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NOSOCOMIAL INFECTIONS RISING IN THE UROLOGY WARD OF CLINICAL COUNTY EMERGENCY HOSPITAL OF BRASOV

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Abstract: *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.*
This clinico-epidemiological study was conducted between 1 Ianuary 2014 - 31 December 2015 and included 37 patients who developed acute diarrhoeal disease (ADD) during hospitalization and were diagnosed with enterocolitis caused by CDI. 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.

Key words: *Infection, Clostridium difficile, Antibiotic-Associated Diarrhea, aetiology, pseudomembranous colitis.*

1. Introduction

Clostridium difficile was originally described as a human enteric pathogen at the Interdisciplinary Conference on Antimicrobial Agents and Chemotherapy in 1977, in New York. [1] Antibiotic associated colitis had been recognized as "a paradox of medical progress that compromise the therapeutic utility of an important group of antibiotics, represents a potential obstacle for the development of new drugs and determine our ability to shape the multitude of clinical observations and pathological into a disease entity". [2] But the original anatomical description is attributed to Finney, a surgeon at Johns Hopkins Hospital, which published its findings in the Bulletin of the Johns Hopkins Hospital in 1893. The patient, a woman aged 22 years, had a gastric-pyloris tumor which was resected in August 1982, ten days after surgery she developed diarrhea that progressed and resulted in patient death at 15 days postoperatively. The autopsy performed revealed "Diphtheritic colitis" and histological sections were first published in 1988 in "Clostridium difficile: Its Role in Intestinal Disease" - Rial D. Rolfe, Sydney M. Finegold. [20]

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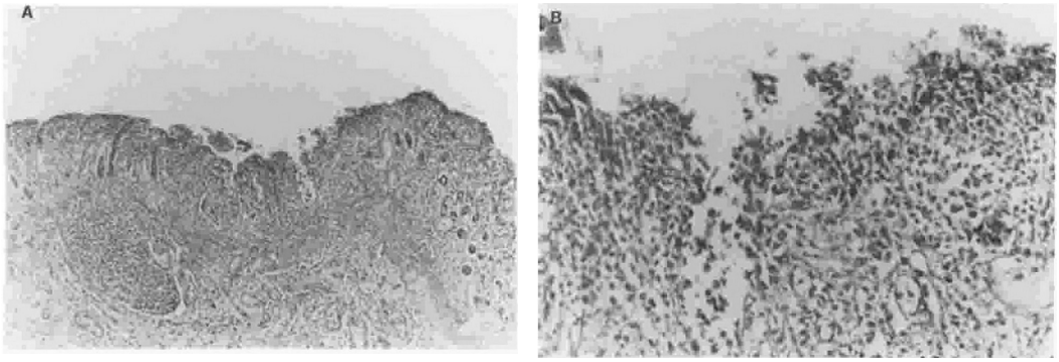

Fig. 1. *Histologic sections of colon from autopsy of Finney's case, September, 1892.*

Antibiotic use is now commonplace, both in hospitals and in the community. Diarrhea is a common complication of antibiotic therapy. Incriminated drug classes are represented in 2% by quinolones, macrolides has a rate of 5%, and other agents such as amoxicillin + clavulanic acid and cefixime can lead to diarrhea in 10% -25% of cases (table 1). [3]

Table 1

Common antibiotics associated with C difficile diarrhea

MOST COMMON
Clindamycin
Penicillin derivatives (especially amoxicillin-clavulanate)
Cephalosporins (especially third generation)
LESS COMMON
Macrolides
Quinolones
Tetracyclines
RARE
Metronidazole
Vancomycin

Most often, antibiotic-associated diarrhea is mild and clears up shortly after interruption of the antibiotic. But in some cases, antibiotic-associated diarrhea can lead to colitis, an inflammation of colon, or a more serious form of colitis called pseudomembranous colitis. Direct toxic effect of antibiotics on the gut may alter its digestive function due to lower number of bacteria that make up the normal intestinal flora or multiplication of pathogenic bacteria. [12]

About 15% to 20% of cases of antibiotic-associated diarrhea are caused by a single bacterial entity Clostridium difficile [4], [15]. Clostridium difficile infections are a growing problem; Enterocolitis C. difficile is recognized as the most common nosocomial gastrointestinal infection.

Clostridium difficile is an anaerobic Gram-positive bacillus able to produce spores. These spores are resistant to heat and can survive in the environment for several months, despite dehydration and

exposure to disinfectants. There have been reports of spores being found on clothing, furniture and equipment in hospital. Thus, these spores contribute to exogenous exposure to C difficile with fecal-oral transmission. The spores survive ingestion to germinate in the intestins to form vegetative state bacilli capable of growth and toxin production.

Pathogenic strains of C difficile can cause colitis and diarrhea through toxin production. [25] Were identified two major toxins: toxin A is a 308kD enterotoxin and toxin B is a cytotoxin 269kDa. Both toxins are capable of stimulating the production of proinflammatory cytokines [25] , which have been implicated in the pathogenesis of pseudomembranous colitis. [15] The toxins act by modifying the regulatory function of cytoskeletal proteins, leading to cell rounding and ultimately cell death. [19]

Recent evidence obtained in vitro tests using human colonic epithelial cell lines suggests, however, that toxin B is 10 times more potent at inducing colonic lesions than toxin A. [21]

Data from the US Center for Disease Control and Prevention - (CDC) show that the number of hospitalized patients who had a diagnosis of infection with Clostridium difficile at discharge increased from 31% ooo persons in 1996 to 61% ooo persons in 2003. [23] The mortality rate associated with Clostridium difficile has been growing between 1999-2002 in the United States between 2001-2005 in England and Wales [22] being between 6% -30% when pseudomembranous colitis is present, but maintaining high even in the absence of colitis. [18] Furthermore, a study conducted in Canada in 2005 shows a mortality rate of 17% at one year. [17]

Enterocolitis with Clostridium difficile presents in a variety of ways, ranging from asymptomatic carrier status to diarrhea and life threatening pseudomembranous colitis. [11] The symptoms usually manifested as profuse diarrhea, which is mucous or watery, sometimes abdominal pain, and fever (Table 2). Leukocytosis a common reaction of infection with C. difficile; The number of white blood cells can lead to over 30.0 × 10 9 / L [24] (Table 2). Extraintestinal manifestations are rare but may include cellulitis, bacteremia, abscess formation in the viscera, reactive arthritis. [13]

Table 2

Clinical presentations

MILD
Diarrhea
Abdominal cramping
Tenesmus
Low-grade leukocytosis
MODERATE
Leukemoid reaction
Fever
Dehydration
Nausea, vomiting
Abdominal tenderness
SEVERE
Sepsis or shock
• Acidosis
• Multisystem organ failure
Tachycardia
Acute abdomen (colonic perforation)
Toxic megacolon
Ascites
Paralytic ileus
Hypoalbuminemia
Diarrhea can actually lessen in severe disease

2. Objectives

This retrospective study aims to assess all patients hospitalized, diagnosed and treated for enterocolitis caused by Clostridium difficile in the Urology Ward of Clinical County Emergency Hospital of Brasov for a period of 2 years.

3. Material and Methods

From 1 Ianuary 2014 to 31 December 2015 were admitted 37 cases which developed during hospitalization Clostridium difficile enterocolitis , for which were extracted information from medical records.

A careful history was taken from all patients regarding medication (antibiotics, proton pump inhibitors IPPs, etc.) received prior to onset of the acute diarrhoeal syndrome, age of patients, sex, associated pathology, biohumoral investigations, possible contamination from other patients who developed acute diarrhoeal syndrome in the same period. Stool frequency, medication, evolution, lenght of hospitalization etc. were recorded.

Diagnosis of Clostridium difficile infection was established.

The age of the patients diagnosed with enterocolitis caused by Clostridium difficile, evaluated in the study, varies from 42 to 89 years old with a median of 70.81 years and 67,5% were aged over 65, with a sex ratio of 4:1 in favor of males, 7 patients (19%) are women, and 30 patients (81%) are men, as shown in table 3.

3. Results and Discussions

From the total of 37 patients enrolled in the study, 7 cases (19%) were recorded in 2014 and the remaining 30 cases (81%) were registered in 2015, 22 patients (59%) required surgery for urologic pathology and the mean duration of hospitalization of patients was 18.21 ± 7 days.

All 37 patients had the same symptom at the onset of desease: accelerate intestinal transit, fever over 380C (11 cases), low-grade fever (4 cases), and inflammatory syndrome was found in 89% of cases (33 patients), 46% of cases (17 patients) had significant leukocytosis (WBC 20,000 / mm3).

In 97% (36 patients) received antibiotic therapy during hospitalization before the start of enterocolitis symptoms, 17 patients (46%) received treatment with cephalosporins, 12 patients (32%) received treatment with cephalosporin followed by fluoroquinolone 2 patients received treatment with derivatives of penicillin antibiotic (amoxicillin-clavulanic acid), 3 patients received imipenem, 2 patients received gentamicin / amikozid.

After the diagnosis of enterocolitis by Clostridiun difficile was confirmed by stool sample, patients were treated per os with vancomycin in 18 cases (49%), vancomycin and metronidazole in 7 cases (19%), metronidazole in 9 cases (24%) and 3 patients were treated with other antibiotics.

It was observed during the study that 5 times overlapped periods of hospitalization of patients who acquired Clostridium difficile enterocolitis and accommodation in the same room.

Hospitalization in the department of infectious disease was observed in 3 of the patients in the study after hospital discharge from the clinic of urology.

Theoretically, proton pump inhibitors (PPIs) may increase the risk of developing CDI by increasing the capacity of spores to vegetative cells converting and survive in the digestive tract. Several meta-analysis found a significant correlation between CDI and use of PPIs. Despite these findings, recent studies have provided conflicting data, many of these analyzes showed no significant relationship between use and development of IPP-CDI, which is why in many treatment guidelines there is no restriction in terms of preventing CDI regarding PPIs use.

However, in our study, although only 5 patients had a history of enteral disorders (gastrointestinal ulcers as a young adult)

and no patient receiving chronic treatment at home with gastric antisecretory agent, a significant percentage of patients with CDI received antibiotic treatment associated with PPI (67,5% - 25 patients), thus raising a question mark over IPPS involvement in the pathogenesis of CDI. [7], [16]

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) [9]. Other studies, involving large population samples, have also demonstrated that the use of PPIs is a risk factor for the development of CDI [8], but some surveys do not agree with this finding. [14]

Results Table 3

Infections per year	**2014**		**2015**		
	7 (18,91%)		30 (81,08%)		
Gender	**Female**		**Male**		
	7 (18,91%)		30 (81,08%)		
Age (years)	70.81 (42-89)				
Hospitalization (days)	18.21 ± 7				
Course of disease	**Favourable**		**Hospitalization in the department of infectious disease**		
	34 (91,89%)		3 (8,10%)		
Clinical and laboratory picture	**Fever**	**Inflammatory syndrome**			**leukocytosis (WBC >20,000 / mm3)**
	15 (40,54%)	33 (89,19%)			17 (45,94%)
Intervention	**surgery for urologic pathology**		**non-surgical**		
	22 (59,45%)		15 (40,54%)		
Antibiotic therapy before the start of enterocolitis symptoms	**cephalosporins**	**cephalosporin followed by fluoroquinolone**	**penicillin antibiotic (amoxicillin-clavulanic acid)**	**imipenem**	**gentamicin / amikozid**
	17 (45,94%)	12 (32.43%)	2 (5,40%)	3 (8,10%)	2 (5,40%)
	29 (78,37%)		One patient did not received antibiotic therapy (2,70%)		
Treatment (oral)	**vancomycin**	**vancomycin and metronidazole**	**metronidazole**		**other antibiotics**
	18 (48.64%)	7 (18,91%)	9 (24.32%)		3 (8,10%)

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.[5]

We should pay special attention in the future to quinolones, because, according to the CDC ("Centers for Disease Control and Prevention") in the United States, mortality

of C. difficile increased by 400% between 2000 and 2007 due to the occurrence of strains resistant to this class of antibiotics.[6]

It is recommended that these patients to be isolated in special wards of the hospital, clearly marked, where patients with CDI from all hospital departments should be treated and relatives and visitors of patients must follow certain procedures to limit the spread of infection.[6]

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. [10]

4. Conclusions:

According to our study, cephalosporins are most commonly used antibiotics before onset of acute diarrhoeal disease, as demonstrated in many other studies, followed by fluoroquinolones.

In 2015 were diagnosed in the urological clinic of Brasov more than 4 times number of cases of enterocolitis caused by Clostridium difficile than in the 2014.

In 8% of cases (3 patients) Clostridium difficile infection has not been cured, patients requiring additional hospitalization in a specialized section of infectious diseases.

References

1. Bartlett, A., Dormandy, K. M., Hawkey, C. M., Stable- forth, P., Voller, A.: *Factor-VIII Related antigen: measurement by enzyme immunoassay*. In: Brit.med.J., 1977, 1, 994-996.
2. Bartlett, J.G., Gorbach, S.L.: *Pseudomembranous enterocolitis (Antibiotic-related colitis).* In: Advances in Internal Medicine, 1977, 22: 455-476.
3. Bartlett, J.G.: *Clinical practice. Antibiotic-associated diarrhea.* In: N Engl J Med 2002; 346(5):334-9.
4. Bartlett, J.G.: *Clostridium difficile: history of its role as an enteric pathogen and the current state of knowledge about the organism.* In: Clin Infect Dis 1994;18(Suppl 4):S265-72.
5. Bliss, D.Z., Johnson, S., Savik, K. et al.: *Acquisition of Clostridium difficile and Clostridium difficile-associated diarrhoea in hostpitalized patients receiving tube feeding.* In: Ann Intern Med 1998; 129:1012-1019.
6. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States,2013 (http://www.cdc.gov/drugresistance/threat-report-2013/); and Vital Signs: Improving Antibiotic Use Among Hospitalized Patients. MMWR March 7, 2014 / 63(09); 194-200.
7. Cohen, S.H., Gerding, D.N., Johnson, S., et al.: *Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society of healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA).* In: Infect Control Hosp Epidemiol., 2010; 31: 431–455.
8. Cunningham, R., Dale, B., Undy, B., et al.: *Proton pump inhibitors as a risk*

factor for Clostridium difficile diarrhoea. In: J Hosp Infect 2003; 54:243–5.
9. Drekonja, D.M., Amundson, W.H., DeCarolis, D.D., et al.: *Antimicrobial use and risk for recurrent Clostridium difficile infection.* In: Am J Med. 2011; 124:1081.
10. Eckmann, C., Wasserman, M., Latif, F., Roberts, G., Beriot-Mathiot, A.: *Increased hospital length of stay attributable to Clostridium difficile infection in patients with four comorbidities: An analysis of hospital episode statistics in four European countries.* In: The european Journal of Health economics. October 2013; DOI 10.1007/s10198-013-0498-8. Available at: http://link.springer.com/article/10.1007/s10198-013-0498-8#.
11. Gerding, D.N.: *Disease associated with Clostridium difficile infection.* In: Ann Intern Med1989; 110(4):255-7.
12. Henderson, K.: *Proceduri stocate în SQL Server. XML, HTML*. Bucureşti. Editura Teora, 2003.
13. Hyun Joo Song, Ki-Nam Shim, Sung-Ae Jung, Hee Jung Choi, Mi Ae Lee, Kum Hei Ryu, et al.: *Antibiotic-Associated Diarrhea: Candidate Organisms other than Clostridium Difficile*. In: Korean J Intern Med. 2008 March; 23(1):9–15.
14. Jacobs, A., Barnard, K., Fishel, R., Gradon, J.D.: *Extracolonic manifestations of Clostridium difficile infections. Presentation of 2 cases and review of the literature.* In: Medicine (Baltimore) 2001;80(2):88-101.
15. Kazakova, S.V., Ware, K., Baughman, B., et al.: *A hospital outbreak of diarrhea due to an emerging epidemic strain of Clostridium difficile*. In: Arch Intern Med 2006; 166:2518–24.
16. Kelly, C.P., Pothoulakis, C., LaMont, J.T.: *Clostridium difficile colitis.* In: N Engl J Med 1994; 330(4):257-62.
Accessed: 06-01-2009.
17. Leonard, J., Marshall, J.K., Moayyedi, P.: *Systematic review of the risk of enteric infection in patients taking acid suppression*. In: Am J Gastroenterol 2007; 102: 2047-2056; quiz 2057.
18. Peláez, T., Alcalá, L., et al.: *In Vitro Activity of Ramoplanin against Clostridium difficile, Including Strains with Reduced Susceptibility to Vancomycin or with Resistance to Metronidazole.* Antimicrob Agents Chemother 2005; 49(3):1157–9.
19. Pepin, J, Valiquette, L., et al.: *Mortality attributable to nosocomial Clostridium difficile-associated disease during an epidemic caused by a hypervirulent strain in Quebec*. In: CMAJ., 2005; 173:1037-42.
20. Pothoulakis, C.: *Pathogenesis of Clostridium difficile-associated diarrhoea*. In: Eur J Gastroenterol Hepatol 1996; 8(11):1041-7.
21. Rolfe, Rial D. and Finegold, Sydney M. (Eds.): *Clostridium difficile: Its Role in Intestinal Disease.* XVI + 408 S., 13 Abb., 23 Tab. San Diego–New York–Berkeley–Boston–London–Sydney–Tokyo–Toronto 1988. Academic Press (Harcourt Brace Jovanovich Publishers). ISBN: 0-12-593410-6.
22. Riegler, M., Sedivy, R., Pothoulakis, C., Hamilton, G., Zacherl, J., Bischof, G., et al.: *Clostridium difficile toxin B is more potent than toxin A in damaging human colonic epithelium in vitro.* In: J Clin Invest 1995; 95(5):2004-11.
23. Schroeder, M.S.: *Clostridium difficile associated diarrhea.* In: Am Fam Physician. 2005; 71(5):921-28.
24. Sunenshine, H.R., McDonald, L.C.: *Clostridium difficile-associated disease: New challenges from an established pathogen.* In: Cleveland Clinic Journal of Medicine, 2006; 73(2).

25. Wanahita, A., Goldsmith, E.A., Musher, D.M.: *Conditions associated with leukocytosis in a tertiary care hospital, with particular attention to the role of infection caused by Clostridium difficile.* In: Clin Infect Dis 2002; 34(12):1585-92.

26. Warny, M., Keates, A.C., Keates, S., Castagliuolo, I., Zacks, J.K., Aboudola, S., et al.: *MAP kinase activation by Clostridium difficile toxin A mediates monocyte necrosis, IL-8 production, and enteritis.* In: J Clin Invest 2000; 105(8):1147-56