Editorial

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Clostridium Difficile Infection and Inflammatory Bowel Disease: What Gastroenterologists and Surgeons Should Know

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Rezumat

Infecția cu Clostridium difficile și boala inflamatorie intestinală: ce trebuie să știe gastroenterologii și chirurgii

În ultimele două decade, în întreaga lume, s-a înregistrat o creştere dramatică a incidenței şi severității infecției cu *Clostridium difficile* (ICD). Simultan cu creşterea incidenței ICD în populația generală, s-a constatat o creştere chiar mai mare a acestei infecții în rândul pacienților cu boli inflamatorii intestinale (BII). Având în vedere că ICD poate mima un episod acut de BII, simptomatologia clinică şi parametrii paraclinici fiind adesea similari, screeningul pentru această infecție este recomandat la orice puseu acut de BII. Tehnica imunoenzimatică pentru detectarea în scaun a toxinelor bacteriene A şi B, deşi are sensibilitate scăzută, este încă cel mai utilizat test diagnostic. Agenții terapeutici recomandați sunt metronidazolul pentru formele uşoare/moderate şi vancomicina pentru infecția severă. ICD are un impact negativ asupra prognosticului pe termen scurt şi lung al BII, crescând necesitatea intervențiilor chirurgicale, rata mortalității şi costurile asistenței medicale. Gastroenterologii şi chirurgii trebuie să aibă un grad ridicat de suspiciune pentru ICD atunci când evaluează un pacient cu puseu acut de BII, întrucât diagnosticul prompt şi tratamentul adecvat al infecției ameliorează prognosticul. Măsuri urgente de prevenire a răspândirii infecției în secțiile de chirurgie/ gastroenterologie sunt mandatorii.

Cuvinte cheie: infecția cu *Clostridium difficile*, boala Crohn, colita ulcerativă, diagnostic, tratament, prevenție

Abstract

Over the past two decades there has been a dramatic increase worldwide in both incidence and severity of *Clostridium difficile* infection (CDI). Paralleling the rising incidence of CDI in the general population, there has been an even higher increase in the incidence of CDI among patients with inflammatory bowel disease (IBD). CDI may mimic a flare of IBD as symptoms and laboratory parameters are often similar, and therefore, screening for CDI is recommended at every flare in such patients. Enzyme immunoassay to detect *Clostridium difficile* toxin A and B in stool is still the most widely used test for CDI diagnosis despite its low sensitivity. Metronidazole for mild/moderate CDI, and vancomycin for severe CDI are the preferred agents for the treatment of infection. CDI has a negative impact both on short- and long- term IBD outcomes, increasing the need for surgery, as well as the mortality rate and healthcare costs. All gastroenterologists and surgeons should have a high index of suspicion for CDI when evaluating a patient with IBD flare, as prompt diagnosis and adequate treatment of infection improve outcomes. Measures must be taken to prevent spreading of infection in gastroenterology /surgery settings.

Key words: *Clostridium difficile* infection, Crohn's disease, ulcerative colitis, diagnosis, treatment, prevention.

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Introduction

Over the past two decades there has been a dramatic increase worldwide in both incidence and severity of *Clostridium difficile* infection (CDI) (1). Today, CDI is recognized as the leading cause of infectious nosocomial diarrhea in developed countries, associated with increased morbidity, mortality, and healthcare costs (2,3).

CDI was first associated with inflammatory bowel disease (IBD) in 1978 (4), but was somehow neglected until 15 years ago, when several studies demonstrated that patients with ulcerative colitis (UC) and Crohn's disease (CD) are at high risk for this infection (5-10). Over this period, the number of UC hospitalized patients with concomitant CDI has more than doubled (7,10) and the colectomy rate has increased by 20% (11) influencing the activity in gastroenterology/surgery settings.

Patients with UC are more susceptible to CDI than those with CD (5,9,10,12). Metronidazole for mild/moderate CDI, and vancomycin for severe infection are the preferred therapeutic agents (13,14). IBD patients (especially those with UC) with superimposed CDI have worse outcomes than those with IBD alone (5-7,10,15), with increased colectomy and mortality rates (5,7,10). Adequate measures such as isolation of infected patients, hand hygiene and protective equipment for healthcare workers and environmental cleaning should be taken in all gastroenterology/surgery settings to prevent spreading of the infection.

This review article summarizes the latest available data on epidemiology, diagnosis, and treatment of CDI in IBD patients. In addition, a short comment on the epidemiology of this infection in our country will be made.

Epidemiology

Large nationwide data analyses (6,7,9-11) and single-center studies (5,8,12) have independently reported significant increased CDI incidence among IBD patients over the last 15 years. Thus, in the USA, in one study using nationwide data, CDI incidence among hospitalized UC patients has doubled over a 7-year period (10), while in another study (13), 47% of their IBD patients admitted with flares had CDI. This trend of increased CDI occurrence in IBD patients reported in the USA has also been noted in Europe and other geographic regions. A study from Belgium reported a nearly 4-fold CDI increase in both IBD and non-IBD patients between 2000 and 2008 (8), while Kaneko et al (14) from Japan, and Kochhar et al (15) from India, found that 40% and 32%, respectively, of their patients with UC flares had superimposed CDI.

Little is known about the incidence of CDI in our country. The lack of well-designed epidemiological studies makes it impossible to know the real dimension of this infection in the general population, and even less in IBD patients. Undoubtedly, we have noted an increased number of patients with CDI in our hospitals during recent years, although it is most likely that many cases have been either undiagnosed because of low levels of awareness for CDI among clinicians or misdiagnosed due to lack of sensitive diagnostic tests. Low level of clinical suspicion for CDI means low frequency testing for *C. difficile*, and subsequently, fewer cases diagnosed. Illustratively, a recent pan-European survey of rates of CDI among 97 hospitals from 34 countries (5 from Romania) showed that in our hospitals the frequency of testing for *C. difficile* was the lowest (3 per 10,000 patient-day compared to 115 from UK or 141 from Finland) (16). It should be underlined that other countries too have been confronted in the past with the same low level of suspicion for CDI (17,18). Thus, in the USA, 69% of internal medicine residents were not aware of the existence of CDI in the outpatient setting and would not test for this infection (17). In Spain, two of three episodes of CDI were not diagnosed because the test was not requested (47.6%) or due to the use of diagnostic tests with low sensitivity (19.0%) (18).

With the exception of few case-reports (19,20), there is not a single published study on the epidemiology of CDI in IBD patients in our country, and such a study is urgently needed. Until then, gastroenterologists and surgeons should maintain a high index of suspicion for CDI in all IBD patients presenting a flare of their disease.

Risk factors

Traditional risk factors for CDI are similar in IBD and non-IBD populations. In addition to prior broad-spectrum antibiotic therapy, other potential risk factors such as advanced age, prolonged hospitalization (especially in ICU), multiple co-morbidities, gastrointestinal surgery, chemotherapy, immuno-suppression, hypoalbuminemia, renal insufficiency, use of nasogastric tubes, use of proton pump inhibitors, and the appearance of a hypervirulent strain of bacterium known as NAP1 (North American pulso-type 1) in some North-American and European areas, have been identified to explain the increased incidence of CDI (21-24).

IBD itself is an independent risk factor for CDI, with a 3-fold increased risk as compared with the non-IBD population (12). Patients with IBD are at increased risk for CDI due to more frequent hospitalization, antibiotic use, and immuno-suppressive therapy compared with general population. IBD patients often require long-term maintenance immunosuppressive therapy which was associated with double risk for CDI (5), while corticosteroid initiation tripled the risk of infection among such patients (25). IBD-specific risk factors include UC patients with extensive disease and high activity (5,9,10,26).

Diagnosis

Watery diarrhea is the cardinal clinical symptom of CDI, although IBD patients may have bloody or mucous diarrhea which are difficult to distinguish from an IBD flare. Laboratory findings in CDI and IBD flares are also similar (leucocytosis, anemia, hypoalbuminemia). As if these aren't enough for the difficulty of differential clinical diagnosis between CDI and IBD flare, at colonoscopy, typical pseudomembranes (virtually pathognomonic for CDI) are

often absent in IBD patients with superimposed CDI. Colonoscopy is not indicated for diagnosis of C. *difficile* (27), although a limited examination, without prior preparation, may be useful for diagnosis, especially in cases of high clinical suspicion for C. *difficile* with negative laboratory assay or for prompt diagnosis of infection needed before laboratory results can be obtained.

There are several diagnostic stool tests for C. *difficile*, and the choice depends on their availability, costs, turnaround time, sensitivity and specificity.

Enzyme immunoassay (EIA) for C. *difficile* toxins A and B is rapid (results within 1-2 hours), inexpensive, and widely available, being used as routine test in most countries including Romania, despite its low sensitivity with high rates of false-negative and false-positive results (28,29). An evaluation report on commercially EIA toxins showed that about 1 in 5 to 1 in 10 cases of CDI were missed, and 1-2 in 10 cases were falsely identified as positive (30). Still, in IBD patients, EIA sensitivity is even lower than in the non-IBD population (5). If the initial test is negative, the value of repeated testing in non-IBD patients is limited and not recommended by current guidelines (14); however, in IBD patients, repeating the test when there is high clinical suspicion for CDI may be useful to yield a positive result (31).

EIA for glutamate dehydrogenase (GDH) antigen detection has high specificity, and results are available in less than one hour. This test is unable to distinguish between toxigenic and non-toxigenic C. *difficile* strains, and a second more specific test is needed on specimens that are GDH positive (14).

Polymerase chain reaction (PCR) - based assays are highly sensitive and specific, commercially available, with results within the hour, making their use very attractive. However, real-time PCR has poor accuracy in differentiating CDI from asymptomatic carriage of C. *difficile*, and this is the greatest weakness of this assay (32,33).

Cell culture cytotoxicity assay and selective anaerobic culture are highly sensitive, but are expensive and time-consuming, and therefore, they are not useful in clinical practice.

Treatment

General measures

General measures include cessation of antibiotic that led to development of CDI, correction of fluid losses and electrolyte imbalances, avoidance of antimotility agents, isolation of patients, hand hygiene in healthcare settings, and environmental cleaning.

Medical treatment

Antibiotics. This paradoxical infection (caused by antibiotics and treated with antibiotics!) requires specific antimicrobial therapy. Two antibiotics, metronidazole and vancomycin, given orally, have traditionally been used in the treatment of CDI and proved to be effective. Similar to non-IBD patients, the choice of antibiotic therapy in IBD patients with CDI should be based on the severity of the disease and on whether it is an initial episode of infection, or a recurrence.

Metronidazole (500 mg orally 3 times per day or 250 mg orally 4 times daily for 10-14 days) is the drug of choice for an initial episode of mild to moderate CDI because it is effective, cheap, and has low drug resistance (34). Following recent reports (11) on failure of metronidazole therapy in hospitalized IBD patients with CDI and increased rate of recurrence of infection, many centers have now adopted vancomycin as first-line therapy in these patients.

Vancomycin (125 mg orally 4 times per day for 10-14 days) is the agent of choice for the first episode of severe CDI (34). In patients with complicated CDI, vancomycin (500 mg orally 4 times per day) combined with metronidazole (500 mg intravenously 3 times per day) is recommended. If ileus is present, vancomycin 500 mg in 100 ml saline as a retention enema 4 times per day is advised. Unlike metronidazole, vancomycin can be used during pregnancy and in children.

Fidaxomicin, approved by the U.S. Food and Drug Administration (FDA) and the European Medicine Agency (EMA) for treatment of CDI in non-IBD, has cure rates of 90%, but there are no data regarding its use in IBD patients with CDI (35).

Probiotics may be effective in preventing recurrent CDI (36) but there is no data on their use either with antibiotics or alone for the treatment of CDI in IBD patients.

Fecal microbiota transplantation (fecal bacteriotherapy) was found to be effective for refractory or recurrent CDI (37) but data concerning its use in IBD patients are scarce (38).

Recurrent CDI, occurring in 10%-30% of IBD patients, is treated similarly to the non-IBD population (14). The first recurrence of CDI should be treated with the same regimen used for the initial episode; however, if severe, vancomycin should be used in those treated initially with metronidazole. The second, third or multiple recurrences should be treated with vancomycin, 125 mg orally 4 times per day for 10-14 days, and then using a tapered (e.g. decrease frequency to twice daily, then once daily) and/or pulsed regimen (every other day to every third day) (14,39).

Surgical treatment

Indications for surgical treatment include severe complications (perforation, toxic megacolon) and failure of medical therapy. Patients with colonic perforation or toxic megacolon require emergent colectomy, but timing of surgery in those with medical therapy failure differs between centers. The operation of choice is total colectomy with ileostomy or proctocolectomy with ileoanal pouch anastomosis (40) if a restorative option is preferred.

Contrasting results have been reported regarding colectomy rate in UC patients with superimposed CDI. Thus, analyse of nationwide data in UK and USA reported high colectomy rates (6,7,11), while some single-center studies found no negative impact of CDI on colectomy rates in UC patients (14,41). These discrepancies could be partially accounted for by differences in threshold for surgery and data collection

methods (42). Variable results have also been reported concerning mortality rates in IBD patients with concomitant CDI. A four-fold higher mortality was reported by two nation-wide studies in the USA (6,10) and even higher in one from the UK (7), while some single-center studies found a similar mortality risk in IBD patients with or without CDI (8,11). High mortality rates reported by some studies may be related to increased use of emergent colectomy in IBD patients with superposed CDI (7).

Prevention

Once a patient with IBD is diagnosed with CDI, the following measures should be taken: isolation of the infected patient in a single room or dedicated wards, hand hygiene (washing with soap and water; do not use alcohol gels) and use of protective equipment by healthcare workers and visitors, as well as environmental decontamination with sporicidal agents such as hypochlorite solutions (43).

Conclusions

Several studies have reported a dramatic increase both in incidence and severity of CDI in IBD patients, particularly in those with UC. Due to similar clinical presentation, CDI may be difficult to distinguish from an IBD flare, and therefore, screening for C. *difficile* is recommended at every flare in such patients. IBD patients with CDI have a higher risk of worse outcomes, including colectomy and mortality rates, than uninfected IBD patients. A high index of suspicion for this infection should be maintained in gastro-enterology and surgery settings, as a prompt diagnosis and treatment of infection improve outcomes.

Conflicts of interest

The authors do not have any disclosures to report.

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