Clostridium Difficile Associated Diarrhea in Children with Hematological Malignancy-Experience from a Pediatric Oncologic Centre, Bangladesh

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Abstract: *Background*: Clostridium difficile Associated Diarrhea (CDAD) is considered to be one of the commonest causes of nosocomial diarrhoea worldwide. Gastrointestinal infections in the form of diarrhoea are common in pediatric oncology patients in Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh. The study was conducted to find out the frequency of Clostridium difficile infection (CDI) among diarrheal children with haematological malignancy.

Materials and Methods: This prospective observational study was conducted from April 2012 to March 2013 at the Pediatric Hematology and Oncology Unit, BSMMU, Bangladesh. Total 58 diarrheal episodes occurred in 51 children with various types of haematological malignancies were included consecutively. Faecal samples of the children were sent to International Centre for Diarrheal Disease Research, Bangladesh (ICDDR, B) laboratory for detection of Clostridium difficile antigen (GDH) and toxins (A and/ or B) by Enzyme Immunoassay (EIA).

Results: Among 58 diarrheal episodes 22.4% faecal samples were positive for GDH, but none of the faecal samples was positive for toxin A and or B. There were a significant association with leucopenia, severe neutropenia; usage of meropenem plus vancomycin, cefepime plus amikacin, imipenem, cytarabine and omeprazole with GDH positive diarrheal episodes.

Conclusion: Positive GDH antigen with a negative result for toxin indicates C. difficile colonization. Among GDH positive episodes, a significantly higher proportion of children had leucopenia, severe neutropenia and usage of some drugs known as risk factors for C. difficile infection. To confirm the CDI advanced tests are needed.

Keywords: C. difficile antigen, C. difficile toxins, Neutropenic diarrhoea, Chemotherapy, C. difficile colonization, Proton- pump inhibitor, Health care infection.

INTRODUCTION

Health-care associated infections (HAI) in pediatric cancer patients are considered to be an important adverse outcome in terms of morbidity and mortality, postponing chemotherapy treatment cycles, as well as prolonged duration of hospital stay and additional costs from the perspective of the caregiver [1]. Clostridium difficile (C. difficile) has emerged worldwide as an important healthcare-associated pathogen and is linked to significant morbidity, economic burden and even mortality [2]. The estimated health-care cost associated with a hospitalized patient who develops C. difficile infection (CDI) is 33-54% greater than that of a similar patient who does not develop CDI [3].

The children with haematological malignancies are a special group in the clinical significance of colonization by C. difficile and haematology/oncology patients are recognized as a frequent source of C. difficile in hospitals amongst the pediatric population by different studies [4-7].

Many factors may explain the increased risk of C. difficile infection in children with cancer, including repeated exposure to broad-spectrum antibiotics, the inherent antimicrobial activity of some chemotherapy regimens, extensive and frequent exposure to healthcare facilities or immunosuppressive effects of chemotherapy, including neutropenia [8-11].

C. difficile exerts its pathogenic effects through the production of toxins, the two most important being toxin A and toxin B [12,13]. Glutamate dehydrogenase [GDH] is a common antigen produced in high amounts by all strains of toxigenic or nontoxigenic C. difficile and

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it is a good antigen marker for the presence of an organism in a faecal specimen [14]. C. difficile infection (CDI) is defined as the acute onset of diarrhoea with documented toxigenic C. difficile or C. difficile toxin, without any other clear cause of diarrhoea [15]. Colonization with C. difficile is defined as the presence of the organism in a person without clinical symptoms like diarrhoea [16].

A definitive diagnosis of C. difficile infection requires laboratory identification of Clostridium difficile toxin in a stool sample and /or visualization of pseudomembranous colitis (PMC), in addition to clinical symptoms (usually diarrhoea) consistent with CDI [17].

Haematological malignancies were the most common (82%) malignancies among treated children in pediatric haematology and oncology department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh [18]. These children frequently face the problem of febrile neutropenia. Diarrhoea was a common complication in neutropenic cancer children [19]. A previous study from this centre found gastrointestinal infections in the form of diarrhoea and dysenteric illnesses were the leading causes of infection in pediatric oncology patients [20]. Considering the significant morbidity, possibility of outbreaks and the emerging threat of hypervirulent strains isolates in various countries worldwide it also seems mandatory to implement continuous prospective surveillance of C. difficile among these children with malignancies who are vulnerable to this opportunistic pathogens.

Unfortunately, C. difficile associated diarrhoea (CDAD) is under-recognized in Asia due to lack of clinical suspicion, difficulty in culturing the organism and cost of toxin assay [21,22]. In Bangladesh, a previous etiological study found that out of 814 children admitted in hospitals with diarrhoea 18 were infected with C. difficile (diagnosed by cell cytotoxin assay) and seven of those cases were concurrently infected with another pathogen [23].

After having the laboratory opportunity from International Centre for Diarrheal Diasese Research, Bangladesh (ICDDR, B) we started to conduct the study in the Pediatric Hematology and Oncology Department of BSMMU over a one -year period to obtain the base-line information on the frequency of C. difficile infection and to create awareness whether it is causing diarrhoea in our children with haematological malignancies.

MATERIALS AND METHODS

This prospective observational study was conducted at Pediatric Hematology and Oncology department, BSMMU, Bangladesh from April 2012 to March 2013. The protocol was approved by the Institutional Review Board (IRB) of BSMMU. Before data collection written consent from the legal guardian of each patient was taken.

A total of 51 Children having age range 1 to 15 years of both sexes with the diagnosis of various types of haematological malignancies were included consecutively who developed diarrhoea, at any point during hospitalization. Diarrhoea was defined as the passage of at least three loose or watery stools within 24 hours.

On 1st day of enrollment, stool samples were sent to ICDDR'B laboratory for identification of glutamate dehydrogenase (GDH) antigen and C. difficile toxin by enzyme immune assay (EIA) C. DIFF CHEK^{TM}-60 and C. DIFFICILE TOX A/B II^{TM} test respectively.

C. DIFF CHEK^{TM}-60- is a commercially available kit for detection of Glutamate dehydrogenase (GDH); C. DIFFICILE TOX A/B II^{TM} is also a commercially available enzyme immunoassay (EIA) kit, an alternative to tissue culture assay for detecting C. difficile toxin A and or B in faecal samples.

On the day of enrollment, Complete blood count with WBC differential was done but no invasive procedure like sigmoidoscopy or endoscopy was done. Data were recorded regarding demographic profile (age, gender, type of haematological malignancy and duration of hospital stay), phase and type of chemotherapy, history of using any antibiotics and gastric acid suppressant during diarrheal episodes. Data were also collected reports of blood, urine and stool culture and PCR for fecal protozoa if any at the time of diarrheal episodes. Editing and compilation of collected data were done manually. Data analysis was done using window based software Statistical Packages for Social Sciences (SPSS) version 12.

RESULTS

During 12-months period, total 58 diarrheal episodes from 51 children were studied. Their age ranged from 1.08 to15 years with mean 5.9 and standard deviation (SD) ± 3.6 years. Among them, 32 were male (63%) and 19 were female (37%). Majority diarrheal episodes (55.2%) were from age group 1-5

Table 1: Enzyme-Linked Immunoassay (EIA) Tests Results of Clostridium Difficile from Faecal Samples of Diarrheal Episodes

Types of test	Result	Types of malignancy during a diarrheal episode			
		ALL	AML	NHL	Total
		No. (%)	No. (%)	No. (%)	No. (%)
		37(63.79)	4(6.9)	17(29.4)	58(100)
C. DIFF CHEK™ -60 test for GDH-antigen	Positive	08 (13.8)	02 (3.4)	03 (5.2)	13 (22.4)
	Negative	29 (50.0)	02 (3.4)	14 (24.1)	45 (77.6)
C. DIFFICILE TOX A/B II™ test for toxins	Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Negative	37 (63.8)	04 (6.9)	17 (29.3)	58 (100)

ALL= Acute Lymphoblastic Leukemia.
AML= Acute Myeloid Leukemia.
NHL= Non-Hodgkin Lymphoma.

years, then from 5-9 years (27.6%). Duration of their hospital stays range from 0 to 43 days with mean 7.16 days and SD ± 8.98 days during episodes of diarrhoea.

Among the studied (51) children, Acute lymphoblastic leukaemia (ALL) was the most common (62.7%) haematological malignancy, then 29.4% had Non-Hodgkin lymphoma (NHL) and 7.9% had Acute Myeloid leukaemia (AML).

Among the faecal samples (58) of the studied children, 13 (22.4%) were found positive for GDH antigen and 45 (77.6%) were negative for GDH antigen by C. DIFF CHEK™-60 TEST but C. DIFFICILE TOX A/B II™ test failed to detect any toxin from any faecal samples (both GDH positive and GDH negative group) (Table **1**).

During the diarrheal episodes, pathogenic bacteria were found only in 23.1% (3/13) GDH positive cases by aerobic stool culture but none in GDH positive cases. Several different parasites identified by PCR in 46.2% (6/13) GDH positive cases and in 78.1% (32/41) GDH negative cases (Figure **1**).

At the time of diarrheal episode majority children (n=47, 81%) were neutropenic with ANC count ≤0.5x10^9/L of blood and severe neutropenia were observed in all of the GDH positive diarrheal episodes. There was a significant association of leucopenia and severe neutropenia with GDH positive episodes (Table **2**).

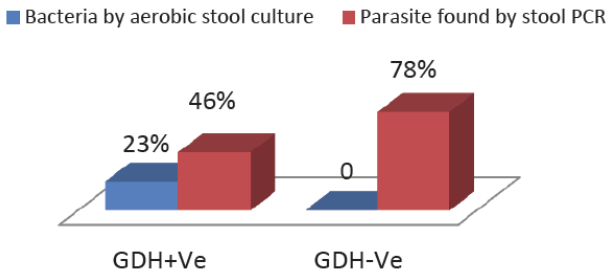

Figure 1: Identified pathogen other than C. difficile in diarrhoeal episodes.

Most of the studied children (n=56; 96.6%) had a history of receiving different types of antibiotics before or during the diarrheal episodes and it was found that significant association with usage of Imipenem, Cefepime plus Amikacin and Meropenem plus Vancomycin with C. difficile GDH positivity (Table **3**).

Episodes of diarrhoea were frequently experienced by the studied children (n=37; 63.8%) while they had

Table 2: Blood Parameters of the Studied Children during a Diarrheal Episode

Blood parameters	GDH +ve (n=13)	GDH -ve (n=45)	Total	P-value*
	(Mean ± SD)	(Mean ± SD)		
T.C (10^9/L)	0.6131 ± 0.4736	1.5204 ± 2.0387	58	0.0083^S
ANC (10^9/L)	0.1131 ± 0.1422	0.7572 ± 1.4394	58	0.0049 ^{S}
Hb (g/dl)	8.2077 ± 1.9623	8.8111 ± 1.9688	58	0.974
PLT (10^9/L)	41.69 ± 31.17	82.29 ± 87.24	58	0.12 ^{S}

*Unpaired t-tests were done to compare means of different blood parameters between the GDH +ve and GDH -ve cases of the diarrhoeal episodes.
^{S}P < 0.05 is considered as significant.

Table 3: Use of Different Antibiotics before or during Diarrheal Episodes

Name of the antibiotic	GDH +ve (n=13)	GDH -ve (n=45)	Total (n=58)	P-value*
	No. (%)	No. (%)	No. (%)	
Antibiotics[#]				
Cefepime	1 (7.69)	2 (4.44)	3 (5.17)	0.641
Cefepime+ Amikacin	5 (38.46)	6 (13.33)	11 (18.97)	0.042 [S]
Cefepime+ vancomycin	2 (15.38)	2 (4.44)	4 (6.90)	0.170
Meropenem	1 (7.69)	0 (0.0)	1 (1.72)	0.061
Meropenem + Amikacin	0 (0.0)	1 (2.22)	1 (1.72)	0.588
Meropenem + Vancomycin	4 (30.77)	4 (8.89)	8 (13.79)	0.044 [S]
Imipenem	2 (15.38)	0 (0.0)	2 (3.45)	0.007 [S]
Others	0 (0.0)	03 (6.67)	3 (5.17)	0.339
Prophylactic Cotrimoxazole	1 (7.69)	14 (31.11)	15 (25.86)	0.896
Prophylactic Levofloxacin	3 (23.08)	8 (17.78)	11 (18.97)	0.668
No antibiotics	1 (7.69)	1 (2.22)	2 (3.45)	0.342

[#]More than 7% of the patients of hematological malignancy with diarrhea were treated more than one category of antibiotic /antibiotic-combination in different time.
*Chi-Square tests were done to compare the proportions of use of antibiotics between the GDH +ve and GDH-ve diarrheal episodes.
[S]P < 0.05 is considered as significant.

Table 4: Use of Different Chemotherapeutic Agents before or during Diarrhoea

Name of the chemotherapeutic agent	GDH +ve (n=13)	GDH -ve (n=45)	Total (n=58)	P-value*
	No. (%)	No. (%)	No. (%)	
Chemotherapy use				
VCR	8 (61.54)	34 (75.56)	42 (72.42)	0.31732
L-aspa	3 (23.08)	17 (37.78)	20 (34.48)	0.32708
Dexamethasone	2 (15.38)	17 (37.78)	19 (32.76)	0.12852
Prednisolone	4 (30.77)	17 (37.78)	21 (36.21)	0.64552
Daunomycin	6 (46.15)	8 (17.78)	14 (24.14)	0.03486 [S]
6-MP	2 (15.38)	12 (26.67)	14 (24.14)	0.4009
HD-MTX	4 (30.77)	17 (37.78)	21 (36.21)	0.64552
LD-MTX	0 (0.00)	6 (13.33)	6 (10.34)	0.16452
Thioguanine	2 (15.38)	1 (2.22)	3 (5.17)	0.05876
Cyclophosphamide	3 (23.08)	12 (26.67)	15 (25.86)	0.79486
HD-Cytarabine	3 (23.08)	0 (0.0)	3 (5.17)	0.00094 [S]
Cytosar	2 (15.38)	4 (8.89)	6 (10.34)	0.4965
Etoposide	3 (23.08)	4 (8.89)	7 (12.07)	0.16758
Mitoxantrone	1 (7.69)	0 (0.0)	1 (1.72)	0.0601
Doxorubicin	3 (23.08)	11 (24.44)	14 (24.14)	0.92034
No use of chemotherapy	00(00)	01(2.22)	1 (1.72)	0.5892

*Chi-Square tests were done to compare the proportions of use of different chemotherapeutic agents between the GDH +ve and GDH -ve diarrheal episodes.
[S]P < 0.05 is considered as significant.

Table 5: Use of Gastric Acid Suppressants before or during a Diarrheal Episode

Name of the gastric suppressants	GDH +ve (n=13)	GDH -ve (n=45)	Total (n=58)	P-value*
	No. (%)	No. (%)	No. (%)	
Gastric suppressants Use	10 (76.92)	32 (71.11)	42 (72.4)	0.952
Omeprazole	04 (30.77)	02 (4.44)	06 (10.3)	0.005 ^{S}
H2-blocker	09 (69.23)	30 (66.67)	39 (67.2)	0.865
Antacid	09 (69.23)	24 (53.33)	33 (56.9)	0.307
No use	03 (23.08)	13 (28.89)	16 (27.6)	0.681

*Chi-Square tests were done to compare the proportions of use of gastric acid suppressants among the GDH +ve and GDH -ve diarrheal episodes.
$^{S}P < 0.05$ is considered as significant.

been passing through induction phase of chemotherapy. Vincristine was (n=42; 72.4%) frequently used antineoplastic agent followed by steroid (n=40; 69%), Anthracycline (n=28; 48.3%), High dose Methotrexate (n=21; 36.2%), L-asparaginase (n=20; 34.5%) and Cyclophosphamide (n=15; 25.9%). The present study found a significant association with usage of high dose Cytarabine with GDH positive diarrheal episodes (Table **4**).

Before diarrheal episode 72.4% (n=42) children had a history of using of gastric acid suppressants like Antacid, H_2-blocker and Omeprazole; usage of Omeprazole shows significant association with C. difficile GDH positive episodes (Table **5**).

DISCUSSION

After Laboratory evaluation of faecal samples by enzyme immunoassay by C. DIFF CHEK^{TM}-60 22.4% of faecal samples were found positive for GDH antigen, but C. DIFFICILE TOX A/B II^{TM} test failed to detect any toxin (A and/or B) both in GDH positive and GDH negative groups (Table **1**). The finding of GDH positivity in children with diarrhoea but without findings of toxin in GDH positive samples denotes that children had colonization or were carriers of C. difficile, and diarrhoea may be due to other cause. This is supported by the argument that "if 20% of hospitalized patients are colonized with C. difficile [15,24,25] and most nosocomial diarrhoea is unrelated to C. difficile infection [26-28], it seems likely that some patients with diarrhoea and C. difficile are carriers, with diarrhoea due to other causes'' [29]. Though there is some explanation that failure to detect toxins may be due to host antibody binding of toxins or low *in vivo* toxin levels from lack of toxin production, a low bacterial burden of C. difficile at the time of testing, or a relative predominance of spores versus vegetative cells [30] and rare complication in toxin negative patients may also be explained by an excessive host response, pre-analytic toxin degradation, or toxin assay insensitivity [29].

Cohen *et al*., [15] found a colonization rate with C. difficile in hospitalized children and adults approximately 20%. Armin *et al*., [31] showed a 25% rate of colonization with C. difficile in children with cancer. The colonization rate of 22.4% of the present study closely similar to above-mentioned studies. In 77.6% of diarrheal episodes, the present study did not find any relation with C. difficile or its toxins, which is consistent with the findings of Wolfhagen *et al*., who also found no relation with C. difficile or its toxin in 75% of the period with diarrhoea in immuno-compromised children [32].

Acute lymphoblastic leukaemia (ALL) was the most common haematological malignancy among the studied children (62.7%). The peak incidence of ALL occurs between 2 to 5 years of age [33] and the current study found maximum samples (55.2%) from the age group of 1-5 years. Gender predominance of male (M:F=1.7:1) was also due to underlying disease distribution as the incidence of ALL is higher among boys than girls [34].

During the diarrheal episodes, pathogenic bacteria were found only in 23.1% GDH positive cases but none in GDH positive cases. It may be due to most of the studied children were getting antibiotics empirically. Several different parasites identified in 46.2% GDH positive cases and in 78.1% GDH negative cases (Figure **1**). This result is higher than the study of Umit et al (2003) where parasite identified in 42.0% of patients with malignancy [35].

At the time of enrollment for diarrheal episode the majority of our children (81%) were neutropenic. In this study, neutropenia was defined as an absolute neutrophil count $<0.5x\ 10^9/L$ [19]. Diarrhoea is a

frequent complication in children with cancer while neutropenic, observed by Sherief *et al*., who found a 55.5% diarrheal episode in neutropenic children [19]. The rate of neutropenia (81%) during diarrheal episodes of the present studied children was even higher. The present study found a significant association of severe neutropenia and C. difficile colonization among children with haematological malignancy (Table **2**).

Prior antimicrobial use is the most important risk factor for C. difficile infection (CDI). Increased duration of antibiotic use and the use of multiple antimicrobials are associated with increased risk of C.difficile infection [15]. Some studies have reported that 35%-75% of children with CDI had antibiotic exposure [36-38]. In the present study, 96.6% of the studied children had a history of receiving different antibiotics before or during the episodes of diarrhoea. Cotrimoxazole (25.9%), levofloxacin (19%), cefepime and amikacin (19%), meropenem plus vancomycin (13.8%) were frequently used antibiotics before episodes of diarrhoea. In contrast to the study of Armin *et al*., [31] and other previous studies [39] present study showed a significant association of C. difficile colonization with the usage of antibiotic Cefepime plus Amikacin, Meropenem plus Vancomycin and Imipenem (Table **3**).

Among the 58 diarrheal episodes, 57 (98.28%) had a history of receiving chemotherapy. Episodes of diarrhoea were frequently experienced by the studied children while they had been passing through induction phase (n=37; 63.8%) of therapy, and next common phase was intensification (n= 12; 20.7%). Armin *et al*. did not find any correlation with the usage of chemotherapy and C. difficile colonization [31] but the present study found a significant association with usage of high dose Cytarabine and C. dificile colonization which is consistent with the study of Murabata *et al*. [40].

Before diarrheal episodes, 72.4% of the studied children had a history of using of gastric acid suppressants like antacid, H_2-blocker and Omeprazole. Pediatric study regarding the role of gastric acid-suppressive therapy in CDI is conflicting [41,42]. But the present study found a significant association with GDH positivity and usage of omeprazole before or during a diarrheal episode (Table **5**).

CONCLUSION

The present study found the colonization rate of C. difficile 22.4% but none was toxigenic. The findings of GDH positivity in children with diarrhoea but without findings of toxin in GDH positive sample denotes that children were carriers of C. difficile and diarrhea might be due to other cause. Among the GDH positive diarrheal episodes, a significantly higher proportion of studied children had leucopenia, severe neutropenia; the history of using some antibiotics, a chemotherapeutic agent and proton-pump inhibitor omeprazole which is suggestive of C. difficile infection, but EIA result was negative for the toxin. So to confirm the CDI advanced test is needed.

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APPENDIX

CDAD: Clostridium difficile –Associated Diarrhea. A case of CDAD, defined as a hospitalized patient with diarrhoea whose stool specimen is positive for C. difficile toxins both A and/or B.

Diarrhoea: Defined as an alteration in normal bowel pattern with the passage of three or more consecutive unformed stools within 24 hours.

Haematological malignancy: Represent a wide range of disorders that include acute and chronic leukaemias, lymphomas and histiocytic disorders.

GDH: Glutamate Dehydrogenase, common antigen produced by both toxigenic and non-toxigenic strains of C. difficile.

ANC = Absolute Neutrophil Count

Hb = Hemoglobin

PLT = Platelet

TC = Total count of White Blood Cell (WBC)

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