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Clostridium difficile infection in a university teaching hospital: focus on recurrences

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ABSTRACT:

Objective: Although Clostridium Difficile Infection (CDI) is the leading cause of hospital infections, limited data on the burden of CDI in Italy are available. The management of relapses is the most important clinical problem to which, to date, there are no definitive solutions. The clinical findings are promising, although further studies are needed to better understand the role of these new therapeutic approaches in the management of CDI recurrence.

Materials and Methods: The study included all patients with CDI evaluated at the Infectious Disease Unit at the University Hospital of Sassari, from 1 January 2015 to 31 December 2017.
Microbiological diagnosis was performed by the search of glutammate dehydrogenase (GDH) and toxin A/B or by PCR. Demographic and clinical data were collected from the patient's medical records.

Results: A total of 35 CDI episodes were identified. All patients were Caucasian with a mean age of 72 years while 26 patients (72.2%) were female. Sixteen cases (45.7%) of CDI occurred in medical wards followed by Surgery Department. Out of the total, 11 were recurrences. In the study performed, out of 17 patients hospitalized in the Infectious Disease Unit, 9 were first infections and 8 were relapses. CDI occurred in the hospital setting in 9 cases; it occurred in the community in 4 cases; it was indeterminate in other 4 cases. The median hospital lenght of stay was 13.6 days, and there were two deaths. The most frequent clinical manifestations were: diarrhea with mucus and blood, watery diarrhea, fever, abdominal pain, renal failure, white blood cell count >16000 or <4000 cells/mm^3. First infections were treated with vancomycin. Recurrents were treated with fidaxomicin in 4 cases and vancomycin in other 2 cases. Two patients with multiple recurrences were treated with vancomycin and fecal transplantation. The analysis of risk factors for recurrences showed that all patients had experienced antibiotic exposure, 7 were > 65 years old, 5 were taking PPIs, 4 had CD subtype 027, 3 had undergone surgical procedures and 3 had suffered from chronic renal failure.

Conclusions: Our data confirm the changing epidemiology of Clostridium and the high recurrence rate of CDI. Community infections accounted for 23.5% of CDI in accordance with the most recent European data. Recurrences represented nearly 47% of cases, exceeding the rate reported in literature. The high percentage of recurrences observed could be ascribed to the characteristics of the patient's risk factors associated with the development of relapse.

Keywords: Clostridium difficile infection, Fecal microbial transplantation, Recurrent infection, Risk factors, Infection control.

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INTRODUCTION

Clostridium difficile infection (CDI) is the leading cause of healthcare associated infections in the United States and European hospitals[1]. Its incidence, severity and relapse rates have increased over the past two decades[2]. Unfortunately, limited data on the burden of CDI in Italy is available and reporting activities are not mandatory and standardized. Classically considered a hospital infection, CDI has become more widespread in recent years[3]. During the past decade there has been an increase in community CDI due to the emergence of hypervirulent strains, changes in health care procedures and different risk profiles among patients. Over 40 risk factors have been associated with CDI. These include pharmacological and host related-risk factors, in addition to clinical characteristics or interventions. Among these, the most important factors are: the use of antibiotics and proton pump inhibitors (PPIs), age > 65, comorbidities such as renal impairment (especially during relapses), immunosuppression, prolonged hospitalization and/or intensive care, the absence of response to targeted antibiotic therapy, the presence of hypervirulent strains, the presence of leukocytosis/leukopenia at diagnosis, and a recent surgery in the gastrointestinal tract[4].

Of major concern is the management of recurrence CD (RCDI) that can be the effect of both reinfection from different strains or non-eradication of the original infection[5]. The recurrence seems to be related with the combination of several factors, such as the inability to reestablish a normal intestinal microbiota, the persistance of *C. difficile* spores, as well as a suboptimal immune response[6]. The RCDI risk can be strongly predicted by the number of prior CDI episodes: the risk of recurrence for patients with a single previous episode of recurrent CDI is estimated to be approximately 40% and is estimated to be 60% for patients with two or more earlier CDI episodes[7].

Since the antibiotic resistance is not a CDI priority problem, both the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) recommend treating the first recurrence of CDI with the same therapeutic agent used in the initial episode, especially if this has been vancomycin or fidaxomicin[5]. In the treatment of multiple recurrences, oral vancomycin is often given in a tapered dose or intermittently, but fidaxomicin can be also used[8].

However, none of the above conventional therapies can restore normal intestinal flora, which is considered the only factor able to contrast the colonization and moltiplication of the bacteria. This result is only achieved with the practice of fecal transplant (FMT), which, therefore, represents one of the most effective treatments available for recurrent CDI.

It is well known that patients with CDI recurrence normally lack dominant bacteria in the colon including Bacteroidetes and Firmicutes[9]. In the literature, the use of antibiotics has been associated with alterations in both structure and function of the microbial community. The conversion of cholesterol to coprostanol and the concentration of urobilinogen and trypsin are significantly reduced if compared to healthy people. It is interesting to note how these variations could be restored after the fecal transplant[10].

FMT appears to be safe and has not been associated with major complications. Fecal transplantation is playing an important role in the therapy of recurrent CDI with remarkable results, achieving success rates of about 90%[11,12].

There are many emerging treatment strategies for RCDI involving the use of non-antibiotics – such as monoclonal antibodies directed particularly to the toxin B considered most implicated in the damage - that have shown promising results[13,14].

The clinical burden of RCDI is highly economic, due to the increased duration of hospitalization, readmission and managing complications. Therefore, the management of relapses is the most important clinical problem to which, to date, there are no definitive solutions. The clinical findings are promising, although further studies are needed to better understand the role of these new therapeutic approaches in the management of CDI recurrence.

MATERIALS AND METHODS

The study included all patients with *C. difficile* infection, evaluated at the Infectious Disease Unit at the University Hospital of Sassari, from 1 January 2015 to 31 December 2017.

The patients enrolled were admitted to the Infectious Disease Unit or assessed by an infectious disease specialist while hospitalized in other units of the same hospital or during an external consultation. The diagnosis was performed with immunoenzymatic methods (VIDAS® *C. difficile* GDH in combination with the test VIDAS® *C. difficile* Toxin A & B - bioMérieux S.A. 69280 Marcy L'Étoile, France- as part of an algorithm in two stages) or with molecular biology methods (test in PCR Real-time Xpert *Clostridium difficile* - GeneXpert Cepheid Inc, Sunnyvale, CA 94089, USA) able to identify, from the sample, the toxigenic and hypervirulent strains (ribotype 027 / NAP1 / B1), based on the recognition of sequences of ctdb genes, the binary toxin and CTDC changed. The use of immunoenzymatic methods or molecular biology methods has depended on the diagnostic algorithm in each specific laboratory. Demographic and clinical data were collected from the patient's medical records. We described demographic data, the origin of CDI and the type of infection (first or recurrent). A subanalysis of the patients hospitalized at the Department of Infectious Diseases was also performed.

RESULTS

A total of 35 CDI episodes were identified. All patients were Caucasian with a mean age of 72 years old; 26 of them (72.2%) were female. Sixteen cases (45.7%) of CDI occurred in medical wards, followed by Surgery Department (10, 28.6%). In 9 cases (25.7%), patients were not hospitalized when the diagnosis was performed. Out of

Table 1. Clinical presentation and laboratory data on admission.

Clinical symptoms and laboratory data	Number of patients
Watery diarrhea	6
Diarrhea with mucus and blood	11
Fever	7
Abdominal pain	7
Hypotension/tachycardia/ disorientation	2
Renal impairment	4
White blood cell count >16000 <4000 µl	3
Candidemia	0

Table 2. Prevalence of risk factors among hospitalized patients with CDI.

Variable	N = 17
Antibiotic therapy *	17 (100%)
Antibiotic therapy combination*	8 (47%)
Age> 65 years	11 (64.7%)
Use of PPI	8 (47%)
Immunosuppression	6 (35.3%)
Non infectious Comorbidity**	14 (82%)

PPI: Proton pump inhibitors; * In the last three months; **cancer, diabetes, arterial hypertension, autoimmune diseases.

the total, 11 (31.4%) were RCDI including 4 multiple recurrences caused by hypervirulent strain 027. In the study on 17 patients admitted to our Infectious Disease Unit, we evaluated the origin of the CDI, the average length of stay in the hospital, the clinical presentation at admission, the outcome, the risk profile of patients and the adherence to the current guidelines for diagnosis and therapy of CDI. According to the ECDC, CDI had been hospital acquired in 9 (53%) cases, community in 4 cases (23.5%) and indeterminate in other 4 cases (23.5%). The average hospital lenght of stay was 13.6 days. CDI was the primary cause of hospitalization in 15 patients (88%) whereas in 2 patients CDI emerged during hospitalization due to hip fracture and cesareans. Clinical presentation and laboratory data on admission were summarized in Table 1. In seven patients the diagnosis was achieved by immunoenzymatic methods with positivity for both GDH and Toxin A / B whereas in 10 patients using molecular biology methods (test in PCR). Nine patients with first infection were treated with vancomycin (the average treatment duration was 12 days). In two cases vancomycin was replaced with fidaxomicin for clinical failure (average treatment duration was 10 days). Relapses occurred in 8 patients (47%). Among them, 2 patients were treated with vancomycin; 4 with fidaxomicin (mean treatment duration of 10 days) and 2 with multiple relapses, with vancomycin followed by the fecal transplant. The average duration of treatment with vancomycin was 12 days. For 11 (64.7%) patients a clinical response was achieved within 5 days from the start of chosen antibiotic therapy. Two out of 17 patients died during hospitalization: a patient due to a gram-negative sepsi and another one due to acute exacerbation of chronic heart failure. The mortality rate was 11.7% (2/17).

In our study, 3 patients were candidate for FMT but one patient had developed a Gram-negative sepsi and died before we could proceed. The procedure approved by the Ethical Committee of the University Hospital of Sassari included the selection of donors from the patient's family. Donors were adequately screened on blood and feces in order to avoid the presence of transmittable pathogens and/or autoimmune diseases, inflammatory bowel diseases, cancer and other factors that could affect the success of the procedure. The receiver, two days after completion of vancomycin therapy, performed a colonoscopy with infusion in the ascending colon of approximately 300 ml of the preparation (fresh faeces <6 hours, processed under a laminar flow hood, diluted with 500 ml of physiological solution sterile bacteriostatic not emulsified and filtered with double gauze).

In the analysis of risk factors for CDI, all patients reported exposure to antibiotic therapy in the previous three months. In 8 (47%) out of 17 cases, the therapy was a combination of two or more antibiotics, while for 3 patients the drug was no specified. The antibiotic regimen received was based on cephalosporins in 6 patients, quinolones in 5, piperacillin/tazobactam in 3, amoxicillin/clavulanic acid in 2, carbapenems, trimethoprim-sulfamethoxazole and gentamicin in 1 case. Eleven patients (64.7%) were > 65 years, 8 (47%) were receiving PPIs, 6 (35.3%) presented a state of immunosuppression relating to the treatment of multiple sclerosis, rheumatoid arthritis, Guillain Barré Syndrome, chemotherapy, COPD (treated with deltacortene) and Sjogren's Syndrome. Fourteen patients (82%) reported at least one severe comorbidity as cancer, diabetes, arterial hypertension, autoimmune diseases. Four patients reported procedures on the gastrointestinal tract in the 3 months preceding the event (3 EGDS, 1 hemicolectomy) and 4 patients had been hospitalized for more than 20 days in the previous 3 months. In a subanalysis performed on patients with a relapse (8, 47%) aimed at assessing the impact of known risk factors for recurrent events, we observed that 7 patients (87.5%) were > 65 years old, all patients had experienced some exposure to antibiotics before the event and 3 before and after the diagnosis of CDI for other concomitant infections, 5 (62.5%) were taking PPI, 4 (50%) were infected by subtype 027, 3 underwent major surgery within the previous 3 months. Finally, 3 patients had suffered from chronic renal failure, while none of the patients with a recurrence had a white blood cell count > 16000 <4000 µl at admission.

DISCUSSION

Our data confirm that CDIs represent an important public health problem for the growing number of cases possibly concerning changes in the epidemiological profile of the infection and to the high rate of recurrence. Community CDI seems to be increasing in frequency since it account-

ed for 23.5% of the total CDI in our cases in accordance with the latest European epidemiological data (20-30%)[15]. The management of relapses especially if multiple, is the most important clinical problem. In our study the relapses accounted for 47% of the total CDI. We also recorded 3 (37%) multiple recurrent forms. Our data exceeded the numbers reported in other recent European study showing a recurrence rate of 25%[16]. The high percentage of relapses observed in our study could be imputable to the characteristics of patients that have a high number of risk factors linked to the development of CD recurrences. These included advanced age, use of antibiotics especially quinolones and cephalosporins[17,18], PPI (5; 62.5%). We also observed a higher number of hypervirulent strains 027 (4; 50%) compared to another Italian study (23%)[19]. Of note, the incidence of hypervirulent strain 027 was possibly understimated since for 7 patients the diagnosis of CDI was based exclusively on immunoenzymatic methods that did not allow any strain identification. Furthermore, we identified the female sex (7; 87.5%) and kidney diseases (3, 37.5%) to be other risk factors as also shown in recent literature[20]. The therapeutic approach was in accordance with the current guidelines that recommend the use of vancomycin as an antibiotic of first choice in primary infections and the preferential use of fidaxomicin in complicated or non-responsive infection and in recurrences. In agreement with the guidelines[5,21] and clinical practice reports[11,12], multiple RCDI were candidate to non-antimicrobial approaches (specifically FMT) given the unavailability of monoclonal antibodies in our hospital during the study period.

CONCLUSIONS

Despite the limitations due to the retrospective design and the small sample size deriving from a single centre, the analysis of our data proves that efforts to contrast the spread of CDI should be guided by the study of risk factors, including those that have been recently identified. CDI frequency and severity emerged in our research suggest the need for a mandatory surveillance system for CDI in Italy. In conclusion, the proper management of new therapeutic approches and risk factors is crucial to reduce RCDI, improving quality of life and reducing negative outcomes.

Conflict of Interest:
The authors declare no conflict of interest.

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