

INCREASING INCIDENCE OF RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION

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INCREASING INCIDENCE OF RECURRENT *CLOSTRIDIUM DIFFICILE* INFECTION (Abstract): *Clostridium difficile* infection continues to be a major cause of infectious enterocolitis, commonly associated with antibiotic use. Infection can lead to relapses, reason why it is considered by clinicians a true challenge. **Aim:** To determine the incidence of recurrent *Clostridium difficile* infection in patients admitted to the Iasi Infectious Diseases Hospital over a six-month period. **Material and methods:** Of the 195 admitted patients, 46 presented for the recurrence of colitis. Data from medical records had been used to identify the patients who met the inclusion criteria. **Results:** Most of the 46 relapses were recorded in individuals aged over 60 with multiple associated comorbidities. The test for *Clostridium difficile* toxin was positive in a significant percentage of cases and the treatment consisted in the administration of vancomycin and normix alone or in combination, along with the treatment of comorbidities. **Conclusions:** Once a relapse occurs the risk of a second relapse is rising, the elderly being most vulnerable. The use of antibiotics should be limited to situations where they are absolutely needed. **Keywords:** RECURRENT CLOSTRIDIUM DIFFICILE INFECTION, VANCOMYCIN, COMORBIDITIES, MULTIDISCIPLINARY COLLABORATION.

Ubiquitous bacterium, *Clostridium difficile* (*C. difficile*) has been incriminated in the causation of infectious enterocolitis, the most common cause of nosocomial diarrhea. The bacterium is part of the normal intestinal microbiota in 3% of the adult population, 10-30% of hospitalized patients, and 60-70% of infants.

C. difficile enterocolitis can occur at any age after antibiotic administration and rarely spontaneously. Patients who receive antibiotic therapy are at 7-10 times higher

risk for developing the disease (1).

Also, patients who are hospitalized for other diseases and those with gastrointestinal surgery in recent history are at higher risk, the incidence being higher among people over the age of 65 (2).

The disease can be cured, may recur or can be fatal. Recurrent *C. difficile* infections represent a major clinical challenge due to their growing incidence. According to the Center for Disease Prevention and Control each year *C. difficile* is involved in

over 500,000 illnesses and one in five people diagnosed with *C. difficile* colitis returns due to the recurrence of symptoms and positivity of stool cultures. Once a relapse occurs, the risk of a secondary recurrence is 45%. It is also estimated that this bacillus is the cause of more than 15,000 deaths in people over 65, about one in 11 patients diagnosed with the infection dying within 30 days of diagnosis (3).

The source of infection are people (with *C. difficile* infection or carriers) who spread the bacteria or contaminate surfaces through hand contact and the environment of patients with colitis induced by this bacterium. Human transmission can be prevented by isolating the *C. difficile* infection cases, the use of gloves and thorough handwashing, environmental disinfection, and by educating the patients/ families (1, 4).

Recurrences are caused by reinfection with the original *C. difficile* strain (due to the presence of resistant spores) and/or reinfection with a new strain from the environment, the exact cause being difficult to determine. What can be said for sure it is that resistant strains do not exist, and therefore, the treatment may be the same as for the primary infection (5, 7). Treatment options for patients with more than one recurrence are becoming more and more limited. Prolonged use of metronidazole is associated with a risk of neurotoxicity, which is why oral v vancomycin is preferred in these cases. Other drugs have been approved as an alternative treatment for relapses: fidaxomicin, rifaximin, probiotics, ion exchange resins (cholestyramine) or fecal microbiota transplantation (6, 7).

MATERIAL AND METHODS

This retrospective observational study

was conducted at the “Sf. Parascheva” Infectious Diseases Hospital from Iasi. It included all patients diagnosed with *C. difficile* colitis admitted between July 1st and December 31st, 2016, the aim being to determine the incidence of recurrent infections. The presence of the causative agent was confirmed by the rapid test for the detection of *C. difficile* toxins A and B, this being the most important inclusion criterion.

A descriptive analysis based on the demographic, clinical, and laboratory data, disease course, therapeutic approach and underlying diseases was carried out using data from patient medical records.

RESULTS

Between July 1st and December 31st, 2016, 195 patients diagnosed with *Clostridium difficile* colitis were admitted. The data collected from medical records as well as from the accompanying documents revealed that 46 patients presented for relapse, the remaining patients being at their first admission for this disease.

The most affected age group was over 60 (71.73% of the cases), with relatively small gender differences (46% women, 54% men). Similar percentages were recorded for the place of residence (54% urban patients, 46% rural patients).

According to history and accompanying documents these 37 patients received antibiotic treatment prior to the first episode of *C. difficile* colitis, the most commonly being used the cephalosporins and fluoroquinolones.

Of the total of 46 patients, 63% were at their first relapse, 17% at the second, and 9% at their third relapse. In 58.69% of the cases, the patients presented themselves directly to our hospital (at the triage or the doctor who had previously treated him),

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32.61% of cases were referred by other specialists and only 8.7% of the cases were referrals from family doctors.

The disease had a favorable course in most cases, with remission of diarrheal symptoms and negativizing of *C. difficile* toxin in stools. Three cases had an unfavorable course, resulting in death due to complications of the associated comorbidities. Because in most cases patients were retired (86.95%), they also had several underlying disorders, the most common being the digestive (including liver cirrho-

sis, hepatitis B, C, colorectal cancer, chronic cholecystitis, gastric/duodenal ulcers), cardiovascular and surgical ones, as shown in figure 1.

Analyzing the observation charts, it was found that all patients had the specific symptoms of the disease (moderate or severe diarrhea, accompanied by abdominal pain), to which symptoms of nausea and loss of appetite were added in 8 (17.4%) patients, vomiting and fever in 5 (10.9%) and 2(4.37%) patients experienced vertigo and abdominal bloating.

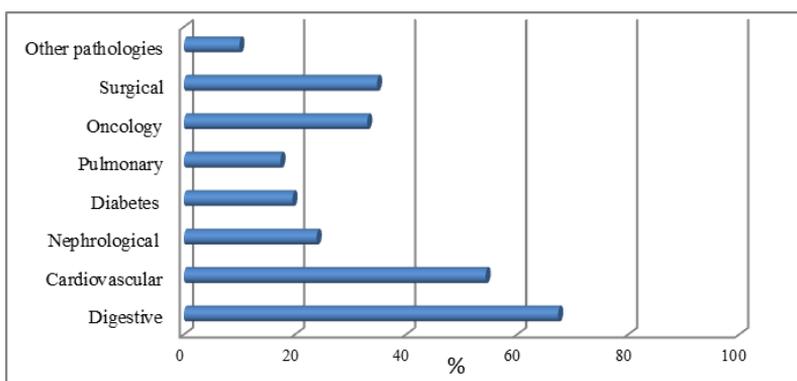


Fig. 1. Distribution of associated comorbidities

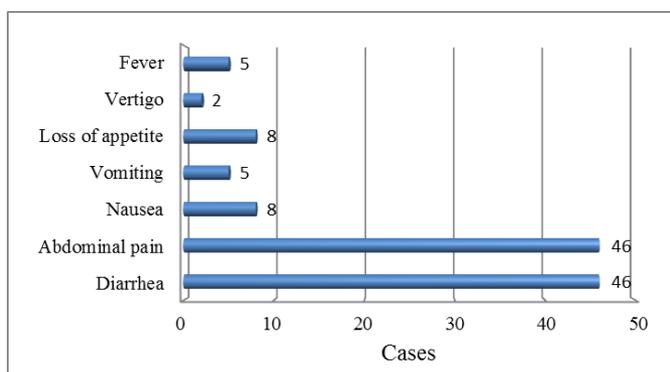


Fig. 2. Distribution of cases by associated symptoms

The positive diagnosis is based on the rapid detection of *C. difficile* toxins A and B in stool samples. In our study group both

toxins (A and B) were detected in 80.43% of cases, toxin A alone in 10.9% cases, GDH antigen in 19.5% and 2.17% of the

results identified nontoxigenic strains.

A significant number of patients also presented clinical-biological changes associated with the disease: anemia (54.34% of cases), predominantly microcytic anemia, the most frequent cause being iron deficiency, or secondary, intrainfectious hypokalemia (39.13% of cases) and hypoproteinemia (39.95% of cases).

Most patients had been hospitalized for more than 8 days (range 3-26 days). All patients received antibiotic treatment during hospital stay. Therapy was initiated after the confirmation of relapse, and its average duration was 7-10 days. Vancomycin treatment was instituted in 80.43% of relapses, normix in 34.78%, and 15.21% of cases were treated with vancomycin and normix combination. In addition to the treatment for *C. difficile* colitis, 67.4% of the patients also received treatment for the underlying diseases.

In the case of patients with a poor general health status with or with associated comorbidities, intensive care physicians as well as physicians of various specialties were consulted to provide the best recovery therapy.

DISCUSSION

Unfounded use of antibiotics has led to a significant increase in the resistance of microorganisms to antibiotics. A major side effect of unfounded antibiotic use is the increased incidence of post-antibiotic diarrhea.

Any antimicrobial medication with intestinal penetration is thought to trigger the disease, even at very low doses. Therefore, those who received prior antibiotic treatment and the elderly are the most vulnerable groups of patients who can develop *C. difficile* colitis, an infectious disease with interhuman transmission, with increased

risk of rebound and death.

The analysis of the data from our study showed that the people aged over 60 years and retired were most commonly affected, with a slightly higher proportion of male and urban population.

Clostridium difficile toxins A and B were positive in most cases, which is essential in the present study, with the occurrence of the specific symptoms of disease in 100% of cases. Patients had multiple associated comorbidities, especially surgical and digestive, but also disturbances in biological assays, which impeded the favorable outcome in three patients who died.

Due to the risk of neurotoxicity of prolonged use of metronidazole, antibiotic therapy with vancomycin (80.43%) and normix (34.78%) alone or in combination was chosen in parallel with the treatment of comorbidities.

CONCLUSIONS

The results of the present study show that recurrences of *C. difficile* infection are frequently diagnosed in patients with multiple comorbidities, especially surgical and gastrointestinal, and additional risk factors include advanced age and history of cancer that represent major problems in the clinical management of patients with *Clostridium difficile* infection.

Our recommendation for preventing the disease is the limitation of antibiotic use, as well as maintaining proper hygiene (of the skin, surfaces and the environment). Also, observance of the indications on food consumption leads to a favorable course of the disease and prevents relapses.

It can be noted that in case of complex treatments the multidisciplinary approach plays an important role in the evolution of the disease and recovery of patients.

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NEWS

HISTOPATHOLOGIC FEATURES OF PROGNOSTIC SIGNIFICANCE IN HIGH-GRADE OSTEOSARCOMA

Osteosarcoma is a malignant mesenchymal neoplasm characterized by bone production. Several types of primary high-grade osteosarcoma are recognized by the World Health Organization, including the “conventional” types encompassed by the chondroblastic, fibroblastic, and osteoblastic subtypes, among others. Despite heterogeneity in histomorphology, most high-grade osteosarcomas receive similar treatment, namely, neoadjuvant chemotherapy typically consisting of doxorubicin, cisplatin, and high-dose methotrexate, followed by surgical resection and maintenance chemotherapy. Although many groups have assessed the contribution of clinical parameters—namely, patient age, sex, anatomic site of primary tumor, tumor size, and metastasis at presentation—in predicting survival outcomes for patients with osteosarcoma, there are limited data concerning histopathologic attributes. Histopathologic prognostic factors represent an essential component to the treatment stratification of many types of cancer. The authors suggest that detailed microscopic examination (tumor pleomorphism, mitotic activity, and morphologic subtype) yields useful prognostic information in high-grade osteosarcoma. In biopsy samples, necrosis and chondroblastic differentiation are adverse features. In resections, quantitation of the extent of residual viable tumor may be of greater clinical relevance than attempting to distinguish necrosis from other noncellular elements. In summary, the integration of clinical and microscopic features is a feasible and effective means for improving prognostication in patients with osteosarcoma. The effective stratification of patients using the proposed scoring system merits further investigation, ideally in prospective cohorts, to validate interobserver reproducibility and predictive ability (Chui MH, Kandel RA, Wong M, *et al.* Histopathologic Features of Prognostic Significance in High-Grade Osteosarcoma. *Arch Pathol Lab Med* 2016; 140(11): 1231-1242).

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