

Double Problem—*Clostridium difficile* and Diabetes

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Abstract: Considered to be the most common cause of nosocomial diarrhea, *Clostridium difficile* infection is a daily clinical reality, and its incidence is increasing globally. Many factors have been implicated in causing this infection, including glucose metabolism disorder. Aim: to evaluate the prevalence of diabetes among patients with *C. difficile* colitis and assessing the risk of disease relapse and extension of the disease, in combination with diabetes mellitus infection. Materials and methods: were included in the study 102 patients known to have diabetes type 1 or type 2 admitted to our clinic between January 2016 and June 2017, from a total of 648 patients diagnosed with *C. difficile* colitis. We used data from observation charts of patients. Results: 98% were suffering from type 2 diabetes, mostly female, respectively from urban areas, 29.4% being at the second hospitalization in our clinic for the same symptoms. Studying the average length of hospitalization, compared with a control group, we noticed the prolongation of hospitalization for patients with metabolic pathology associated with approximately 7 days. Conclusions: Diabetes is a risk factor for the occurrence and recurrence of *C. difficile* infection, an additional risk factor being the age.

Key words: *Clostridium difficile*, diabetes, multidisciplinary approach, risk factor.

1. Introduction

C. difficile colitis is the most common in-hospital infection which causes infectious diarrhea with increased risk of recurrence and death. The infection is widely spread throughout the world, including in Romania, its incidence being steadily rising in recent years as a result of the selection of a hypervirulent bacterial strain (NAP1-027 ribotype) with the potential to produce severe clinical manifestations of disease with resistance increased to the antibiotics commonly used in medical practice (third and fourth generation of cephalosporins, fluorochinolones, carbapenems) and higher risk of therapeutic failure [1].

Clostridium difficile is an anaerobic gram-positive, spore-forming bacillus that can persist in unfavorable environmental conditions. The bacterium is naturally present in the microbacterial flora of the colon in a large proportion of newborns and babies under one year, at 2-5% of the general population and in the

proportion of 10-30% in hospitalized patients [2].

Transmission of *C. difficile* infection occurs via the digestive tract (fecal-oral transmission), directly from the patient or the asymptomatic carrier to the contact (other patients, medical staff, carers) or indirectly by contact with objects contaminated with spores or vegetative forms [3]. The main reservoir of infection is in particularly represented by patients with clinically manifest disease (diarrhea) and asymptomatic carriers. Also, the bacteria can survive for a long time on affected areas. Also, the bacteria can survive for a long time on infected surfaces. Therefore, any surface, material or medical device that is contaminated can serve as a source of infection [4].

The clinical picture in *C. difficile* infection may vary from mild diarrhea to inflammatory processes, altered colonic mucosa, with the appearance of pseudomembrane. The evolution of the infection is dictated by the individual characteristics of the patient (risk factors, associated diseases) and the speed and accuracy of the treatment [1]. However, even under the right and complete treatment, it is estimated that the risk of relapse (defined as the recurrence of clinical

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disease manifestations in the first 2-3 months of the previous episode) is 20-27%. Mostly relapse is due to the persistence of spores in the digestive tract, but it can also be discussed the infection caused by a new strain of *Clostridium difficile* and the exact cause being difficult to specify [5].

An important factor in the disease occurrence is the consumption of antibiotics, but the patient's comorbidities should not be ignored. The most common associated pathologies are: diabetes, oncological diseases, surgical and nonsurgical, digestive diseases, kidney failure or heart failure [6].

Over time, several studies have been conducted on regarding the possible relationship between the occurrence of *C. difficile* colitis and diabetes mellitus. The association between diabetes and increased susceptibility to infection with *C. difficile* is not supported by strong evidence, but existing ones demonstrate that diabetes increases the risk of metronidazole treatment failure and, implicitly, the risk of recurrence of infection. Studies have demonstrated that diabetes increases the risk of recurrent *C. difficile* infection with OR (95% CI) 2.99 (1.88, 4.76) [7, 8]. Another study, conducted in 651 patients showed that diabetes was found to be a significant independent risk factor for *C. difficile* recurrence (adjusted OR ranged from 3.79 to 5.46, p -value < 0001).

Recent studies have shown a relationship between intestinal microbiota and metabolic diseases such as obesity and diabetes. Extending hospitalization to patients with diabetes may influence the development of nosocomial *C. difficile* infection, another study shows [9].

The aim of this study was to assess the prevalence of diabetes among *C. difficile* colitis patients admitted in the clinic, for a period of 18 months and at the same time, we asked the question whether the association of infection with diabetes increases the risk of relapse and cause the disease to train.

2. Method and Materials

We conducted an observational retrospective study to patients admitted to the "Sf.Parascheva" Infectious Diseases Hospital for a period of 18 months (January 1st, 2016 and 30 June 2017) which associate *C. difficile* infection and diabetes.

To this was included in the study 102 patients known to have diabetes type 1 or type 2 admitted to our clinic between January 2016 and June 2017, from a total of 648 (15.7%) patients diagnosed with *C. difficile* colitis in that period.

Data on the symptoms, the personal pathological history, the laboratory findings, the previous treatment and the treatment of the infection, respectively of the metabolic disorder, were taken from the observation sheets of the patients.

3. Results and Discussions

There have been investigated 102 patients known with diabetes (98% DZ type 2 and 2% DZ type 1) and diagnosed with colitis with *C. difficile*. Patients are between the ages of 36 and 86 with a median age of 68 years, 82.35% being retired. There has been a predominance of female sex, as well as people from urban areas.

Regarding nosocomial transmission of infection, 42% of the cases were hospitalized by transferring from different clinics (Fig. 1). We observe larger addressability from gastroenterology, diabetology or cardiology departments. It is important to know the departments from which each patient (where applicable) is coming, because only in this way we can differentiate a nosocomial infection from a community one.

Also, from the accompanying sheets of the patients, we could note that 54% of them were treated with antibiotics before the onset of the symptomatology. We recall that *Clostridium difficile* is involved in the production of infectious colitis associated with the use

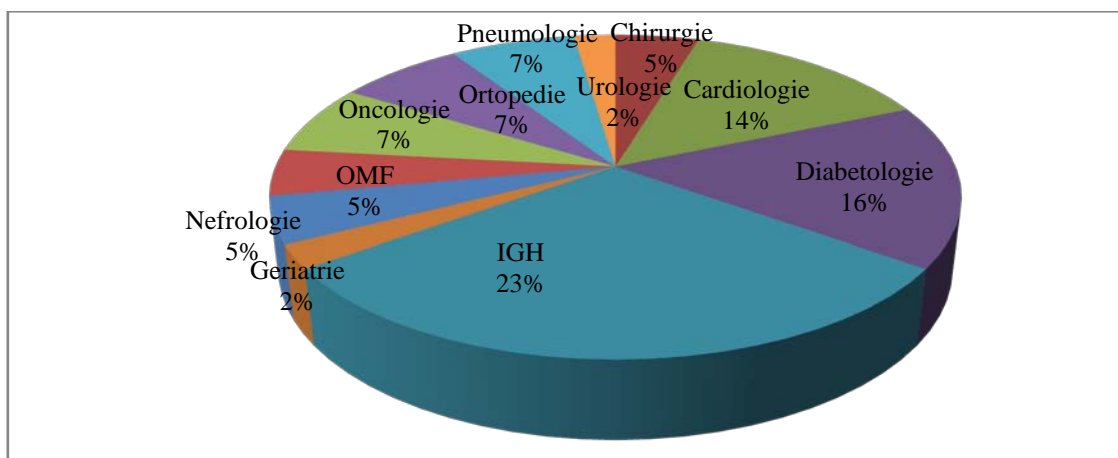


Fig. 1 Distribution of medical specialties that guide the patient to the Infectious Diseases Hospital.

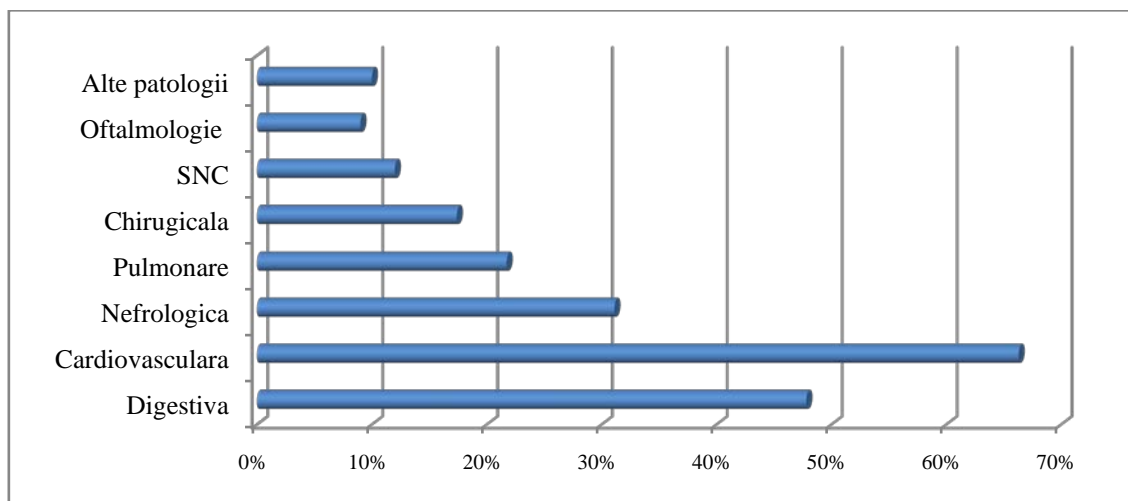


Fig. 2 Distribution of associated comorbidities.

of antibiotics, the most incriminated antibiotics being cephalosporins, fluoroquinolones and lincosamides

The presence of the etiological agent was confirmed by the rapid test detection of toxins A and B for *C. difficile* in the faeces, an important criterion for inclusion in the study. Thus, both toxins were positive in 77 (75.5%) cases, toxin A in 20 (19.6%) cases and GDH (glutamate dehydrogenase) in 5 (5%) cases. Positive diagnosis is based on the isolation of toxins for *C. difficile*.

As a result of the anamnesis, we could point out that 30 (29.4) of patients were at the second hospitalization in our clinic for the same symptomatology. According to CDC (Centers for Disease Control and Prevention) reports one in five patients has recurrences. But in our

study we can see that the ratio is one to three.

From the point of view of the clinical picture at admission, the presence of diarrheal stools, vomiting, abdominal pain, symptoms characterizing *C. difficile* infection was followed, but the fever, headache or inappetence was also observed. All patients experienced typical disease symptoms, in 13 cases associated with fever, and thus the disease evolution was much slower, requiring antibiotic therapy (besides the specific *C. difficile* infection treatment with Vancomycin/Metronidazole).

Regarding the associated comorbidities, these were synthesized in Fig. 2. The predominance of the cardiovascular pathology, followed by the digestive and nephrological one, is noted. Associated

pathologies may represent risk factors of the disease, aggravating the progression and prolonging hospitalization.

Most shows as changes in laboratory values, we can correlate disease, inflammatory syndrome (79.4%), anemia (55.8%), hyponatremia and low protein levels (33.3%) and a smaller percentage of hepatocytolysis syndrome, nitrate retention syndrome and hypokalaemia.

Dehydration syndrome, revealed by determination of serum levels of sodium, potassium, and total protein, was not a major component of the disease. We believe that addressability in the service of infectious diseases was done in a timely manner, so severe dehydration cases were minimal.

Regarding the metabolic pathology, we recall that 100 (98%) patients suffered from type 2 diabetes and only 2 (2%) of type 1 diabetes mellitus. The complications were observed in 19 cases, predominant microvascular complications (57.89% diabetic neuropathy, 31.57% diabetic nephropathy, 10.54% other retinopathies).

Treatment of patients included in the study was pathogenic, with an average duration of 7-10 days (29% of cases > 13 days). Treatment with Vancomycin (62.17%), Metronidazole (12.56%) and the combination of Vancomycin + Metronidazole (25.25%) were initiated. Along with the treatment of metabolic imbalance and hydroelectrolytic rebalancing, combating fever, associated with the hygienic-dietary regimen, with slow but favorable evolution.

We also looked at the median duration of hospitalization for two types of patients: relapsed patients with and without diabetes, and without relapses, with or without diabetes. Lot A was composed of 154 patients in the first episode of colitis with *C. difficile*, 77 of whom are associated diabetes mellitus. And lot B was made up of 50 patients with infectious colitis, including 25 diabetics.

It was obtained for group A the median hospitalization days for 7 days, respectively 10 days in

those with diabetes, and for group B the median of hospitalization days was 11 days and 15 days respectively for diabetic patients.

All patients were discharged or transferred to other medical units and no deaths were recorded.

4. Conclusions

According to our study, we can conclude that diabetes is a risk factor for the onset and recurrence of *C. difficile* infection, one in three patients returning to diarrhea syndrome. Plus as a risk factor is the advanced age, so problems can arise in the therapeutic management of patients with ICD and the disease to be slow.

We considered that the length of hospitalization is an exhaustive comparison parameter because it includes associated pathologies. The prolongation of hospitalization was observed in patients with associated metabolic pathology, in the case of the other patients evaluated, comparatively, there was a reduction of approximately 7 days of hospitalization.

C. difficile infection is a major health problem, both in Romania and in the world, with a high addressability in infectious diseases clinical, which makes the intervention of physicians quick and optimal. At the same time, intensifying prophylactic measures will lead to an increase in patients' quality of life and lower costs.

Given the increasing prevalence of clostridium infection, use of antibiotics widely by family doctors and especially changes in the microbial flora found in various diseases, it is necessary to monitor and study the infection at all levels.

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