapeutic methods. But because the clinical care of this infection is performed under a wide variety of settings, from Primary Care to different hospital specialties, these recommendations have not always been sufficiently well incorporated into clinical practice. In fact, a wide plurality of treatment options is available in terms of the approach and treatment of CDI.

Therefore, implementation of these guidelines is crucial, considering CDI is a serious health issue, not only for the individual patient (increasing early and late morbidity and mortality, and compromising the quality of life), but for the health system as well (involving the high cost of primary episodes and recurrences) [1], both of which pose a threat to the sustainability. So, a complete strategy has been put forward to optimize the way this infection is approached, at the level of each specific case, as well as at the collective level, inclusive of a "macro" vision of management planning from epidemiology to prevention, on a global scale.

OPTIMIZATION IN THE CLINICAL EVALUATION AND "INDIVIDUAL" MANAGEMENT

Recent guidelines and recommendations are based on the goal of achieving sustained cure. So, from "classical pharmacological treatment" as metronidazole and vancomycin, new treatment (fidaxomicin (FDX), bezlotoxumab (BZL) and fecal microbiota transplant) or strategies (extended regimens of fidaxomicin, vancomycin in pulsed "taper" regimes) have been

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incorporated FDX (in standard or extended regimen) and BZL provided a percentage of clinical resolution close to that of the comparator (vancomycin), but showed a lower rate of recurrence, thus indicating better therapeutic success over time (sustained cure). Fecal microbiota transplant has been reported as the best treatment in multiple recurrence.

These new treatments have high economic cost and less accessibility, which is a factor that is included in the guidelines for the choice of treatment. On the other hand, it is important to note that CDI and its recurrence also have a high impact on health. CDI recurrence is related to increase in hospital admissions, delay in therapeutic procedures, in quality of life and especially, increasing frailty in elderly patients.

For the reasons cited above, the effective translation of these recommendations into regular clinical practice needs to be done, keeping in mind several c variables namely, proper patient stratification, knowledge of recommended treatments, accessibility-availability concept, and the recurrence factor.

Patient stratification. Patients were stratified for treatment selection traditionally based on the relationship of the infection to clinical severity and number of episodes of infection.

The severity has been evaluated using different scores, but the relevance in distinguishing mild or moderate infection, but the relevance beyond serious infection, is less in currently guidelines because metronidazole is no longer regarded as the first-line of treatment. It is used as an option only for severe episodes, in patients revealing intolerance to the oral route, or the onset of shock or paralytic ileus, in which cases the treatment guidelines remain unchanged.

Distinctions drawn between the first episode, first recurrence and subsequent episodes were made depending upon the higher probability of the recurrence of successive episodes. The earlier guidelines chose the treatments that ensured more efficacy in terms of recurrence for the first or successive recurrences. Although the current guidelines continue to maintain this basic scheme, the best treatments in first episodes have been included, and their prioritization has been proposed, considering the other risk factors for recurrence.

Therefore, a study of the assessment of the risk of recurrence is proposed, incorporating the other risk factors apart from the number of episodes. In fact, 15-25% recurrence risk is estimated in a first episode, with vancomycin as the treatment option. Several works have been published in an attempt to identify the risk factors for recurrence, drawn from highly heterogeneous series, applying different "definitions" of both risk factors and the time span for recurrence. From this angle, a meta-analysis done recently indicates the factors, which present low level of evidence as follows: age (above 65 or 75 years) and a prior episode, as the factors which offer the most evidence (to a moderate extent), as well as an earlier hospitalization, where the episode bears some relationship to care healthcare and prior/concomitant use of proton pump inhibitors [2].

Using predictive models [3] different scores have been proposed, which combine the risk factors with different relative weights, but despite enabling the achievement of a kind of more accurate risk stratification, they include limitations in their predictive ability [4].

New risk factors have been identified as well, namely the quantity of immunoglobulins versus the toxins, intestinal microbiota (in terms of composition and diversity), and the amount of *C. difficile* present in the feces; further, the presence of predisposing genetic factors [5] will likely be a better indicator, in a future time, to identify patients possessing a higher risk of recurrence.

Recommended treatments. Regarding the of the first episode, barring for the ACG guidelines (which assign to vancomycin and fidaxomicin like first choice), the guidelines established by the IDSA and ESCMID show fidaxomicin as the first choice, and vancomycin as an "acceptable" alternative, or when a situation of "limitation of resources" arises. In such events, the fidaxomicin usage is established as a priority for patients who have high risk of recurrence. Metronidazole is not the recommended option and is permitted to be used solely when the vancomycin or FDX is unavailable. The use of BZL is suggested only for patients having a minimum of one risk factor, guaranteeing its accessibility (IDSA), or when FDX is not available.

Controversy continues to exist, both in the literature and in clinical practice, with respect to the removal of any indication for metronidazole, which could still offer a few specially selected opportunities for use in clinical practice.

Despite the fact that the conclusion drawn by the Cochrane review in 2017 indicating the superiority of vancomycin to metronidazole and FDX to vancomycin, the benefit of using metronidazole was noted for "its far lower cost compared to the other two antibiotics" [6].

Data from two series performed recently in real life throw more light on the earlier findings of the lower efficacy of metronidazole. In a Veterans cohort which included 3,566 patients (treated from 2010 to 2014) and showing a recurrence rate of 10.2% after 30 days, the factors related to the recurrence were assessed by employing a propensity score. It was noted that when metronidazole was the medication used, it exhibited behavior that rendered it a risk factor for patients below 65 years of age [7]. In another series [8] patients were treated prior to and post the implementation of the guidelines (1,809 vs 1,799 patients), with 70 vs 20% of patients being given metronidazole, respectively. Of interest, no differences were identified in terms of failure of treatment or appearance of recurrences (mean age 65 years) when compared to vancomycin.

Therefore, it appears that in some patient subgroups (as in patients with low risk of recurrence with mild disease, younger than 65 years and without other risk factors) metronidazole could be given as the alternative treatment. The higher accessibility of metronidazole in our country is not contingent upon its cost but upon the internal dispensing policy of the hospital pharmacy, where vancomycin continues to be subject.

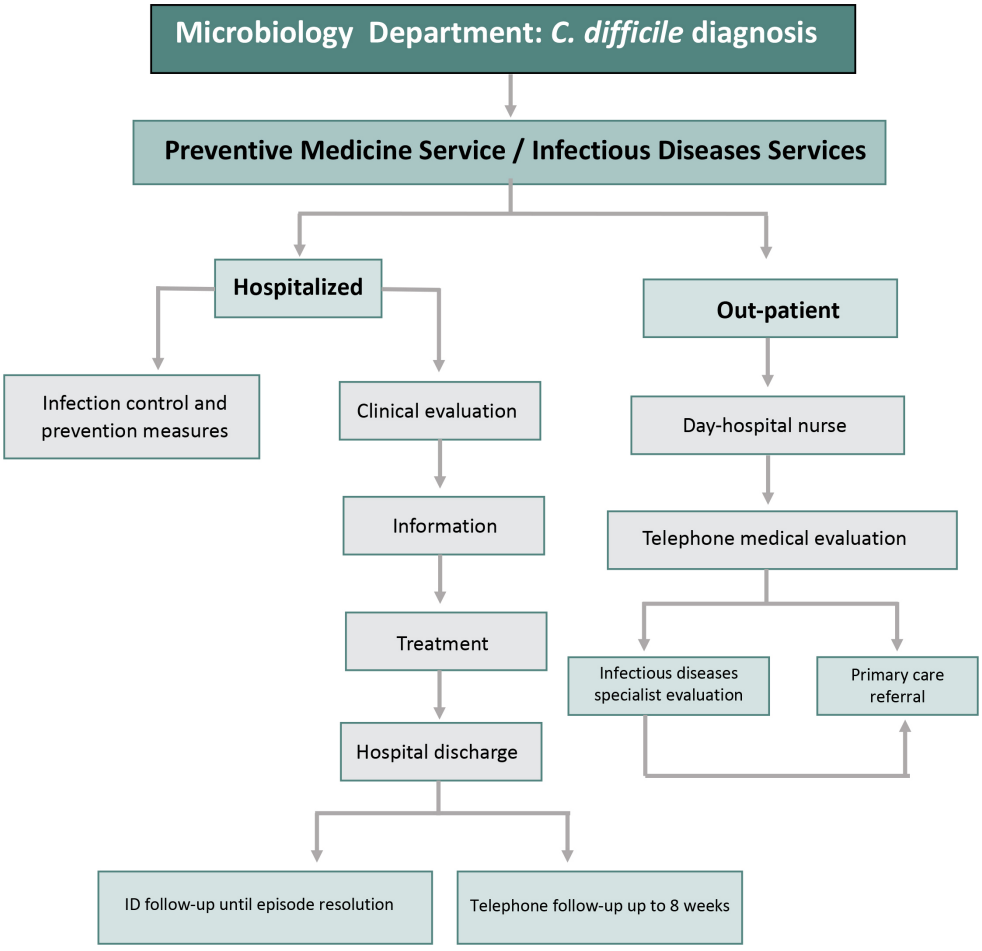

Figure 1 A clinical pathway for CDI evaluation.

With respect to the priority position given to the FDX versus BZL, no comparative studies between the two drugs are available to provide proof as to which one is the better alternative for sustained healing. While FDX is regarded as the more accessible one because it can be orally administered, it must be noted that the direct cost of both medications is similar in our country (although not in the United States). In the post-hoc analyses of the pivotal study [9] the patient group in which BZL was given reveals higher efficacy than the comparator, as seen in its indication for recommendation in the guidelines (age >65 years, immunosuppression, prior episode of CDI, severe intensity of disease or high-risk ribotype).

In terms of the treatment of recurrences, there are a few dissimilarities between the guidelines. The IDSA guidelines list FDX as the recommended drug in the first recurrence, in either the standard or extended regimen; the alternative is to taper vancomycin or BZL, using the identical scheme for the second recurrence, adding rifaximin, and shifting the fecal microbiota transplant from the second recurrence. In the European guidelines, however, the indication proposed is by alternating the medication given in the prior episode, preferably with the inclusion of FDX and BZL; also, vancomycin is recommended on a tapered dosage in the event of the drugs mentioned being absent or unavailable, and with the inclusion of TMF from the second recurrence.

From observational studies, both FDX and BZL show lower efficacy from the first and, definitely, the second recurrence [10-12]; hence, probably positioning these drugs in the second recurrence and thereafter, provides a sign of their lower efficiency. In the event of a second recurrence and particularly in the subsequent ones, the most effective treatment today is FMT. Yet, it remains as a not very accessible treatment option in most centers. Higher accessibility can be attained by ensuring the availability of lyophilized capsules manufactured in reference research centers with stool banks or by using commercialized formulae to facilitate the transfer of microbiota by the manufacturing companies, which can thus assure that all patients get fair access to them [13].

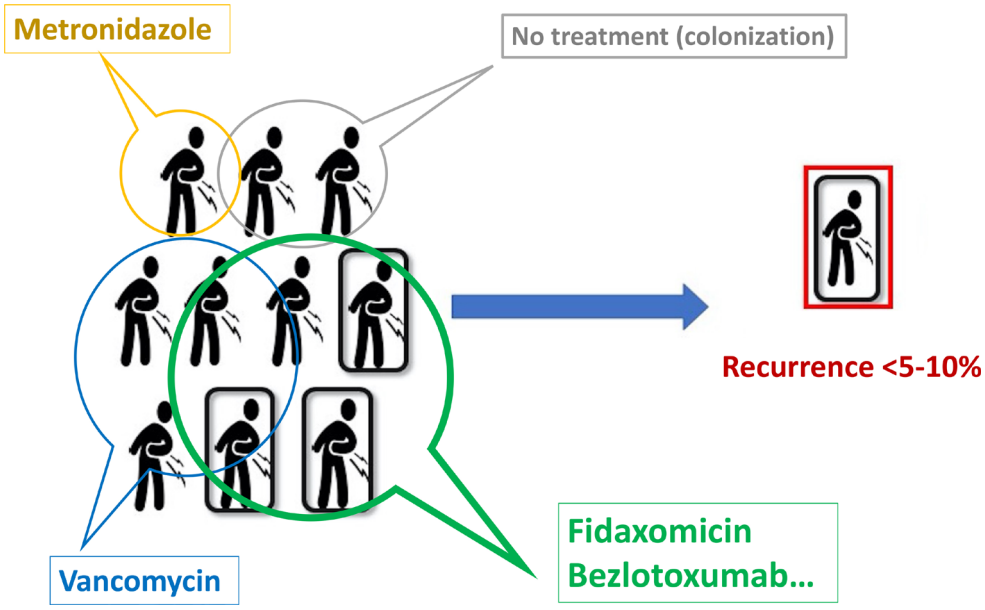

Figure 2 Optimization in the efficiency of the evaluation of *C. difficile* infection: identification of infection-colonization, population identification according risk factors of recurrence

The concept of accessibility/availability. Although the guidelines position FDX and BZL based on data from clinical trials, all the guidelines include the concept of accessibility/availability for choosing treatment. In our country, this "accessibility or availability" concept is governed by the alleged "Therapeutic Positioning Report" determined by the Spanish Agency for Medicines and Health Products (AEMPS, the regulations of the autonomous communities and the Infection Commission Commission/Hospital Pharmacy Services. This report is drawn up after hearing and assessing the suggestions proposed by different scientific societies, and they have reserved these new drugs (FDX or BZL) for use in the first or even second/successive recurrences.

All these regulations are basically built upon the cost evaluation studies (cost-effectiveness) of each drug. Despite that fact that a substantial number of these have been published, one recent review raises the criticism that a majority of these reports are promoted by the pharmaceutical industry and hence are not applicable between different countries and health systems. This is because the price and financing body may differ, as well as the value of the QUALYS/DALYS, and the difference in their time horizon, for which a local assessment is a necessity, with independent analysis [14].

These studies fail to evaluate adequately two factors that can determine the cost-effectiveness of the treatments in the real world. On the one hand, a good estimation by experts is needed, where the distinction is made between colonization and infection; this can decrease the prescription of treatments by around 15-20%. On the other hand, the "non-tangible" influence exerted by the recurrences in some patients, the apparent "lost window of opportunity", must be assessed, which includes the delayed administration of chemotherapy cycles, performance of major surgeries, or reception of transplants, as well as in terms of quality of life (family and domestic, social and work).

OPTIMIZATION IN GLOBAL HEALTH STRATEGIC PLANNING: A CLINICAL PATHWAY

For the proper translation of the recommendations of these guidelines into clinical practice, and assurance of the efficacy and cost-effectiveness of the resources, several key aspects must be considered:

- Correct identification of infection and colonization.

- Therapeutic objective: Sustained cure of the CDI (prevention recurrences).

- Identification the risk of recurrence and the clinical impact and prognosis of the recurrence, to enable the treatment decision.

- Optimization in the indication of the different treatments.

- Clinical follow-up between the various departments and levels of care, which ensure the early identification of new episodes of recurrence.

- Selected, pertinent and practical data to facilitate involving the patient and relatives in managing and following up of the CDI episode (empowerment). An adequate clinical evaluation that allows to identify colonization and infection, select the best treatment according risk factors of recurrence, will optimize the effectivity of treatment well as accessibility and equity throughout the health system (Figure 1).

This approach can be optimally structured by designing a clinical pathway of care for CDI patients.

In different scenarios, clinical pathways have been known to enhance the results of a specific health problem, through clinical care optimization and the speedy and efficient incorporation of available scientific evidence. The impact of this process directly relates to the appropriate design and coordination that facilitates solving any issues that are present, and opening up a way for smooth and efficacious implementation [15].

In order to develop a clinical pathway, four basic pillars have been proposed [1] a structured and normally multidisciplinary intervention plan, [2] transfer of the scientific evidence or general clinical guidelines of the intervention plan to the local structures, [3] presentation of the steps involved in the course of treatment in detail, as a plan and algorithm and, [4] standardization of care for specified populations, as the ultimate goal [16].

These pointers may help in developing a clinical pathway for CDI care, coordinated by the Stewardship teams (Figure 2). This will permit identification of patients having a microbiological diagnosis of CDI, provision of clinical assessment by a team of specialized and competent health care personnel, and availability of pertinent data and accessibility for patients during follow-up, which can thus facilitate early detection of recurrence. Such a clinical pathway will provide an effective route through which several of these recommendations cited in the guidelines or consensus documents can be incorporated into the daily clinical practice in managing CDI, as indicated by the variety of experiences in our country.

CONFLICT OF INTEREST

Authors declare no conflict of interest

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