Urological Pathology Complicated by Infection with Clostridium Difficile: Retrospective Analysis of Cases and Risk Factors

I. Sandu[1,2], G. Predoiu[1], R.A. Danau[1,2], R.C. Petca[1,2], B. Braticevici[1,2], C. Toma Dumitrescu[1], V. Jinga[1,2]

[1] *"Prof. Dr. Th. Burghele" Clinical Hospital, Dept. of Urology, Bucharest, Romania*

[2] *University of Medicine and Pharmacy "Carol Davila" Bucharest, Romania*

Abstract

Introduction and Objectives. The continuous and excessive increase in antibiotic use in Romania has led to the occurrence of enterocolitis by Clostridium Difficile. The aim of the paper is to analyze the association of the development of infections with enterocolitis trigger germs and exposure to broad spectrum antibiotics.

Materials and Methods. Between January 2015 and March 2017, we conducted a retrospective study to assess the incidence and prevalence of patients with Clostridium Difficile. Patients who have experienced symptoms have been tested for C.Difficile infections by immunological tests - toxin A, B and GDH. A number of factors such as age, gender, basic urological pathology, antibiotic treatment administered, and number of days until diagnosis of C. difficile infection were followed.

Results. We enrolled 134 patients who developed C.Difficile infections. The mean age was 66.85 ± 12.187 years. The gender distribution was 100 males (74.6%) and 34 women (25.4%). The highest prevalence was in the case of HBP, 26 cases (19.4%), followed by lithiasis pathology - 23 cases (17.2%), and infiltrative vesicular tumors 23 cases (17.2%). The most frequent class of antibiotic prescribed to trigger symptomatology (4-6 diarrheal, explosive, watery stools) was the third generation cephalosporins, 77 cases (57.5%), followed by carbapenems, 21 cases (15.7%). The median duration of administration until the onset of manifestations was 4.77 ± 3.02 days. Positivity of all immunological markers was found in 84 cases (62.7%), 24 patients (17.9%) had only positive GDH associated with the clinical profile. There is no strong correlation (Pearson's R = 0.235) between the number of days of antibiotic treatment and the positivity of toxins ($p < 0.001$).

Conclusions. Applying rational use of antibiotics and controlling nosocomial infections nationwide is one of the ways to limit the above process.

Key-words: C. difficile infection, antibiotic related diarrhea, urologic pathology.

Correspondence to: Dr. Predoiu Gabriel M.D.
Clinical Hospital "Prof. Dr. Th. Burghele"
20 Fundeni Av., sector 5, code 050659, Bucharest, Romania
Tel: +40735576218
e-mail: gabriel.predoiu@gmail.com

Introduction And Objectives

Clostridium difficile is an anaerobic gram-positive, spore-forming, toxin-producing bacillus that is transmitted among humans through the faecal–oral route. The relationship between the bacillus and humans was once thought to be commensal, but C. difficile has emerged as a major enteric pathogen with worldwide distribution. Hospitalizations for C. difficile infection among nonpregnant adults doubled from 2000 through 2010 and were projected to continue to increase in 2011 and 2012, especially as laboratories transition to more sensitive C. difficile assays. In the United States of America epidemiologic surveillance studies show that C. difficile infection is responsible for approximately 453000 new cases each year. It is also estimated that a quarter of those infections are community acquired. In Romania, Clostridium difficile infection has an unknown incidence and prevalence due to the lack of precise data regarding hospital acquired CDI (Clostridium difficile infection), lack of sensitive testing, antibiotic overuse. Antibiotic associated diarrhea one of the primary clinical manifestations of C. difficile infections. The clinical manifestations can range from antibiotic associated diarrhoea, C. difficile toxic colitis, pseudomembranous colitis and even to death in severe cases. The most common form of presentation of CDI is antibiotic associated diarrhoea and can be found in 26-60% in an healthcare related setting to <0.1% in an outpatient setting[1-3]. It is estimated that cost of care for patients that develop C. difficile infection increases fourfold. There are estimation that CDI cost an extra 3.2 billion dollars each year[4].

Clostridium difficile infection is a growing public health problem in al countries due to overuse of high powered antibiotic. There are even new extremely virulent types of CDI like 2002 reported NAP1 (North-American pulsed-field gel electrophoresis type 1) that is responsible for geographically dispersed hospital associated disease, witch shows an evolution of towards current clinical practice regarding this disease but also lack of preventive measures to be applied to hospitalized patients.

C. difficile colonizes the large intestine and releases two protein exotoxins. Infection is transmitted by spores that are resistant to heat, acid, and antibiotics. The spores are plentiful in health care facilities and are found in low levels in the environment and food supply, allowing for both nosocomial and community transmission[5]. Colonization is prevented by barrier properties of the fecal microbiota; weakening of this resistance by antibiotics is the major risk factor for disease. Advanced age, antineoplastic chemotherapy, and severe underlying disease also contribute to susceptibility[6].

The use of antibiotic in urology is largely empiric due to the fact that urological associated infections have the potential to severely complicate the natural evolution of almost any urological pathology. Due to this high use in antibiotic use we observed an increase in the number of cases diagnosed with CDI. The goal of the study is to present information about C. difficile infection, its management, identify potential risk factors to for development of this disorders.

Materials And Methods

The goal of this study was to evaluate cases of C. difficile infection that occurred in urologic patients admitted into our clinic for various reasons. We realised a retrospective observational study from January 2015 to March 2017 that identified 134 patients that were admitted for various urological and non-urological pathologies and developed antibiotic associated diarrhoea. All patients that presented symptoms (defined by more than 2 diarrheic stools per day, with or without abdominal distention and/or pain) had stool samples collected and testing of C. difficile was realised[7]. The method of testing was by using the CerTest Clostridium difficile GDH + Toxin A+BÓ, is based on the principle of a qualitative immunochromatographic assay for the determination of Clostridium difficile Glutamate Dehydrogenase (GDH), Toxin A and Toxin B in stool samples[7, 8]. Interpretation of results we done according to the table below:

Table 1. Interpretation of Cer Test for C. difficile infection as indicated by manufacturer.

	A (GDH)	B (Toxin A)	C (Toxin B)	Interpretation of the results
1.	-	-	-	There are no GDH, Toxin A and Toxin B of *Clostridium difficile*.
	GREEN	GREEN	GREEN	No infection caused by *Clostridium difficile*.
2.	+	+	+	There are GDH, Toxin A and Toxin B of *Clostridium difficile* presence.
	GREEN-RED	GREEN-RED	GREEN-RED	Infection caused by *Clostridium difficile*.
3.	+	+	-	There is GDH and Toxin A presence. Infection caused by *Clostridium difficile*.
	GREEN-RED	GREEN-RED	GREEN	
4.	+	-	+	There is GDH and Toxin B presence. Infection caused by *Clostridium difficile*.
	GREEN-RED	GREEN	GREEN-RED	
5.	+	-	-	There is GDH presence. Infection caused by *Clostridium difficile*.
	GREEN-RED	GREEN	GREEN	
6.	-	+	+	If this result appears it must be repeat the test using a fresh sample. If results are again positive for Toxin A and B and negative for GDH, the sample should be considered positive for Toxin A and B.
	GREEN	GREEN-RED	GREEN-RED	
7.	-	+	-	If this result appears it must be repeat the test using a fresh sample. If result is again positive for Toxin A and negative for GDH, the sample should be considered positive for Toxin A.
	GREEN	GREEN-RED	GREEN	
8.	-	-	+	If this result appears it must be repeat the test using a fresh sample. If result is again positive for Toxin B and negative for GDH, the sample should be considered positive for Toxin B.
	GREEN	GREEN	GREEN-RED	
9.	Any other result			Invalid result either A, B, or C, we recommend repeating the assay using the same sample with another test

In all of the 134 patients included we registered variables such as age, gender, underline pathology that lead to development of antibiotic related diarrhea, the number of days of antibiotics administered until the start of gastrointestinal symptoms, type of antibiotic administered by class of antibiotics, results of Cer Test as to the presence of toxin A, toxin B and GDH. As opposed to the national and European guidelines for the diagnosis and management of C. difficile infections we considered and included in the study patients that presented diarrhea and only had the GDH positive. Prior to statistical analysis the number of days of antibiotic administrations until the development of symptoms were grouped into three categories, as follows: less than 5 days, 6 to 10 days and more than 11 days. After chart review, recording of variables into our database, statistical analysis followed using IBM IPSS v22.

We consider that limitations of study design are represented by the retrospective observational nature, lack of information about prehospitalization administration of antibiotics and prior hospitalization within the last 6 months.

Results

Statistical analysis of our compiled database, of 134 patients admitted and treated in our hospital that developed C. difficile infection, revealed upon descriptive statistics that we had 34 (25.4%) females and 100 (74.6%) men with a mean age of 66.85 years with a standard deviation of 12.187 years. Analysis of days of antibiotic exposure variable showed that we had a mean number of days 4.77 until development of symptoms, while standard deviation was 3.02 days that signifies a wide range of variance (table 2).

Upon chart review we noted the underline pathology for which the was admitted to our hospital. Results show that we had predominantly obstructive urological cases that associated some form of urinary tract infection. We identified as a basic causes of admittance to our hospital predominantly patients with benign prostatic hyperplasia (19,4%), muscle invasive bladder cancer (17,16%), ureteral stone disease (11,19%) and also prostate cancer (11,19%). There is a high probability of selection bias due to the fact that these are predominant pathologies found on our wards, which we consider to be another limitation of the study.

Graphical analysis of underline pathology on chart review

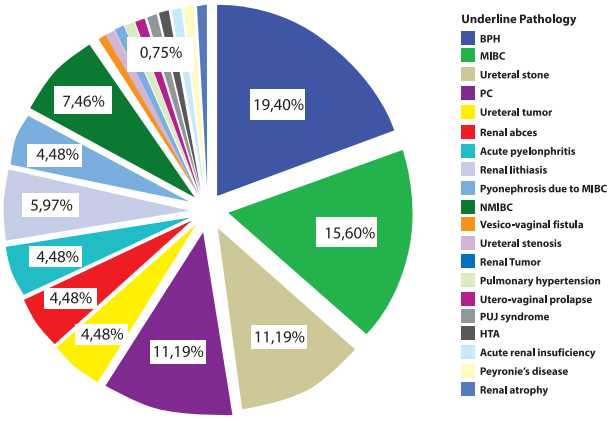

Figure 1. Pie chart showing results of baseline pathology our hospital.

Table 2. Descriptive statistics of enrolled patients that detail statistical relevant information regarding age and number of antibiotic days of exposure.

		Age	Days Of Antibiotic Exposure	Gender		
Mean		66,85	4,77	Count	Percent	
Median		67	4	34	25,4	Female
Mode		56	2	100	74,6	Male
Std. Deviation		12,18	3,02			
Variance		148,51	9,12			
Minimum		42	1			
Maximum		91	18			
Percentiles	25	58	2			
	50	67	4			
	75	77,25	7			

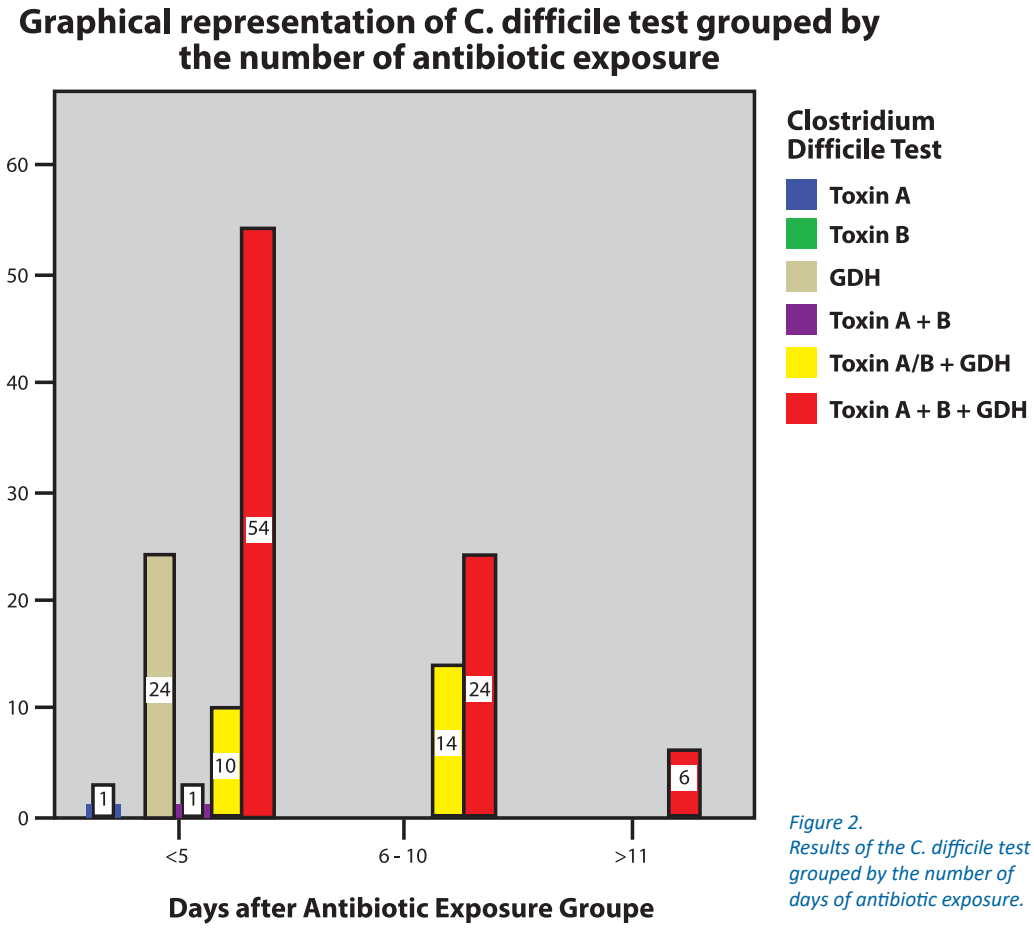

Figure 2.
Results of the C. difficile test grouped by the number of days of antibiotic exposure.

After database formation we grouped the variable "Days of antibiotic exposure" into three categories as follows: positive test for C. difficile in less than 5 days from the start of antibiotic exposure, positive test from 6 to 10 days, and positive test after more than 11 days. This grouping helped us graphically determine the highest prevalence of C. difficile infection in regard to the number of days of antibiotic exposure. It can be observed that the highest number of C. difficile cases appeared within 5 days from the start antibiotics. In total these cases represent 67,16% of study group (n=90). Out of these 90 patients 54 had toxins A and B positive, as well as GDH.

A total of 44 patients had C. difficile infection diagnosed after 6 or more days of antibiotic exposure.

Antibiotic Exposure		
	Frequency	Percent
Aminoglycoside	17	12,7
Cephalosporins 3ed generation	77	57,5
Carbapenems	21	15,7
Fluoroquinolones	2	1,5
Cephalosporins + Fluoroquinolones	8	6,0
Cephalosporins + Aminoglycoside	6	4,5
Penicilins	3	2,2
Total	134	100,0

Table 3. Frequencies table of antibiotic classes mostly used and associated with development of C. difficile.

Chart review of antibiotic type used, showed that most prevalent were third generation cephalosporins with a total of 77 cases (57,5%), followed by carbapenems with a total number of 21 cases (15,7%) and aminoglycosides with 17 cases (12.7%). Correlation analysis of antibiotics used until development of symptoms and the number of days of exposure after grouping showed a Pearson's R coefficient of 0.235 with a $p<0.006$.

Performing of one-way ANOVA function with variables age and number of days of antibiotic exposure revealed that age did not correlate with development of C. difiicile test with a ANOVA function result of $F=1.434$, $p<0.226$ which means that age is not a risk factor for development of C. difficile infection. ANOVA function of C. difficile test and days of antibiotic days of exposure was calculated $F=3.671$, $p<0.007$ which means that the number of days of antibiotic exposure are low to moderately correlated with development of antibiotic related C. difficile infection.

Conclusions

Most urological pathologies imply some sort of obstruction of the genito-urinary tract that leads to infection. Treatment of these infectious complications is done by the use of broad spectrum antibiotics, which can lead to the development of C. difficile associated diarrhoea. Our study aimed to identify potential risk factors for the development of these kind of clinical manifestations. We had 134 patients that had their charts retrospectively analysed and found that in our hospital there is an inclination for the use of third generation cephalosporins, carbapenems and aminoglycosides which mostly dictated by the fact that most patients have severe urinary tract infections with multiple antibiotic resistance[9]. Simple grouping of patients by days of antibiotic exposure until development revealed that most of the C. difficile infections arose in first five days of antibiotic exposure. Statistical testing of the hypotheses that class of antibiotics used and number of days of administration will directly correlate with the diagnosis of C. difficile infection, showed that there is only a low to moderately statistical correlation within the two variables, and thus demonstrating our hypothesis. Class of antibiotics administered also moderately correlates with the development of this type of nosocomial infection[10]. In the light of our findings and accounting for the weak points of our study we conclude that there is a need for better and more judicious antibiotic usage in urology wards, limitation, or careful usage of cephalosporins and also to reduce the time of antibiotic administrations per patient to the minimum necessary.

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