CDI Infection in Patients with Multiple Organ Dysfunction

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Clostridium difficile infection (CDI) rates in the United States and the world have increased in the last decade, along with associated morbidity and mortality. CDI symptoms can range from mild diarrhea to severe cases including pseudomembranous colitis and toxic mega colon and death. We performed a retrospective study including 130 patients with multiple organ failure who developed Clostridium difficile infection, admitted to the Iasi Sf. Parascheva Infectious Diseases Hospital in the interval January 1st, 2014 – June 1st, 2016; in order to highlight the high incidence of it and showing how we can manage this situations. An increased number of patients with Clostridium difficile infection and multiple organ dysfunction, in 2015 and 2016 was noticed. The profile of the patient from our study is a female with the age over 65 years old, coming from the rural area. Many of the admitted cases were patients enrolled in Hemodialysis Center. Cardiovascular disease was the most common associated pathology (60.79%), followed by renal failure (42%). Charlson comorbidity index showed 3-4, for 97 cases. The specific antibiotherapy for CDI was administrated for 5-7 days to 21 days long. In 73% of the cases the CDI was treated, 17 cases recorded relapse, and one case died. Clostridium difficile is the most common enteric pathogen in hospitalized patients. Standardized procedures to implement hygienic measures and restricted use of antibiotics are necessary to control the widespread occurrence of CDI in immunocompromised renal patients.

Keywords: Clostridium difficile infection, multiple organ dysfunction, Charlson comorbidity index, metronidazole, vancomycin

Clostridium difficile is a gram positive, anaerobic bacterium generally associated through ingestion. *Clostridium difficile* infection (CDI) rates in the United States and the world have increased in the last decade, along with associated morbidity and mortality. CDI symptoms can range from mild diarrhea to severe cases including pseudomembranous colitis and toxic mega colon and death [1].

Estimated U.S. health-care-associated CDI incidence in 2011 was 95.3 per 100,000, or about 293,000 cases nationally. Incidence is higher among females, whites, and persons 65 years of age or older [2]. About one-third to one-half of health-care onset CDI cases begin in long-term care, thus residents in these facilities are at high risk [2,3]. Community-associated CDI complicates measuring the effectiveness of prevention within an institutional setting [4]. Additionally, the pathogenesis of CDI is complex and not completely understood, and onset may occur as late as several months after hospitalization or antibiotic use.

The estimated mortality rate for health-care-associated CDI ranged from 2.4 to 8.9 deaths per 100,000 population in 2011[2]. For individuals ≥ 65 years of age, the mortality rate was 55.1 deaths per 100,000, CDI was the 17th leading cause of death in this age group [1,5].

Hypervirulent *C. difficile* strains have emerged since 2000. These affect a wider population that includes children, pregnant women, and other healthy adults, many of whom lack standard risk profiles such as previous hospitalization or antibiotic use [6]. The hypervirulent strains account for 51 percent of CDI, compared to only 17 percent of historical isolates [7,8].

In recent years, infections with Clostridium difficile have become more frequent in immunocompromised renal and transplanted patients [9].There is widespread uncertainty as to the optimal management and prevention of this problem, particularly in the above patient group.

Pathogenic strains of *Clostridium difficile* produce an enterotoxin (toxin A) and a cytotoxin (toxin B) which cause mucosal damage and inflammation of the colon. It previously was thought that toxigenic strains of *C. difficile* always produce both toxin A and toxin B, but recent studies have demonstrated the presence of toxin A(-) B(+) strains among clinical isolates [9].

Non-specific, but suggestive hints pointing to *C. difficile* infection include leukocytosis, hypalbuminaemia and faecal leukocytes. In hospitalized patients, a prompt search for *C. difficile* infection has been recommended in cases of unexplained leukocytosis. Delay in establishing the diagnosis is known to increase the risk of death in *C. difficile* colitis. Testing the stool of asymptomatic patients is not clinically useful and is not recommended [9].

In symptomatic patients, however, the most sensitive test to establish the diagnosis of infection with *C. difficile* is the stool culture. In contrast, the toxin B cytotoxicity test is the most specific examination [10]. It is recommended to perform both tests for maximal diagnostic sensitivity and specificity [11].

Metronidazole (250 mg four times a day) or vancomycin (125 mg per os four times a day) for 10 days are recommended as effective treatments. Metronidazole may be preferable to avoid induction of vancomycin resistance in other nosocomial bacterial species. Another advantage of metronidazole is lower cost. Vancomycin should be reserved for patients who do not tolerate metronidazole or have not responded to its administration [9,12].

Several treatment protocols have been proposed for patients with multiple relapses of CDI. One approach is to use a 4–6 week regime of tapering, followed by pulsed doses of vancomycin (125 mg every 6 h for 7 days, followed

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by 125 mg every 12 h for 7 days, 125 mg/day for 7 days, 125 mg every other day for 7 days and 125 mg every 3 days for 7 days) [9,12].

Normalization of the faecal flora is important to prevent a continued overgrowth with *C. difficile.*

Experimental part

Material and methods

We performed a retrospective study in order to highlight the high incidence of cases with *Clostridium difficile* infection in patients with multiple organ dysfunction, showing how we can manage this situations.

Our study included 130 patients with multiple organ failure who developed *Clostridium difficile* infection, admitted to the Iasi Sf. Parascheva Infectious Diseases Hospital in the interval January 1st, 2014 – June 1st, 2016.

The study protocol included the following data retrospectively analyzed: epidemiological, clinical and evolutive features, positive diagnosis (finding the *Clostridium difficile* A or B toxin in the stool exam), treatment, course and prognosis.

Results and discussions

The distribution of the study cases showed an increasing trend in the number of patients with *Clostridium difficile* infection and multiple organ dysfunction, in 2015 (fig. 1),

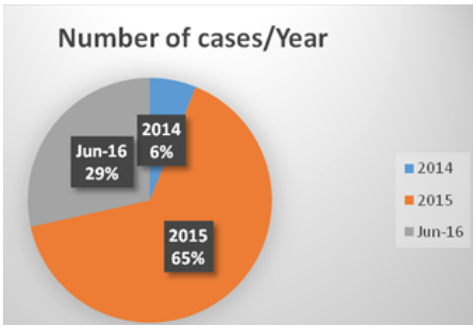

Fig. 1. Distribution of CDI cases per year

for the year 2016 being estimated also a high number of cases as can be seen from the same figure 1.

The profile of the patient from our study is a female with the age over 65 years old, coming from the rural area (fig.2, fig.3).

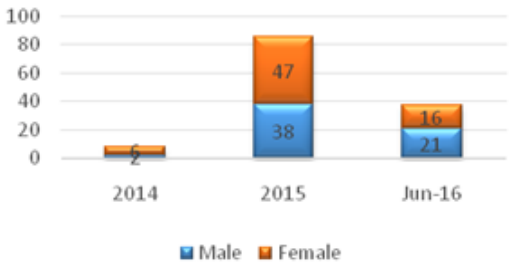

Fig. 2. Case distribution by gender/year

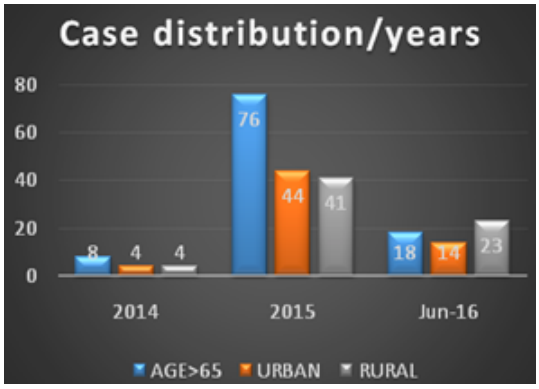

Fig. 3. Distribution of CDI cases per year according to origin area

The fever was present from the beginning of the admission in almost all of the cases (93%), and also the declarative diarrhea syndrome objectified and subsequently finding positive the toxins A and B *Clostridium difficile* in stool examination.

The laboratory revealed the presence of the inflammatory syndrome with leukocytosis (white blood cells > 12.000/mmc) and the polymorphonuclears predominance, in most of the cases.

Many of the admitted cases were patients who were enrolled in Hemodialysis Center.

Also, most of the cases had other previous hospitalization in internal medicine sections (50.76%).

As associated pathology, the cardiovascular disease was the most common (60.79%), renal failure in almost 42% of the cases, and the neoplasms were found in 15 cases (table 1).

None of the cases did not necessitate intensive care admission.

Characteristic	Number	Percentage
Mean age, y (SD)	70.17	
Age>65 years	102	78.46%
Urban area of residence	62	47.69%
Recent hospital admission		
Internal medicine	66	50.76%
Surgery	21	16.15%
Healthcare association	4	3.07%
None	39	30%
Associated pathology		
Neoplasms	15	11.53%
Renal failure	54	41.53%
Hepatic syndrome	36	27.69%
Respiratory system disease	46	35.38%
Cardiovascular disease	79	60.79%
Metabolic disorder	68	52.30%
Antibiotic therapy	63	48.46%
ICU admission	-	-
CDI relapse	17	13.07%
Charlson comorbidity index		
0	-	-
1-2	8	6.15%
3-4	97	74.61%
5+	25	19.23%

Table 1
CHARACTERISTICS OF PATIENTS WITH *CLOSTRIDIUM DIFFICILE* INFECTION

Prior antibiotiotics classes commonly used	Cases	Percentage
Aminopenicillins	10	7.69%
Flouroquinolons	15	11.53%
3rd generation cephalosporins	12	9.23%
Macrolides	7	5.38%
Lincosamides	15	11.53%
Rifamycins	8	6.15%

Table 2
PRIOR ANTIBIOTIC THERAPY

Antibiotic schemes
Metronidazole 1.5g/day oral administration
or
Metronidazole 1.5g/day oral administration + Vancomycin 500 mg/day oral administration

Table 3
ANTIBIOTIC THERAPY USED FOR ENROLLED PATIENTS WITH CDI

Table 4
ANTIBIOTIC THERAPY USED FOR ENROLLED PATIENTS WITH CDI

Prognosis	Cases	Percentage
Cure	95	73.07%
Relapse	**17**	**13.07%**
Death	1	0.76%
Unknown	17	13.07%

According to Charlson comorbidity index; which predicts the one-year mortality for a patient who may have a range of comorbid conditions, such as *heart disease, AIDS,* or *cancer*; the most frequent score was 3-4, for 97 cases (table 1). In 17 cases was recorded CDI relapse.

More than half of the patients (51.53%) had prior antibiotic therapy, especially being used lincosamides, second or third group flouroquinolons, aminopenicillins, third generation's cephalosporins, macrolides, and rifamycins (table 2).

According to the literature, Clindamycin, cephalosporins (in particular third generation cephalosporins such as cefotaxime and ceftriaxone) and broad spectrum penicillins are notorious for provoking CDI. Aronsson et al., showed that cephalosporins are implicated 40 times more often in CDI than narrow spectrum penicillins (9,13).

The hospitalization period was between 5 and 21 days with an average of about 10 days. During hospitalization, other antibiotic therapy was needed for different associated infections, commonly being used Rifaximin, Nitrofurantoin, cephalosporins and carbapenems. Those doses were adjusted depending of the renal insufficiency degree, after creatinine clearance according to the internationals guide.

The specific antibiotherapy for CDI was administrated for 5-7 days to 21 days long (table 3).

The prognosis depend of the comorbidity, associated pathology, the immunosuppressed degree, and also the age. In 73% of the cases the CDI was treated, 17 cases recorded relapse, and one case died (table 4).

Conclusions

Our study revealed that *Clostridium difficile* infection is commonly recorded in immunosuppressed patients that are enrolled in Hemodialysis program or that had recent history of antibiotic treatment, being hospitalized in surgery or internal medicine units.

The clinical picture and laboratory findings are similar like is described in literature.

Unfortunately it can be seen an increasing number of cases of CDI in immunosuppressed patients with the age over 65 years old, coming from rural area, in the last two years.

That why it is very important to establish suitability of antibiotic administration in different cases of infection, choosing a right antibiotic, for certain period, only if it's necessary to avoid this infection in the cases that the organism is already immunosuppressed.

It is known that antibiotic agents that are active against anaerobic bacteria present the greatest risk because they alter the intestinal microecology [14].

Some specific standards of hygiene are required, in hospital or during healthcare association, such as: isolation precautions for staff and visitors, use disposable gloves and gowns, wash hands frequently with liquid soap and disinfect them frequently, do not share blood pressure cuffs, stethoscopes, tourniquets, thermometers, etc. with non-infected patients, provide private room or cohort isolation, have patients with CDI share toilets only with other CDI residents, clean rooms and environment regularly, transfer of CDI patients.

Also the specific treatment must be according to the CDI and immunosuppressed patient status. Time from symptom development to septic shock may be reduced in the hypervirulent strains, making quick diagnosis and proactive treatment regimens critical for positive outcomes.

Clostridium difficile is the most common enteric pathogen in hospitalized patients. Standardized procedures to implement hygienic measures and restricted use of antibiotics are necessary to control the widespread occurrence of CDI in immunocompromised renal patients.

All of these in order to manage properly the Clostridium difficile infection.

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