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Editorial

Clostridium difficile infection in inflammatory bowel disease

Clostridium difficile (Cd) is an anerobic, gram-positive, spore-forming bacterium that is widely distributed among human communities and usually found to be involved in opportunistic, nosocomial, and antibiotic use-related infections. In the last few years an increase has been reported in the incidence and severity of these infections, which are now among the most common nosocomial infections in both Europe and North America. Furthermore, the relationship between infection by *Clostridium difficile* and inflammatory bowel disease (IBD) has been widely addressed by the scientific literature, showing increased infection rates among patients with IBD, particularly among those with colonic involvement (both in ulcerative colitis and colonic Crohn's disease), and a more severe course as compared to the general population. Several studies have estimated that the incidence of Cd infection lies between 2.8 and 3.73 % among patients with ulcerative colitis (UC), and is around 1 % among patients with Crohn's disease, as compared to rates below 0.5 % among the general population. It is similarly estimated that 8.2 % of patients with UC and 1 % of patients with Crohn's disease (CD) are silent Cd carriers with no clinical manifestations of active disease. Recent longitudinal studies have shown a significant, steady increase in the incidence of infection during the past few decades, rising up to 5 % of patients with IBD. This increased incidence has also been reported in pediatric patients. Indeed, a recent prospective, multicenter study by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) not only confirmed such findings in a population of children with IBD *versus* a control group of celiac children on a gluten-free diet and with adequate control of their underlying condition (7.5 % *versus* 0.8 %; p = 0.008), but also demonstrated rates even higher than reported for adult series (1). In this study, the identification of Cd-related toxins was associated with active disease in 71.4 % of patients with predominant colonic involvement (up to 85.7 % of cases). However, in contrast to adult studies, no differences in incidence were observed between patients with UC and patients with CD.

The pathogenetic factors contributing to Cd infection in patients with IBD remain unclear, albeit the infection is thought to result from local immune deficiency secondary to chronic inflammation, a consequence of barrier function compromise, from therapy-related immunosuppression, and from flora imbalance. Infection by Cd in patients with IBD has been associated with greater morbidity, higher number of flare-ups, poorer response to treatment, and poorer outcomes (colectomy, number and duration of hospital admissions, need for treatment escalation, visits to emergency rooms, and mortality) (2,3). In fact, mortality is considered to be between 3.2 and 6 times higher in patients with IBD and Cd infection (may reach up to 25 %) when compared to patients with IBD and no Cd infection. Similarly, up to 10-35 % of patients in this situation will require colectomy. The aforementioned poorer prognosis

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of these patients would have seemingly resulted not only from the infectious germ itself (which may induce from pseudomembranous colitis to toxic megacolon) but the infection might activate the innate immune response, which would facilitate greater aggression by the underlying disease (4). Another relevant aspect to be considered is that Cd infection may recur in 11-30 % of cases after a first treatment cycle, be it the result of activity by the baseline strain or by reinfection with that same strain or a different one, which usually occurs between 1 and 3 weeks after antibiotic therapy completion. From all the above, it is recommended that Cd infection be screened in any patient with a flare-up or a worsening clinical status, particularly in the presence of bloody diarrhea with poor response to rescue therapy.

Various studies have tried to determine the potential risk factors associated with a higher probability of Cd infection in patients with IBD. IBD is considered an independent risk factor itself regarding Cd infection, and the same factors associated with infection in the IBD-free population have been traditionally posited here (advanced age, prolonged hospitalization, use of antibiotics, use of steroids). In this respect, the risk factors that seem to weigh more for patients with IBD include those related to therapies, including antibiotics (preferentially quinolones, clindamycin, cephalosporins, and penicillins) as well as proton pump inhibitors and immunosuppressants. Background or new-onset corticoids would increase the risk for infection three-fold and mortality two-fold, regardless of dosage and duration. While information is scarce on the potential involvement of other immune modulating therapies, as is the case with thiopurines and methotrexate, these also seem to enhance the risk for infection, particularly in patients with UC. As regards anti-TNF medications, their onset seems to bear no relation with the development of Cd infection, and some papers even suggest a protective role (5). As for the remaining factors associated with incidence among the general population, a higher risk has been reported in association with advanced age, although the mean age of patients with IBD is younger as compared to subjects without IBD. Furthermore, a difference versus the general population is that patients with IBD most commonly acquire the infection in the outpatient setting (47-79 %), even though the number of nosocomial infections in this group is on the rise.

In the paper published in the present issue of the *Revista Española de Enfermedades Digestivas (Spanish Journal of Gastroenterology)* by Ramos Martínez and colleagues (6), the authors retrospectively study the potential risk factors for the development of active infection by Cd in a cohort of 15 patients with IBD in our setting (8 CU, 7 EC) *versus* patients with IBD and no infection, as well as patients diagnosed with Cd infection and no underlying IBD. The authors confirm some already reported data, as is the fact that Cd-related diarrhea in this group of patients preferentially involves younger patients as compared to the general population (mean age 36 *vs.* 73 years), with a higher rate of contagion in the community (up to 87 %) at the expense of nosocomial forms, and that it seems to be more closely related to previous therapy with proton-pump inhibitors rather than antibiotics. The latter aspect is one of the most relevant findings in this study. Gastric acidity has a protective role against vegetative Cd forms, and limits their passage to distal digestive tract regions. Previous studies have reported the role of PPIs in this infection among the general population, albeit few data were until recently available regarding patients with IBD. The potential association of these drugs in the patients included in this series (66 % for IBD, 80 % for controls without IBD) should, according to these authors, question their use, leading to a thorough selection of candidates who really need them. In contrast, only 20 % of patients with IBD developing this infection had previously received antibiotics, which suggests a potential contribution of impaired intestinal flora to these cases, regardless

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of changes brought about by said medication, in the pathogenesis of infection by Cd. Furthermore, the authors find no increased risk for infection associated with the use of anti-TNFs, which is consistent with prior studies.

Despite limitations (short series, retrospective analysis), the above study contributes to the understanding of the potential risk factors associated with a high morbidity and mortality complication in patients with IBD that is potentially managable -infection by Cd.

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