Clostridium difficile infection - a challenge for any urological service

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Abstract

Introduction. Clostridium difficile infection (CDI) remains the most common cause of *hospital-acquired infections* and is an immediate threat to public health that requires urgent and aggressive measures.

Material and methods. This clinico-epidemiological study was conducted between April 2014 - January 2015 and included 18 patients who developed acute diarrhoeal disease (ADD) during hospitalization and were diagnosed with enterocolitis caused by CDI.

Results. In addition to antibiotics or combinations of them which were used in all 18 cases, the study confirmed many other factors associated with the occurrence of CDI infection: older age, use of proton pump inhibitors (PPIs), postoperative ileus, enemas. Fluoroquinolones were the most common antibiotics used before the onset of ADD. Laboratory picture may indicate the severity of the problem, mortality rates within the study being 16.66%.

Conclusions. The concern regarding the proliferation of CDI *hospital-acquired infections* impose a set of sustained therapeutic and administrative measures in terms of transferring patients on special wards or isolating them on the wards they were diagnosed.

Keywords: complication, Clostridium difficile, pseudomembranous colitis

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Introduction

Clostridium difficile infection (CDI) remains the most common cause of *hospital-acquired* diarrhea, the number of hospitalized patients diagnosed with CDI increased from 139,000 in 2000 to 336,600 in 2009, the cost of their treatment being around $ 1 billion annually [1]. In fact, CDI exceeded the number of infections caused by methicillin-resistant *Staphylococcus aureus*, as the most common hospital-*acquired* infection [2]. This bacterium is, along the carbapenem-resistance of *Enterobacteriaceae* and antibiotic-resistance of *Neisseria gonorrhoeae*, according to a report issued by Centers for Disease Control and Prevention (CDC) in 2013, an immediate threat to public health in the US that requires urgent and aggressive measures. According to this report, there are 250,000 infections per year requiring hospitalization or already affecting hospitalized patients, of which there are 14,000 deaths per year and at least $ 1 billion per year are spent as additional medical costs [3]. Although the resistance to antibiotics which are used to treat CDI infection is not yet a problem, the bacteria spreads rapidly, because it has a natural resistance to many drugs used to treat other type of infections. In 2000, a fluoroquinolones-resistant strain was identified, this antibiotic being commonly used to treat other infections. This strain has spread across North America and Europe [3]. Many studies have focused on development of CDI antibiotics (ampicillin, amoxicillin, clindamycin and cephalosporins - especially the 3rd generation cephalosporins). An important task for the urologist is preventing and treating urinary tract infections. In this context, does the prescribed antibiotic for prophylaxis and therapy not facilitate the occurrence of CDI infection? Is there any possible correlation between urological pathology and triggering of acute diarrhoeal episode? What is the urologic patient profile that is more likely to develop this medical condition? Can we make clear correlations on medication (antibiotics or other classes of substances) that has been previously used and the risk of *hospital-acquired* acute diarrhoeal syndrome (ADD) caused by CDI? Is there an ideal treatment scheme of CDI infection correlated with age, pathology and urological disease?

This reasons, considering that lack specific data in the Romanian literature, led us to conduct a prospective study in order to evaluate this delicate situation, which could become a major health problem due its incidence and consequences.

Material and methods

This clinico-epidemiological study was conducted between April 2014 - January 2015 and 18 patients who developed acute diarrhoeal disease during hospitalization (ADD) and were diagnosed with enterocolitis caused by *Clostridium difficile,* based on detection of toxin A and B have been enrolled in the study. 21 patients who had ADD, but the confirmation of this diagnosis failed for various reasons (the urgent need to initiate antibiotic therapy with metronidazole/vancomycin because of clinical and biological condition of the patient, sample analysis was impossible for technical reasons) were excluded from this study.

A careful history was taken from all patients regarding medication (antibiotics, proton pump inhibitors IPPs, etc.) received prior to onset of the ADD, associated pathology, possible contamination from other inpatients who developed ADD in the same period. Stool frequency, medication, duration until healing, etc. were recorded.

Diagnosis of *Clostridium difficile* infection was established.

Results

Demographic characteristics of the patients are shown in Table 1. Sex ratio of all 18 patients with CDI was 3: 1 in favor of males, 58.8% were aged over 65 and those who died after developing complications of CDI infection were older than 75 years.

Within the study group, 16 patients developed CDI after performing an urologic intervention and all 18 patients received antibiotics *before* the *onset of symptoms* within 8 weeks before admission, 10 of them receiving multiple antibiotics. The most commonly used antibiotics were: fluoroquinolones (nine cases), cephalosporins (five cases), amoxicillin / clavulanic acid (three cases), *sulperazone* (three cases), colistin, meropenem and gentamicin (two cases) and one patient received a parenteral combination of tazocin and vancomycin. No correlation between the occurrence of ADD and previous use of a certain antibiotic was found.

Table 1

Gender	Female	Male
	4 (22,22%)	14 (77,77%)
Age (years)	63,5 ± 17,8 (17-89)	
Hospitalization (days)	13,55 ± 4,9	
Course of disease	Favourable	Death
	15 (83,33%)	3 (16,66%)
Clinical and *laboratory picture*	Fever	Inflammatory syndrome
	8 (44,44%)	16 (88,88%)

All 18 patients have had the same symptom at the onset of disease: accelerated intestinal transit, fever above 380C (5 cases), low grade fever (three cases). The diagnosis was based on toxins A and B detection in stool specimens, 89% of them having inflammatory syndrome (16 cases) and seven of them having significant leukocytosis (WBC 20,000 / mm3) and one patient have had thrombocytopenia. *Total protein was measured* at six patients and five of them have had hypoproteinemia.

The most important comorbidities were *as follows*: cardiovascular disease (10 cases), diabetes (three cases), one case of hepatitis B and splenectomy. No patient received *chronic antisecretory therapy* at home, but 83.33% (15 cases) of those who developed CDI have had parenteral antibiotic administration associated with a proton pump inhibitor.

A possible risk *factor* for the *occurrence* of CDI could be *postoperative dynamic ileus*, according to our study 88.88% of the patients developed this infection after performing an urologic surgery.

From all 18 patients who received antibiotic therapy in order to eradicate CDI, eight of them received both metronidazole and vancomycin, nine of them have had only metronidazole and only one patient received just vancomycin, all treatments being administered per os. Three patients had unfavorable outcome and died due to toxic megacolon (table 2), other four patients were transferred to the Infectious Diseases ward and the rest of the patients continued metronidazole therapy at home for 10 days. One group of three patients and another group of two patients were diagnosed with CDI in the same period and were hospitalized in the same room and we can take into account possible contamination of them.

Three patients who died were aged between 75 and 78 years and had significant associated diseases (atrial fibrillation, ischaemic heart disease, hypertension), one of them underwent an extensive surgery (hemostasis cystectomy) and another patient had a complication after surgery that required surgical reintervention (bladder perforation and subsequent evisceration). Only one of them had fever (over 39°C) and diarrhoeal stools, but all three had significant inflammatory syndrome and only one had hypoproteinemia. In all three patients there was an association of preoperative antibiotics: two patients received a double association of antibiotics (ciprofloxacin with amoxicillin / clavulanic acid and sulperazone with colistin) and another patient received a triple combination (initially, he received levofloxacin and subsequently, meropenem and colistin were associated). Two of these patients died 8 days after onset of ADD and the third patient died next day after onset of ADD.

Table no. 2

	Patient 1	Patient 2	Patient
Age	75	78	78
Comorbidities	FiA	A-fib, *AHT*, *IHD*	Pulmonary fibrosis
Intervention	Bilateral ureteral catheterization	Transurethral resection TUR-V	Hemostasis cystectomy
Complications	No	Cystography, evisceration	no
Paraclinic picture	CRP=445 mg/l	GA=16.900/mm^3 hypoproteinemia	GA= 31.000/mm^3
Antibiotic therapy	Amoxicilin + clavulanic acid	Levofloxacin, followed by meropenem, colistin	Colistin + sulperazone
Days from ADD onset until death	8	8	1
Hospitalizations days	15	48	19

Discussions

Clostridium difficile was described for the first time by Hall and O Toole in 1935 [4]. It was called „*difficile*" because this bacteria was *difficult to culture*. After the introduction and increasing the use of broad spectrum antibiotics in the late 20th century, this bacteria was correlated with antibiotic associated diarrhea and it was described an *association of it with* the development of *pseudomembranous colitis*.

Once the context was defined, the incidence of this bacteria *has been continuously increasing.* Currently, it *play an important role* in *nosocomial infections*, contributing to *prolongation of hospital stay* and, thus, of costs, morbidity and mortality [5].

Clostridium difficile is a Gram-positive, strictly anaerobic, spore-forming bacterium that can lead to a wide range of intestinal disorders ranging from *mild self-limiting* to severe diarrhea, to pseudomembranous and fulminant colitis which is a *potentially life-threatening* disease [6]. The spores are widespread in the environment where they can survive for a long time and they are *spread through* the *fecal-oral* route to the susceptible patients.

Clostridium difficile is considered to be part of the normal intestinal flora of children and it can be isolated from almost 5% of healthy adults and from one third

of hospitalized asymptomatic patients. The incubation period, starting from patient exposure to onset of symptoms, is not known with certainty. There are three studies that estimated the incubation period to be about 2-3 days. However, the high risk of developing CDI can persist over several weeks after completion of antibiotic treatment, due to a prolonged alteration of the normal intestinal flora. [7]

Numerous variables implied in accurate evaluation of ADD rise the problem of risk factors:

Older age was an important risk factor, a 10-fold increase of risk for developing CDI in patients aged 60 to 90 years was noted. In fact, 90% of all deaths were patients over 65 years of age. In a study conducted over a period of 6 years in an urology ward in the UK, Hossain found a mean age of patients with CDI between 23 and 93 years (mean age of 73 years), only six of the 33 patients (18%) were under 65, compared with our study in which 41.2% were under 65 years. [8]

Antibiotic usage increases the risk of *CDI* by *8-10*-fold during the treatment or within one month after therapy and 3-fold for the next 2 months. [9] Many studies have focused on development of CDI ampicillin (or *amoxicillin*), clindamycin and cephalosporins (especially the 3rd generation cephalosporins (TGC) such as cefotaxime, ceftriaxone or ceftazidime). Regarding TGC Ryley [10] showed an almost perfect correlation between use of it, on the one hand, and the increased risk of CDI, on the other hand. Thomas demonstrated that indigenous colon microflora provides an important host defense by inhibiting the overgrowth of *C. difficile* and of other pathogens. *Antimicrobial therapy can disrupt* this *host defense*.[11] One study suggests that, in patients with diarrhea, colonic microflora diversity decreases due to the proliferation of certain types of bacteria. [12]

The administration of multiple antibiotics more than 10 days was also associated with an increased risk of CDI development.[13] Antibiotics that were associated with the lower incidence of CDI were aminoglycosides, macrolides, sulfonamides, and tetracyclines. Although the correlation with CDI is higher for certain antibiotics, all antibiotics, including vancomycin and even metronidazole on rare occasions, have been reported to be a cause for CDI. Even so, exposure to antibiotics is not a prerequisite to develop CDI. In one study, 24% of patients with CDI have not used antibiotics and 9% have received antibiotics less than 3 days. Of those who did not use antibiotics, 75% were hospitalized or had contact with a person with ADD. [14]

Recent clinical studies have suggested that antibiotic resistance of particular CDI strains, could play an important role in the epidemiology of the disease (Table 4).[15] CDI strain resistance to clindamycin was associated with large outbreaks of CDI. [16]. Clindamycin-resistant strains can thrive in an environment where other commensal bacteria are removed in the presence of clindamycin.

The same concept is likely to be true for cephalosporins and fluoroquinolones when administered to a patient exposed to *C. difficile* strains that are resistant to these antibiotics. Similarly, the emergence of fluoroquinolone resistance among epidemic forms of *C. difficile* and some non-epidemic strains resulted in increased associations between these agents and CDI because of these fluoroquinolone-resistant strains.[17] In our study, 9 patients (50%) received *fluoroquinolone antimicrobial* drugs before onset of CDI, although seven of them have received simultaneously other antibiotics, too.

The correlation between CDI and β-lactamase inhibitors, such piperacillin-tazobactam, it may be rare because these antibiotics could inhibit the activity of many CDI strains. [18] According to our study only one patient who developed CDI have received piperacillin-tazobactam. *C. difficile* strains are fully resistant to most cephalosporins. [15] Thus, it's no surprise why cephalosporins appear to be involved in almost all studies which have established the risk factors for CDI. [19] The use of second and third generation cephalosporins, such as cefuroxime, ceftazidime, cefotaxime, ceftriaxone is associated with a particularly high risk for CDI. [19] In 1994, the administration of second and third generation cephalosporins to patients was identified to be a major risk factor for developing of CDI in an outbreak at the Veterans Administration Medical Center in New York [20]. Our study do not confirm this because quinolones are frequently associated with antibiotic therapy that preceded the onset ADD.

In the 2000s, studies have continued to involve cephalosporins as a leading class of antimicrobial agents associated with CDI, having a higher odds ratios (ORs) than fluoroquinolones, despite the higher attention received by fluoroquinolones. [21,22,23]

Not all patients which receive antibiotics and are exposed to *C. difficile* develop ADD. This is attributable, in a certain degree, to other variables involved in the pathogenesis of this complex disease, including the immune system ability to produce an *anti-toxin* A *IgG antibody* as response to *C. difficile* infection. [24] In our study, all 18 patients received antibiotic therapy before development of CDI.

In one study, patients who have not developed high titers of *anti-toxin* A *IgG antibodies as* response to their first episode of CDI were 48 times more likely to develop recurrent CDI than patients who had an adequate immune response. These are the reasons why older people are more likely to develop CDI. [25]

The use of broad spectrum antibiotics is the most important r*isk factors associated* with the *occurrence of this infection*. Cephalosporins, aminoglycosides, quinolones, all antibiotics have been incriminated as main causative agents of CDI associated diarrhea [16,27], this being also demonstrated by our study, fluoroquinolones being those that were most commonly associated with CDI. Special attention should be paid in the future to antibiotic combinations because these „cocktails" seem to play an important role in the development of CDI, as demonstrated both in our study and in Bignardi's study which was conducted in 1998. [28]

In another study, the use of multiple antibiotics resulted in increased risk of CDI and in one retrospective cohort study, the incidence of CDI has increased simultaneously with the number of antibiotic administrations. [29] When CDI infection becomes endemic, antibiotics used for perioperative prophylaxis increases the risk of developing CDI. [30] In one study, 17 (23%) of 74 *patients who underwent surgical procedures* had positive stool cultures for CDI, samples being analyzed 2 weeks after *perioperative administration* of a single dose of cephalosporin. All these patients had negative *perioperative stool* cultures. [31]

The *most commonly antimicrobials associated* with *CDI*, according to studies, are clindamycin, penicillin, and cephalosporins. [32] Perhaps, because of wide scale use of fluoroquinolones among both, inpatients and outpatients, the usage of these agents has been recently considered a risk factor for CDI. Almost all antibiotics have been associated with CDI. [29]

Theoretically, *proton pump inhibitors* (PPIs) may increase the risk of developing CDI by increasing the conversion ability of spores to *vegetative* cells and to survive in the digestive tract. Several meta-analyses have found a significant correlation between PPIs use and CDI. Despite these findings, recent studies have provided conflicting data, many of these analyzes have not demonstrated a significant relationship between PPIs use and development of CDI, which is why in many treatment guidelines there is no restriction regarding IPPs use for prevention of CDI.

However, in our study, although only 2 patients had a history of gastroenterological disorders (gastrointestinal ulcer as young adult) and no patient received gastric antisecretory agent as a chronic treatment at home, a significant percentage of patients with CDI received antibiotic therapy associated with PPIs, raising thus a question mark over IPPs involvement in the pathogenesis of CDI. [33,34]

A case-control study, based on records of UK pharmacies, *has demonstrated* that the adjusted relative risk for community-acquired CDI was 3.5 (95% CI, 2.3 - 5.2) for PPIs usage (vs. PPIs not usage) and 8.2 (95% CI, 6.1-11.0) for antibiotic usage (vs. antibiotic not usage) [54]. Other studies, involving large population samples, have also demonstrated that the use of PPIs is a risk factor for the development of CDI [35], but some surveys do not agree with this finding. [36]

Enemas, laxatives, gastrointestinal stimulants, enteral feeding (especially postpyloric feeding) could lead to a 10-fold increase of risk of developing CDI, which is explained by the fact that it was shown that gastric acidity eliminates 99% of vegetative forms of CDI cells. [37]

There is a wide range of clinical manifestations starting from asymptomatic disease (about 20%), colitis with or without pseudomembrane, to a fulminant form or toxic megacolon. One study showed that approximately 5% of patients with CDI have had *clinical features* for „acute abdomen", two of five patients who underwent exploratory laparotomy have presented no diarrhea episode before the intervention [38]. Usually, the diarrhea begins *5-10 days* after antibiotics are started, but it can start 1 to 10 days after completion of antibiotic therapy. *Bloody diarrhea is uncommon*. (5-10%). [39] *Fever* is a *common symptom* in 30 - 50% of cases [40], 44.44% of patients included in our study have had fever.

Leukocytosis, h*ypoalbuminemia* and increased serum creatinine are highly suggestive of CDI. Leukocytosis is common (50-60%) in CDI. In patients who have had no hematologic malignancies and have had more than 30,000 WBC, the CDI was confirmed at 25% of them. An increase in WBC may even precede the onset of diarrhea and abdominal pain. CDI leads to a loss of proteins, particularly of albumin. [19] The decrease of protein level less than 2.5 g/dl or the decrease of albumin is associated with a poor prognosis. Bartlett noted that hypoalbuminemia in individuals who have diarrhea after antibiotics are started could be a sign of CDI. [41]

Although CDI is often a nosocomial infection, approximately 20% of CDI is *community-acquired*. There is a study conducted in a hospital from Minnesota, all patients who were hospitalized more than 24 hours were tested for CDI toxin, without having the suspicion of

CDI. 31 (9.7%) of 320 samples were positive for CDI. [42]

CDI diagnosis is based on clinical manifestations, on detection of either toxin A or of both toxin A and B, or sometimes on endoscopy in suspected cases of pseudomembranous colitis. A *diagnosis* of *CDI should* be considered only in patients with *diarrhea*, unless an ileus due CDI is suspected. [43]

The detection of cytotoxicity by *filtered culture sample* is considered to be the „gold standard" of diagnosis, having a high sensitivity (94-100%) and specificity (99-100%). However, this *testing needs a time* of 1-3 days for processing and requires both laboratory equipment suitable for cell culture and specialized medical staff, and also this test can lead to *high costs*. *Isolation* procedure of *C. dificille* is a method of high sensitivity (may be used as potential screening, but the longer processing time makes it less clinically and epidemiologically useful), but certainly, all this is not enough to establish the diagnosis of CDI. To certify the diagnosis, the culture should always be combined with a cultivation method for detection of *toxigenesis*.

CDI toxin detection by enzyme immunoassay (EIA) is used to detect toxins A and B in stool samples. It remains the main method of diagnosis in most clinics because of fast processing and high efficiency. This test provides the results in 2 to 6 hours, having a specificity of 95-100%, but its sensitivity is low 65-85%. [44]

The first treatment measure of a patient with suspected or documented CDI includes discontinuation of antibiotic therapy, if possible, supportive measures such as rebalancing electrolyte and hydration. Antiperistaltics should be avoided as they may mask the symptoms and hasten the development of toxic megacolon. [45]

Metronidazole and vancomycin are the first line treatment of CDI and although both are effective, none of them proved to be superior to other. [46] Metronidazole administration, as first intention treatment, has the advantage of a low cost, of avoiding selection of resistant enterococci and because can be administered intravenously in patients with digestive drug intolerance. Oral or intravenous metronidazole therapy (250 mg four times a day or 500 mg every 8 hours) for 10 days is recommended as first choice treatment of mild cases of CDI.

Vancomycin can be used as initial therapy in patients having contraindication or intolerance to metronidazole, or in patients who have severe CDI or they live in a region with a high prevalence of 1/027 NAP. Moreover, vancomycin should be reserved for patients who have had an unfavorable response after 5-7 days of treatment with metronidazole. Administered in recommended dosage, metronidazole and vancomycin have similar efficacy, having a therapeutic response rate of 90-97%. Fulminant cases should receive both oral vancomycin and intravenous metronidazole, despite low responses from clinical trials regarding this association. [47]

Of the 3388 patients admitted in the study during this period in our Urology department, 18 have been *diagnosed* with *Clostridium difficile* (0.56%), a much higher incidence compared with the study conducted by Hossain in a Urology department from Portsmouth, UK, between 2000-2005 (0.21). Of the 29 deaths cases occurred in the last year in our clinic, 3 deaths were caused by CDI (10.34%).

It is difficult to quantify the role of surgery in the development of this infection because, as noted in our study, in 88.23% of the cases, CDI appeared just few days after surgery (10 of them after 2-4 days postoperatively), all patients have received antibiotic therapy before and after surgery.

There is no *significant correlation* found between PPIs use and development of CDI, which is why in many treatment guidelines there is no restriction on PPIs usage. However, in our study, although only two patients have had a history of gastroenterological disorders (gastrointestinal ulcer in youth) and no patient received gastric antisecretory agent as a chronic treatment at home; a significant percentage of patients with CDI received antibiotic therapy associated with PPIs, raising thus a question mark over IPPs involvement in the pathogenesis of CDI.

According to the study, most patients developed CDI in the same time and they were admitted in the same room, and this could be explained by the transmission route of this infection. Certain rules must be followed regarding treatment and handling of patients when they are subject to certain interventions or to the nursing process in the hospital, medical staff should follow strict hygiene measures, the most important measure beeing washing hands with soap and water (not using alcoholic solutions) that can not be replaced by any other measure with respect to efficiency. We should give special attention in the future to quinolones, because, according to the CDC („Centers for Disease Control and Prevention") in USA, the mortality due to *C. difficile* increased by 400% between 2000 and 2007 due to the emergence of resistant strains to this antibiotic class. [3]

It is recommended that such patients to be isolated in special wards of the hospital, clearly marked, where CDI patients coming from all departments of the hospital should be treated and relatives and visitors of the patients must follow certain procedures in order to limit the spread of infection.

European Centre for Disease *Prevention and Control* (*ECDC*) has estimated that the potential cost of treatment of CDI could be 3 billion euros per year and it's expected the doubling of this number over the next four decades [32]. ECDC estimated the CDI impact of the costs in England ranging from 5.000 to 15.000 euros per case [32].

A study based on data collected from 4 European hospitals showed that patients from England (2007-2009) have had a prolongation of hospital lenght of stay due to CDI to 16.09 days, followed by Germany (2008-2010) to 15.47 days, Spain (2008 -2010) to 13.56 days and Netherlands (2008-2009) to 12.58 days. This data demonstrate that in European countries in patients with complications due to CDI, the infection causes a statistically significant increase of hospital length of stay. This important for optimizing resource allocation and budgeting, both nationally and locally to ensure that hospitalization duration of CDI patients is minimized. [48]

In the past three years since this bacterium was first discovered in our country, as a result of the specific tests performed at national level, it was shown that Clostridium difficile has affected thousands of Romanian people (only 1,237 cases in 2013 as preliminary estimation, performed just in few hospitals in the country). We did not found statistical data to give us an idea about the dimension of the problem in our country and about financial implications arising from the occurrence of this hospital-acquired infection.

Conclusions

Concern about the proliferation of CDI hospital-acquired infection urged health authorities in Romania to require rapid reporting of all CDI cases and to set measures for the transfer of CDI patients in Infectious Diseases Clinics or for their isolation on the wards where they were diagnosed, which is, in many cases, a big problem. Discretionary use of antibiotics will inevitably lead to an increase in the number of patients who develop CDI, because the use of any antimicrobial agent may be a risk factor for intestinal colonization with CDI. We believe that immediately after ADD have started, the patient should be isolated in a separate room to prevent disease dissemination. According to our study, fluoroquinolones are most commonly used antibiotics before onset of ADD and not cephalosporins, as demonstrated in many other studies. We intend to investigate in future studies whether IPPs association to antibiotic therapy may accelerate the occurrence of CDI.

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