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Clostridium Difficile Infection - An Optimistic View

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Abstract

Background: *Clostridium difficile* infection (CDI) is one of the most common infectious complications affecting vulnerable patients, i.e., after surgery or immunosuppressive therapies, posing a significant risk in an oncological unit.

Materials and methods: We analyzed data recovered from 164 cases of CDI during the period of 2014-2016 in the Regional Oncologic Institute Iasi, majority admitted in the surgical and hematological units. In all cases diagnostic was confirmed if stool samples tested positive for GDH and at least one of the toxins A or B.

Results: The study shows a large population of elder patients (median age 64 years) with female dominance (54%). Out of 117 surgical cases 64% had surgical procedures on the gastro-intestinal tract. Although 20% of patients had equivocal symptoms from admission, the average interval (from admission) until first symptoms developed was 7 days. The confirmation of the diagnosis came in the next day/24h in 68% of cases, leading to initiation of efficient therapy. Although CDI is regarded as an antibiotic associated disease, our data revealed that only one third of patients received antibiotic treatment in the last 3 months. Among the risk factors that may have an influence over development of CDI, antisecretory therapy was delivered to 37% of cases. Epidemiology reports showed that less than 8% of patients had previous contact with other CDI confirmed case. Overall mortality was 4.87% and CDI related mortality was 0.85%.

Conclusions: Even though CDI still poses a great threat during prolonged hospitalization and is especially dangerous in oncologic patients, the early recognition of disease onset and the easy access to diagnostic tests triggers an immediate course of treatment and decreases complication and the risk of spreading.

Keywords: *Clostridium difficile*; Toxins; Risk factors; Early diagnosis; Antibiotics

Introduction

Clostridium difficile is an anaerobic, Gram-positive, spore-forming, toxin-producing bacteria identified as a cause of colitis associated with antibiotic use [1]. Previous exposure to antibiotics is the most important risk factor for CDI, leading to modification of the normal flora of the colon and decreasing the intestine's resistance to colonization [2]. Other risk factors for CDI are inflammatory bowel disease, immunodeficiency, hypoalbuminemia, malignancies, organ transplantation and mechanical bowel preparation. Despite the development of CDI therapy there is a growing incidence, severity, mortality and recurrence of this condition [3]. The high rate of recurrent CDI raises a question mark over current treatment recommendations of the first episodes of CDI [4,5].

Materials and Methods

We identified all reported cases of CDI during the period of 2014-2016 using the digital database of the center for control, surveillance, and prevention of transmissible diseases in the Regional Oncologic Institute Iasi. All cases are registered in the database immediately after diagnosis, followed by epidemiological investigation and standardized protocols for isolation and protection of contacts. The admission charts were studied to extract the following information: age, sex, date of admission and release, date of CDI confirmation and toxin negativity. We also checked for antibiotic use in the last 3 months, administration of gastric-antisecretory medication, previous hospitalization or contact with CDI-confirmed patients. For the surgical cases we gathered data about the date and type of intervention performed.

Diagnosis of *Clostridium difficile* colitis

Even if symptoms can be variable, typical symptom is watery diarrhea up to 15-30 stools per day [1,3]. Some patients can complain of abdominal pain or cramps in association with fever or leukocytosis. Because mild diarrhea can be present, our protocol suggests that every patient with more than 4 stools in the last 24 hours has to be tested for CDI. Stool samples collected from patients with symptoms are sent to the laboratory to be tested for GDH antigen and toxins A and B through enzyme immunoassay (EIA) test [6]. Results are considered positive when both GDH antigen and toxins A or B come out positive [7].

Treatment of first infection

Metronidazole and vancomycin remain the mainstays of CDI treatment. Current guidelines recommend oral metronidazole for initial mild to moderate episodes or first recurrence [8]. Oral vancomycin is recommended for initial severe episodes, or first or second recurrence [3,4]. The treatment protocol we use in our hospital indicates oral administration of 500 mg metronidazole and 500 mg vancomycin each every 6 h. Each patient was isolated in a room properly signaled, with limited access and using special decontamination measures.

Results

The analyzed data revealed 164 cases of CDI during the period of 2014-2016 in the Regional Oncologic Institute Iasi, admitted in our

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units for median intervals of 10 days. Most of cases were diagnosed in the two surgical wards (more than 65%), 24% of cases appeared in the hematology department, 6% occurred in the intensive care unit, the rest being isolated cases in other clinics of the institution (oncology, pneumology, palliation) (Figure 1). Risk factors for CDI may be divided into three general categories: host factors (immune status, co-morbidities), exposure to CD spores (hospitalizations, community sources, long-term care facilities) and factors that disrupt normal colonic microbiome (antibiotics, other medications, mechanical bowel preparation, and surgery) [9].

Host factors

The demographic analysis shows very little difference between sexes, with female dominance: 88 patients were females, while 76 were men. We must underline here that all patients had a diagnosis of malignancy, with negative influence on their immune status. The mean age of 64 years is partly explained because most patients admitted at the institute are in the 6th or 7th decade of life, but also because CDI is usually affecting people over 55 [10] (Figure 2).

Exposure to *Clostridium difficile*

Although almost 20% of patients had equivocal symptoms from admission, it took an average 7 days until first relevant symptoms arisen, with variations between 1-44 days. More than half of our patients, 54% had previous hospitalization in the last year, mostly being recently released from gastroenterology clinics. The epidemiological analysis revealed that only 7.92% of all patients had been in close contact with a previously confirmed case of CDI.

In 68% of cases the confirmation of diagnosis through laboratory tests was performed in the same day or the next 24 hours. Because symptoms are not always very prominent from the beginning, it took an average of 2 days until the diagnosis was confirmed and the appropriate treatment along with infection control protocols was initiated.

Normal flora disruption

Antibiotic treatment prior to CDI is the most incriminated factor in the appearance of this disease through the disruption of the normal flora [11,12]. Our experience shows that 40% of patients did not receive any antibiotic in the last 3 months. 25% received a single dose of antibiotic, usually second generation cephalosporin, as part of the intravenous preoperative prophylaxis. The rest of 35% of patients have received antibiotics in a continuous manner or in combination in the last 3 months, in 58% of cases administered in our facility.

Among other medication that may be a potential risk factor for development of CDI are gastric acid-suppressive medications, such as histamine-2 blockers and proton pump inhibitors (PPIs), possibly by allowing *C. difficile* spores safe transit through the hypo- or achlorhydric stomach of patients treated with these agents. In our study we found that more than one third of patients, (37%) received such therapy, as PPIs are used for prophylaxis against stress-related mucosal damage.

Colorectal patients

The association with gastro-intestinal surgery is independently associated to a *Clostridium difficile* positivity status [13]. This is also supported by our data, whereas in 64% of the surgical cases the management included a procedure, usually of high complexity, on the gastro-intestinal tract.

Out of all 117 surgical patients we reported a number of 16 cases who were operated on the upper GI tract and 62 cases with colo-rectal surgery. The distribution is the one seen below: 33.87% low anterior resections with total or partial mesorectal excision, 27.42% sigmoid or left colectomies with colo-rectal anastomosis or colostomy, 16.13% right hemicolectomies, 14.51% with previous colorectal surgery (ileostomy closures, complications), 8.06% abdomino-perineal excisions (Figure 3).

Analyzing the patients with highest risk for developing CDI, we found that nearly 44% of patients underwent resection of right, left or sigmoid colon as part of the surgical treatment of colon cancer, accompanied by complete mesocolic excision. Following the logic of a proportional law of distribution the striking value here would be the very small number of abdomino-perineal excisions (8%) performed in our unit in comparison with the low anterior resections (34%), demonstrating the interest for sphincter-preservation techniques whenever possible. In almost 15% of cases CDI affected patients there was a surgical procedure following previous colo-rectal surgery. Most of the procedures were ileostomy loop closures and the rest was surgery performed for inherent complications (anastomotic leakage, ileus, intraabdominal abscess).

The overall mortality rate was 4.87% (8 out of 164). If we consider only the surgical patients, we reported only 4 deaths in 117 patients,

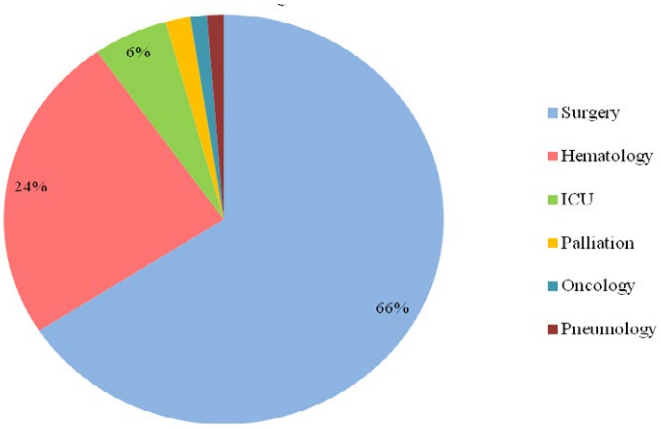

Figure 1: Distribution of CDI cases in different departments.

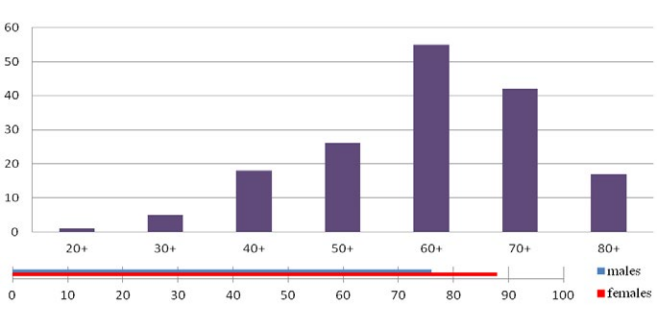

Figure 2: Age and gender distribution of CDI cases.

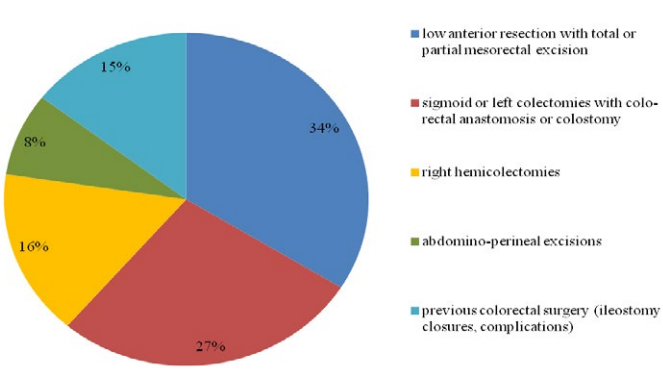

Figure 3: Distribution of CDI cases according to surgical procedure type.

leading to a rate of just 3.41%. We must note that among the 4 patients that died, 2 patients developed late anastomotic fistulas after low anterior resection and 1 patient had duodenal fistula following subtotal gastrectomy, the 4th patient associated very high risk cardiovascular disease and developed acute renal failure after nefrectomy. For the first 3 patients CDI was an aggravating factor, but not the main cause of death, since they tested negative for *C. difficile* toxins long before exitus, making the CDI related mortality to be 0.85% (1 out of 117).

After the confirmation of diagnosis and the initiation of treatment patients were released after a median time of 6.5 days, with variations between 1-45 days. All patients were asymptomatic on release, the majority of them having been tested negative for *C. difficile* toxins.

Discussion

The number of CDI cases per year and the distribution of them among units of our institution is consistent with the data shown in other studies [10,14]. It is only normal to discuss about risk factors when you consider studying CDI, as we could recognise predisposing risk factors previously discussed (antibiotic therapy, GI surgery, gastric acid-suppressive medication, and previous hospitalization/contacts) in 154 out of 164 patients (94%).

The risk of CDI is increased up to 6 times during antibiotic therapy and in the subsequent month after antibiotic therapy [15]. Although nearly all antibiotics have been associated with CDI, clindamycin, third-generation cephalosporins, penicillins and fluoroquinolones have traditionally been considered to pose the greatest risk [8,16]. However newer studies show that there was no clear association between overall cephalosporin usage (or any cephalosporin) and CDI incidence [17]. The prophylactic dose given immediately before surgery is associated with dramatically reduced rates of wound infection and post-operative sepsis [18]. It is likely that any slightly increased risk of post-operative CDI associated with such prophylactic use of antibiotics would be outweighed by benefit [8].

While most studies suggest a higher risk for CDI during PPI treatment, there are contradictory reports in literature [19]. Given that acid suppression drugs may be over-prescribed in surgical settings, consideration should be given to stopping PPIs in patients at high risk of CDI [8].

The rate of recurrence after a first bout of CDI treated with metronidazole or oral vancomycin is approximately 25%. After a first recurrence, the risk of additional recurrences is at least 40% [4]. Fidaxomicin was approved in 2011 for treatment of CDI, but its place in therapy has yet to be determined [12,20]. Some studies show that teicoplanin was significantly superior to metronidazole and vancomycin for initial bacteriologic response [2], but came with significantly increased costs. New treatment strategies that reduce the toxicity of already-bound toxin, or prevent toxin binding to the colon, are needed [5]. The alternative treatment using calcium aluminosilicate uniform particle has proven effective *in vitro* by sequestering toxins A and B to undetectable levels [11].

The disruption of the normal colonic flora by the use of mechanical bowel preparation or the use of preoperative oral antibiotics was not associated with an increased incidence of *C. difficile* infection in some studies [21], while others showed a higher rate of infection [22] or no significant difference [23]. A recent study suggested that the prevalence of *C. difficile* colonization is high in preoperative colorectal cancer patients, and the colonization is not acquired in the hospital. Antibiotic susceptibility testing showed all isolates were susceptible to vancomycin and metronidazole [24].

We must note that all interventions in our institution were performed in an elective manner, being a known fact that patients undergoing an emergency operation are at higher risk of developing CDI than those having operations performed electively [25]. These types of interventions are usually followed by a number of post-operative complications. Postoperative diarrhea and high stoma output, whether in patients who are *C. difficile* positive or not, are related to significantly more surgical site infections, longer hospital stays and more readmissions [26].

A very important aspect we must underline is that 85% of the procedures included laparotomy and the formation of an anastomosis, most frequently a colo-rectal one, either by manual suturing or by means of a stapling device. Since most oncological patients may possess little resources this could lead to low albumin levels, which is a marker for poor immune function [27]. Poor anti-toxin IgA antibody response has been associated with increased risk of recurrence after an episode of CDI and immunosuppression has been associated with the development of CDI, thus low albumin may be associated with CDI through poor immune function. Postoperative impairment of cell-mediated immunity is another potential risk factor for CDI which may last a couple of days after surgery [7].

Several studies show that colectomy, small-bowel resection and gastric resection are associated with the highest risk of *C. difficile* infection [25], also supported by our data. Some not so frequent circumstances of CDI revealed in our study are procedures after previous colo-rectal surgery, like ileostomy loop closures. Even if CDI is an uncommon complication for such a small intervention, patients undergoing stoma closure are at high risk for an adverse outcome if they have CDI [28,29].

The very small number of cases in the oncological ward, just 2 patients out of 164, may be encouraging the supposition that chemotherapy is not a predisposing risk factor for CDI, but for the early onset of CDI negative diarrhea [14]. We need to take into account that the median stay in the oncology clinic is only 3 days. It is statistically proven that hospital stays longer than 10 days increase the risk of exposure and a transfer from a medical ward is a significant parameter for CDI [10].

The small rate of less than 8% for contact between a confirmed case of CDI and other patients concurs to the idea that the rapid implementation of isolation measures has a beneficial role against spreading of the disease, controlling the transmission of *C. difficile* [30]. We stress on the significance of low threshold for CD testing in a surgical unit, providing an early diagnostic with excellent results in CD eradication, mortality and morbidity.

Conclusion

Our study comes to demonstrate that CDI is still a major complication in any oncological unit and the incidence is not diminishing. We also showed that even if we understand the risk factors involved, we cannot yet erase them completely. They will continue to affect our patients in different proportions as they are part of the multimodal treatment.

Understanding these risk factors may provide information on further risk factors and will allow risk-stratification. There are studies that show there is a significant lack of knowledge concerning *C. difficile* infection amongst healthcare professions, amongst consultants and nurses. This should encourage us to further provide education for the healthcare worker regarding risk factors and will reduce the clinical impact of CDI by encouraging increased vigilance and therefore earlier detection.

Rapid and accurate testing will not only save money overall by initiating appropriate treatment and instating infection control protocols sooner, but will possibly reduce the length of hospital stay and the morbidity rate.

Conflict of Interest

Authors have no conflict of interest to disclose.

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