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Risk Factors Associated with *Clostridium difficile* Infection in A Pediatric Hematology-Oncology Ward with Analysis of the Infection Control Measures

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Abstract

Introduction: The impact of *clostridium difficile* infection (CDI) on patients' health and hospitals' cost is significant. Currently CDI is recognized as an increasingly important pathogen in children with increasing incidence among pediatric patients. Data is scarce on the incidence and risk factors of CDI in Saudi Arabia, especially in pediatric oncology population. In this study, we report the first outbreak of CDI in pediatric hematology-oncology ward in Saudi Arabia and describe the associated risk factors for CDI.

Methods: This is a descriptive, epidemiologic hospital based case-control study of pediatric Patients in hematology-oncology ward who had CDI in an outbreak from January 2012 to June 2013 at a tertiary hospital in Saudi Arabia, matched randomly to a control group who were admitted in the same ward during the study period. The main outcome measure was the adjusted odds ratio estimates of potential risk factors for CDI infection. We also describe the control measures that were implemented to control this outbreak.

Results: Risk factors associated with CDI were antibiotic use with cotrimoxazole being the most used one, and length of hospital stay. Controls were found to have been treated more with penicillins and aminoglycosides.

Conclusion: Factors associated with CDI infection are often complex and maybe confounded by local variables, antibiotic exposure and lengthy hospital stays are among many risk factors for CDI in high -risk populations. Our study also highlights the importance of infection control measures in controlling and preventing outbreaks of CDI.

Keywords: *Clostridium difficile*; Pediatric; Hematology-oncology; Infection control; Hydrogen peroxide

Introduction

Clostridium difficile is An anaerobic spore forming gram positive bacilli [1,2]. It is transmitted through fecal-oral route and can cause *clostridium difficile* infection (CDI) when there is alteration in normal bowel flora mostly secondary to antibiotic use. Infections with *Clostridium difficile* ranges from asymptomatic carrier or mild diarrhea to pseudomembranous Colitis [3,4]. It is the most common cause of health-care associated diarrhea [5].

The incidence of CDI is increasing worldwide especially after the emergence of North American pulsed-field gel electrophoresis type 1 (NAP-1) strain which was identified in 2002 and was the cause of multiple outbreaks of CDI. NAP-1 strain is known to produce greater quantities of Toxin A & B with higher risk of relapse resulting in more series disease [1]. Regarding the incidence of CDI in Saudi Arabia, There is only one small study in 2010 describing the annual prevalence which is around 1 per 1000 discharge [6]. But there is no published data on CDI in pediatric hematology-oncology population.

CDI prevalence in pediatrics population is low, but currently it is recognized as an increasingly important pathogen in children. There is increasing incidence of CDI among pediatric patients with estimated annual incidence rate of 2.6-4/1000 admission in published reports CDI accounted for 32% of diarrheal episodes among hospitalized pediatric patients [7].

NAP-1 is reported to affect pediatric population, but at lower rate than in adults [8]. Distinguishing *clostridium difficile* carrier state from infection is important in pediatric age group, as carrier state ranges between 25-81% in infants less than 2 years [9]. This is more problematic when PCR is used as it can identify the organism in the absence of Toxin production. CDI is more frequently reported among children hospitalized with cancer compared to non-cancer [9]. Chemotherapy alters the intestinal flora being a risk factor for CDI in this patient's population. Malignancy itself is also considered as a risk factor. Among the pediatric population, hematology-oncology patients are often the most frequently affected by CDI likely due to the combination of chemotherapy and broad spectrum antibiotic use [10].

The goal of this study was to identify significant risk factors for acquiring CDI during an outbreak in pediatric hematology-oncology patients at a Saudi Arabian hospital using a case-control study. We also describe the different outbreak control measures implemented.

Methods

This is a descriptive, epidemiologic hospital based case-control study of pediatric patients in the hematology -oncology ward who had CDI in an outbreak from January 2012 to June 2013 at a tertiary hospital in Saudi Arabia, matched randomly to a control group who

were admitted in the same ward during the study period. The main outcome measure was the adjusted odds ratio estimates of potential risk factors for CDI infection. We also describe the control measures that were implemented to control this outbreak. To our knowledge this is the first report from Saudi Arabia.

Setting

King Fahad specialist hospital is a tertiary hospital and an oncology center with a pediatric hematology oncology ward consisting of 45 beds. Patients admitted to the hematology oncology ward were included in the prospective surveillance for CDI from January, 2012 to June, 2013, this was part of the institution's key performance indicator (KPI) for the Management of Multi drug Resistant Organisms (MDROs). During this surveillance a cluster of CDI cases was identified.

Population

All pediatric patients with Hematological or solid organ malignancies who developed CDI from January, 2012 to June 2013 were included. Twenty-three cases of CDI were identified; fifteen out of the twenty-three had acute leukemia (others had Hodgkin lymphoma, osteosarcoma, Ewing sarcoma, neuroblastoma, abdominal malignancy).

All the twenty- three patients received multiple courses of different antibiotics. Twelve patients had hospital onset CDI, nine patients had community onset health care associated CDI and two patients had community onset CDI.

Definitions

Cases of CDI were defined as follow [11]:

Clostridium difficile associated diarrhea is defined as diarrhea with positive clostridium assay using PCR for detection of *clostridium difficile* toxin gene

Hospital –onset is defines as onset of symptoms 3 days after admission to a health-care facility.

Community onset healthcare facility associated (CO-HCFA) is defined as Onset of symptoms within 4 weeks after being discharged from a health-care facility.

Community associated (CA) is defined as onset of symptoms occurs outside a health-care facility or <3 days after admission to a health-care facility and has not been discharged from a healthcare facility in the previous 12 weeks

Microbiology

Xpert *C. difficile*/Epi PCR assay was performed on any diarrheal stool. The Xpert *C. difficile*/Epi assay is a multiplex real-time PCR that detects tcdB, the binary toxin gene (cdt), and the tcdC gene deletion at nt 117) [11].

Case control

Patients who had CDI were matched 1:2 to a randomly -selected controls who were hematology- oncology patients admitted to the same ward during the study period. The controls were selected in such a way that the distributions of case patients and control patients were similar over dates of hospitalization. Controls were selected from the population of patients whose surveillance or clinical *clostridium difficile* testing was negative.

Data collection

Medical records of patients with and without CDI were reviewed, and the following information was collected (as outlined in Tables 1-3).

- Demographic data (age, gender).
- Host-related factors (underlying malignancy, neutropenia, chemotherapy, antibiotic use).
- Hospital related factors; length of stay.
- Types of antibiotics used

Data analysis

In this study, three methods have been used to calculate the p value, which are z-test, t-test and chi-square test.

Z-test, was implemented to analyze:

- Antibiotic used in general
- Neutrpenia
- Chemotherapy
- Sex

T-test, was used to analyze:

- Number of antibiotics used.
- Length of hospital stay
- Age

Chi-square test, was used to analyze:

- Staying Room
- Specific antibiotic used (Pencillin, Aminoglycoside.,etc).

P value less than 0.05 is reported as "statistically significant". Otherwise, it is reported as "not significant".

Results

Between January 2012 and June 2013 a total of 23 cases of CDI were identified. The cases were matched randomly to 46 controls who had hematological or solid organ malignancy and were admitted to the hospital during the same period. As a result of the matching process the distribution of cases and controls were similar in terms of age and sex (Table 1).

	Cases	Control	P value
Age	Mean 5.9	Mean 6.7	0.27
Sex (male)	43%	57%	0.27

Table 1: Characteristic of CDI cases and controls.

The case patients were more likely to have received antibiotic (100% vs. 88%, P value 0.016). With cotrimoxazole being the most used one (25% vs. 3%, P value 0.031).

They were more likely to have a longer hospital stay (18 days vs. 10 days, P=0.009), more likely to have received more than three different antibiotic classes, though this was not statistically significant (p=0.99),

both cases and controls were receiving chemotherapy (p=0.57), refer to Table 2 for details.

Controls were found to have been treated more with penicillin's and aminoglycosides (P=0.001, 0.0001 respectively), the use of other antibiotic classes didn't show any statistically significant difference (Table 3). These results maybe limited due to the small sample size.

	Cases (n=23)	Control (n=46)	P value
Neutropenia	61%	79%	0.13
Chemotherapy	96%	93%	0.57
Antibiotic use	100%	88%	0.016
No. Of antibiotics	Mean 3	Mean 2	0.99
Length of hospital stay	Mean 18 days	Mean 10 days	0.009

Table 2: The risk factors that were found significantly associated with CDI.

Antibiotic	Cases	Control	P value
Penicillin	19%	39%	0.001
Aminoglycoside	17%	42%	0.0001
Carbepenem	5%	9%	0.52
Cotrimoxazole	25%	3%	0.031
Vancomycin	2%	3%	0.9
Cephalosporin	20%	1%	0.07
Quinolones	3%	1%	0.83
Macrolide	8%	1%	0.52
Clindamycin	2%	0%	0.88

Table 3: The association between specific antibiotics and CDI.

Management of the outbreak

The recognition of the significant increase in CDI cases in this high -risk population led to the implementation of infection control measures.

A multidisciplinary meeting was held to plan for the measures to mitigate the spread of the bacteria to other patients. A series of educational sessions on *Clostridium difficile* infection were conducted.

Pediatric oncology patients who had diarrhea were isolated in a single room with on suite toilet and dedicated patient equipment and supplies until the stool test results were known.

After discharge non reusable items in the room were discarded and reusable ones were decontaminated with 5000 ppm chlorine releasing agent [12,13].

All vacated patient rooms were exposed to H_2O_2 Vaporizer machine before admitting new patients in it. Pediatric Oncology Day Care (PODC) rooms visited by ambulatory patient for chemotherapy were included in the exposure to H_2O_2 Vaporizer machine and the use of sporicidal chlorine releasing agent [13,14].

Hand hygiene using soap and water was encouraged over the alcohol based hand rub while the cluster of infection is still not controlled [12].

Guidelines for Antibiotic Usage in Febrile Neutropenia were finalized and were implemented [12].

July, 2013 was the end of the outbreak as no new cases were identified, this persisted over the following three months.

Discussion

CDI has a huge impact on the morbidity of hospitalized patients. NAP 1 strain has led to increase incidence and mortality from CDI [15]. Generally speaking *Clostridium difficile* incidence is less in pediatric population than in adults [9]. Although CDI was thought to be a rare disease in pediatric age group, it is now identified as a significant cause of morbidity in pediatric inpatient population especially oncology patients and patients with IBD or other GI disorders [7]. *Clostridium difficile* was reported to be the most common cause of nosocomial diarrhea in pediatric population [7]. Exposure to antibiotics was one of the main risk factors for CDI in many reports, the highest risk was with using broad spectrum cephalosporins, clindamycin and fluroquinolons [16]. This was also observed in our study and cephalosporins use was more observed in the CDI case group (20% vs. 1%, P=0.07), P value was insignificant likely due to the small sample size. Clindamycin and fluroquinolons were not used in our institution frequently enough to assess their association with CDI. The length of hospital stay is another well-established risk factor for CDI [16]. This was also the case in our study with CDI cases having a mean of 8 more days of hospital stay compared to the controls [18 vs. 10, P=0.009]. Malignancy is identified as an important also a risk factor for CDI, especially the combination of neutropenia and prolonged courses of antibiotics our study included only hematology- oncology patients with the majority of them having hematological malignancy as a diagnosis. Salgado et al, described an outbreak from October 2004 till May 2005 and they reported that hematology/oncology ward has the highest rate of CDI [17]. In one study, in adult with hematological malignancy, the risk of CDI was 7%. Another study, in adult with AML, the incidence of CDI was 18% and 9% of chemotherapy courses. The risk factors that were identified in this study include number of antibiotics, duration of antibiotics and duration of neutropenia [18] while in our study we could not find association between the number of antibiotics used and CDI, mainly due to the small sample size. There is limited data in the literature describing CDI in pediatric hematology/oncology patients. The incidence of CDI is 15 folds higher in hospitalized children with cancer than in those without cancer [9]. Price, et.al reported that 11% of pediatric patients with acute myeloid leukemia (AML) had CDI and that 3% of the chemotherapy courses were associated with CDI [18]. In our study most of the cases and controls were receiving chemotherapy, as part of the matching for controls, so no statistically significant association was determined.

Outbreaks of CDI in pediatric oncology wards were described in the literature with an incidence as high as 13%, the identified risk factors for the different outbreaks were neutropenia and lymphoid malignancy, in another prospective survey of pediatric oncology patients with gastroenteritis,15 cases (14%) were caused by CDI, with intra-venous antibiotics use for more than 1 week being the major risk factor [19]. The association between neutropenia and CDI is not well established as some studies found no association between CDI and

neutropenia, this was also the case in our study as control patient had more neutropenia compared to the case studies [79% vs. 61%,P =0.13]. One study showed that neutrophils may play a role in pathogenesis of CDI [20].

Controlling CDI outbreaks is best done with the implementation of optimal infection prevention and control measures combined with antimicrobial stewardship programs [21]. It is reported in various studies that 49% of CDI infected patients' rooms and 29% of asymptomatic carriers' rooms are contaminated by *Clostridium difficile*, making environmental transmission of CDI an important factor in causing outbreaks due to environmental persistence of the spores [14]. Terminal cleaning with chlorine based solution led to the reduction in the CDI rate, $p<0.05$ [22,23] . H_2O_2 vapor has been an effective tool for surface decontamination as demonstrated in various studies [13,22,24]. Another infection prevention and control measures are improving hand hygiene practices using water and soap, with appropriate transmission based precautions patients [25]. We were able to control this outbreak with the implementation of this multipronged intervention strategy.

Our study had some limitations. First, the total number of CDI cases is small. Second, the study was limited only to one center, because of these factors it is difficult to generalize our results to other centers in Saudi Arabia. Despite these limitations, we consider that this study sheds some light on this problem in Saudi Arabia pediatric hematology-oncology population and calls for bigger studies involving multiple oncology centers.

Conclusion

The factors associated with CDI are often complex, and may be confounded by local variables.

Although this is the first report from Saudi Arabia describing CDI in pediatric hematology-oncology patients, this is rather under detection rather than true low incidence, as patients have many risk factors for developing CDI, and more vigilant screening is needed to identify at risk patients.

Active surveillance, early identification of outbreaks and the implementation of strict infection control measures are the keys to control outbreaks successfully with antimicrobial stewardship as being one of the most important interventions [5].

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