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ORIGINAL ARTICLE

Observational Study

Pathogens causing diarrhoea among Bangladeshi children with malignancy: Results from two pilot studies

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Author contributions: Karim S, Begum F, Begum M, and Islam A contributed to the study conception and design; Karim S, Begum F, Tarafdar MA, Islam MJ, and Ahsan MS contributed to data acquisition, collation, and curation; Rashid H, Malik B, and Khatami A contributed to the data analysis and interpretation; All authors contributed to the drafting, editing, reviewing, and final approval of the article. Karim S and Begum F have made equal contributions to the manuscript.

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Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrolment.

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Abstract

BACKGROUND

Diarrhoea is a frequent symptom in children with cancer, and occurs due to a composite effect of underlying disease and immunosuppression consequent to therapy, malnutrition, and non-infective aetiologies such as mucositis. In a large proportion of cases, the aetiology of diarrhoea remains unknown but is often attributed to multiple pathogens including parasites.

AIM

To identify and describe the pathogens causing diarrhoea in Bangladeshi children with cancer.

Conflict-of-interest statement: There are no conflicts of interest to disclose in relation to this manuscript.

Data sharing statement: No additional data are available. These data, in part, were presented at the 46th Congress of the International Society of Paediatric Oncology Toronto, Canada on 22nd–25th October, 2014, and at the 50th Congress of the International Society of Paediatric Oncology Kyoto, Japan on November 16-19, 2018.

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METHODS

Two cross-sectional pilot studies were conducted involving paediatric oncology patients with diarrhoea. Stool samples were collected from children who were hospitalised with or without being treated with chemotherapy during the study period, and had diarrhoea at any stage during their admission. In the first study, stool samples were tested by conventional microbiological methods and by polymerase chain reaction for parasites, and by immunoassays for *Clostridium difficile*. In the second study, conventional microbiology was conducted for bacteria and parasites including an enzyme-linked immunosorbent assay for *Cryptosporidium* antigen, and in a subset, immunoassays for *Clostridium difficile*.

RESULTS

In the first study *Giardia lamblia* was detected in 68.5% of samples, *Entamoeba histolytica* in 13%, *Cryptosporidium* in 5.6%, non-toxigenic *C. difficile* in 22.4%, and other bacteria in 5.2%. In the second study, *E. histolytica* was detected in 10% of samples, *Cryptosporidium* in 4.3%, *G. lamblia* in 1.4%, *C. difficile* in 5.1%, and other bacteria in 5.7% of samples.

CONCLUSION

These pilot data suggest that parasites are important aetiologies of diarrhoea in Bangladeshi children with malignancy. While molecular diagnostic tools detect an array of stool pathogens with greater sensitivity, conventional diagnostic methods are also useful.

Key words: Bangladesh; Cancer; Child; *Cryptosporidium*; Gastroenteritis; Parasite

Core tip: In these two pilot studies, pathogens responsible for causing diarrhoea in Bangladeshi children with cancer were explored. In both studies, there were an abundance of parasites including *Giardia lamblia*, *Entamoeba histolytica*, and *Cryptosporidium*, as well as some bacteria, notably non-toxigenic *Clostridium difficile*.

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INTRODUCTION

Diarrhoea is a frequent symptom in children with cancer[1], and occurs due to a composite effect of underlying disease and immunosuppression consequent to therapy, malnutrition, and non-infective aetiologies such as mucositis[2]. In a large proportion of cases, the aetiology of diarrhoea remains unknown but is often attributed to multiple pathogens including parasites[3,4].

In immunocompromised individuals, intestinal parasitic infections may run a severe course, at times leading to fatality[5]. However despite this, there are limited data on the epidemiology of such infections among children with malignancy in South Asia. In urban slums of Bangladesh, about five diarrhoeal episodes per year are reported among otherwise healthy infants[6], and in a typical year, a tertiary hospital admits more than 3600 children for diarrhoea, a significant proportion of which are caused by intestinal protozoa[7,8]. As the leading cause, *Giardia lamblia* has been shown to account for about 15% of identified pathogens causing diarrhoea in young children in urban slums of Bangladesh, while *Cryptosporidium* and *Entamoeba histolytica* each account for about 4%[6]. However, the profile of pathogens causing diarrhoea among Bangladeshi children with malignancy is not yet described.

To this end, we presented the results of two pilot studies describing the frequency of pathogens identified during episodes of diarrhoea among paediatric oncology patients admitted to a tertiary referral hospital in Bangladesh. The role of cheaper and

more widely available conventional microbiological tests (as opposed to molecular diagnostics) in detecting those pathogens was also investigated.

MATERIALS AND METHODS

Participants and data collection

Two pilot cross-sectional studies were conducted at Bangabandhu Sheikh Mujib Medical University Hospital (Dhaka, Bangladesh): The first one from April 2012 to March 2013, and the second from March 2016 to February 2017. Both studies involved hospitalised children with malignancies who developed diarrhoea, defined as an alteration in normal bowel pattern with the passage of three or more consecutive unformed stools within a 24 h period, during their admission. The two study designs differed slightly as summarised in Figure 1. Children with cancer who were hospitalised with or without being treated with chemotherapy during the study period and had diarrhoea at any stage during admission and whose parents/guardian provided consent to participate were eligible for inclusion. For the included children, a separate data form was used each year for collecting demographic and clinical data including age, gender, type and stage of cancer, phase of treatment, and hydration and circulatory status.

In the first study, following recruitment, a fresh stool sample was collected into a pre-labelled container for microscopy for parasites, cysts, and ova and aerobic culture on selective media for enteric bacterial pathogens using standard protocols. In addition, multiplexed, real time, polymerase chain reaction (PCR) for *Cryptosporidium* spp, *E. histolytica*, and *G. lamblia* was conducted on 54 of the total 58 samples using a commercial assay as described elsewhere[9]. A second stool sample was collected for identification of *Clostridium difficile* toxin and glutamate dehydrogenase by enzyme immunoassays (EIAs) using TOX A/B II™ and C. DIFF CHEK™-60 (TechLab®, Blacksburg, VA, United States). Some methodological details were presented at the 46th Congress of the International Society of Paediatric Oncology in Toronto, Canada 22nd–25th October, 2014, and the results of this study have been published in brief as conference proceedings[10].

In the second study, a single stool sample was collected in a pre-labelled container for microscopy for parasites, cysts, and ova and aerobic culture on selective media for enteric bacterial pathogens using standard protocols, as well as an enzyme-linked immunosorbent assay (ELISA) for *Cryptosporidium* using the *Cryptosporidium* Ag ELISA kit (DRG Diagnostics GmbH, Marburg, Germany). In a random subset (n = 39), *C. difficile* antigen and toxin were also investigated using TOX A/B II™ and C. DIFF CHEK™-60 immunoassays.

On the first day of diarrhoea, blood samples were obtained for complete blood count and serum creatinine and electrolytes, as part of the routine diagnostic workup. In both studies, blood tests were conducted at the Paediatric Haematology and Oncology Laboratory of Bangabandhu Sheikh Mujib Medical University; while in the first study, stool microbiology, ELISA, and molecular tests were carried out at the Microbiology laboratory of the International Centre for Diarrhoeal Disease Research (Dhaka, Bangladesh), in the second study, stool microbiology and ELISA were carried out at the Microbiology Laboratory of Bangabandhu Sheikh Mujib Medical University.

Data analysis

Data were collated on a master Excel spread sheet before importing to Statistical Package for Social Sciences software (IBM SPSS Statistics for Windows, version 25.0; IBM Corp., Armonk, NY, United States). Categorical data were expressed as number and proportion while continuous data were expressed as range with measures of central tendency and/or dispersion. Some patients had more than one episode of diarrhoea and hospitalisation, and each presentation was counted separately towards the final denominator.

RESULTS

First study

During a 12-mo period from April 2012 to March 2013, a total of 58 diarrhoeal episodes were experienced by 51 patients. The demographic characteristics of children included in the study are outlined in Table 1. Of note, more than 50% of the children with diarrhoea included in the study were aged < 60 mo. Pathogens detected are listed in Table 1. There was an abundance of *G. lamblia* (68.5%), and non-toxigenic *C.*

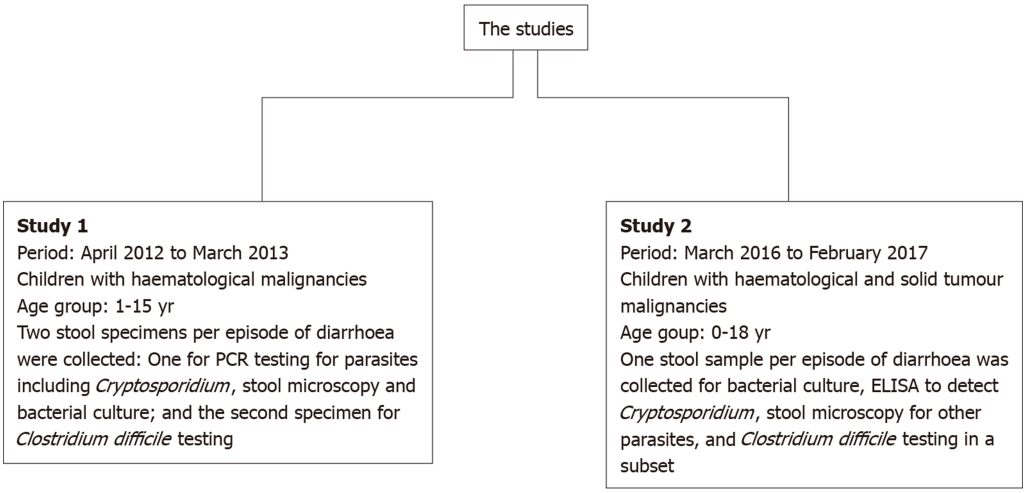

Figure 1 Summary of study methods. PCR: Polymerase chain reaction; ELISA: Enzyme-linked immunosorbent assay.

difficile was detected in 13 episodes (22.4%).

In all but two episodes (96.6%), the children had a history of receiving antibiotic therapy or prophylaxis, on average 3.9 d (range 1-16) prior to or during the episode of diarrhoea. Antibiotics received included prophylaxis with oral trimethoprim-sulfamethoxazole (25.9%) or levofloxacin (19%), and treatment with cefepime plus amikacin (19%) or meropenem plus vancomycin (13.8%).

All three children with *Cryptosporidium* infection were male, aged 3.5, 4.5, and 6 years; two of them had acute lymphoblastic leukaemia (ALL) and the other had non-Hodgkin's lymphoma. All three had severe neutropenia, with absolute neutrophil counts (ANCs) of 150, 20, and 180 per μL. Two patients had multiple parasitic co-infections: one with all three tested parasites and the other with *G. lamblia* and *Cryptosporidium* (Table 2). One of these children had severe dehydration.

Second study

During a 12-mo period from March 2016 to February 2017, a total of 70 diarrhoeal episodes were experienced by 66 patients. The demographic characteristics of children included in the study and the pathogens detected are outlined in Table 1. Of note, about 60% of children with diarrhoea included in the study were aged < 60 mo and the majority of pathogens detected were parasites.

Two out of three children with *Cryptosporidium* infection were male, aged 2.5 and 4 years, and the other was female, aged 5 years. One had rhabdomyosarcoma, another had a primitive neuroectodermal tumour, and the third patient had ALL. Two had severe neutropenia with ANCs of 20 and 40, and the other had ANC of 790 per μL (Table 2).

DISCUSSION

These two pilot studies show that parasites, notably *G. lamblia*, are responsible for a large proportion of diarrhoeal aetiologies among children with malignancy in Bangladesh. A greater number of potential pathogens were detected with PCR compared to ELISA and conventional microbiological methods, as demonstrated in other studies[11]; however, the latter is still found to be useful.

Apart from an exceptionally high detection rate of giardiasis in the first study, the epidemiological profile of parasites was similar to that found among otherwise healthy Bangladeshi children with diarrhoea[7]. *G. lamblia* was detected at a significantly higher rate than among otherwise healthy Bangladeshi children 15.2%[6], and in children with cancer in other countries with a similar socioeconomic profile such as Mexico (28.7%)[12]. These differences may be attributed to both the study population (children with malignancy *vs* otherwise healthy children) as well as study methodologies (use of PCR in the current study, compared to conventional microscopic detection in the Mexican study). This could also be because of selection bias, as some children with diarrhoea or episodes of diarrhoea may have been missed.

Interestingly, the *Cryptosporidium* burden reported in these pilot studies (4%-5%) is similar to what has been reported in children with cancer in neighbouring countries; *e.g.*, 3.8% in Iran, 4% in Turkey, 2% in Malaysia, 1.3% in India, and 9.6% in Egypt[4,13-16].

Table 1 Patient demographics and laboratory results of hospitalised paediatric oncology patients with diarrhoea at Bangabandhu Sheikh Mujib Medical University hospital, *n* (%)

Particulars	Study 1[1]	Study 2[2]
Male:Female	32:19	47:19
Age in mo, range (mean)	13-180 (70.8)	11-216 (73.2)
Age group		
≤ 60 mo	32 (55.2)	41 (58.6)
61-120 mo	16 (27.6)	15 (21.4)
> 120 mo	10 (17.2)	14 (20)
Diagnosis		
ALL	37 (63.8)	40 (57.1)
NHL	17 (29.4)	10 (14.3)
AML	4 (7.9)	7 (10)
Others		1 (1.4)
Solid tumours		12 (17.1)
Phase of treatment		
Induction	37 (63.8)	43 (61.4)
Consolidation	14 (24.1)	10 (14.3)
Maintenance	6 (10.3)	12 (17.1)
Not applicable	1 (1.7)	5 (7.1)
ANC category		
< 500/mm^3	47 (81)	42 (60)
≥ 500/mm^3	11 (19)	28 (40)
Number of bowel motions/d		
≥ 10	29 (50)	10 (14.2)
6-9	19 (32.8)	40 (57.1)
≤ 5	10 (17.2)	20 (28.6)
Pathogens detected in stool samples		
Giardia lamblia	37 (68.5)[2]	1 (1.4)
Entamoeba histolytica	7 (13)[2]	7 (10)
Cryptosporidium	3 (5.6)[2]	3 (4.3)
Clostridium difficile	13 (22.4)	2 (5.1)[2]
Campylobacter jejuni	2 (3.4)	1 (1.4)
Salmonella spp	1 (1.7)	1 (1.4)
Shigella sonnei	0 (0)	1 (1.4)
Vibrio cholerae	0 (0)	1 (1.4)

[1]Each episode of diarrhoea was included as a separate event counting towards the denominator used for each characteristic, with the exception of gender (where each child was counted only once irrespective of the number of episodes of diarrheal experienced);
[2]In the first study, only 54 of the total 58 samples were processed by polymerase chain reaction for parasites, and in the second study *Clostridium difficile* was investigated in only 39 randomly selected samples out of the total 70 samples, of which 2 were positive, none were toxin-positive. ALL: Acute lymphoblastic leukaemia; AML: Acute myeloblastic leukaemia; ANC: Absolute neutrophil count per μL; NHL: Non-Hodgkin's lymphoma.

The slight variation in these rates is likely because of disparities in testing practice, diagnostic methods used, age groups included, and study designs[1,11]. Conversely, an Australian study that investigated 149 stool samples from 60 paediatric oncology patients with diarrhoea found none to be positive for *Cryptosporidium*. Contamination of drinking water may be the source of many *Cryptosporidium* infections in Bangladesh, whereas in Australia exposure to contaminated recreational water (*e.g.*, swimming pools) is the most common source of infection[17]. A comparative study involving Jordanian children demonstrated that compared to children without cancer, paediatric oncology patients had higher prevalence of *Cryptosporidium* infection (5.1% *vs* 14.4%, $P \leq 0.05$)[18]. These data suggest that the aetiological role of *Cryptosporidium* is dependent on cancer as an underlying co-morbidity, as well socio-economic and geographic variables among others.

In our setting, in the first dedicated pilot study, 22.4% children were found to be

Table 2 Summary of paediatric oncology patients with diarrhoea from whose stool samples *Cryptosporidium* was detected

Patients	Age in yr	Gender	Primary diagnosis	Phase of treatment	Preceding hospital stay in d[1]	Frequency of bowel motions/d	Fever	Mucositis	Stool micros-copy	ANC
Study 1										
Patient 1	4.5	Male	NHL	Induction	15	16	Present	Present	11-20 pus cells per HPF	150
Patient 2	3.5	Male	ALL	Maintenance	0	6-9	Present	Absent	> 50 pus cells per HPF	20
Patient 3	6	Male	ALL	Maintenance	0	3	Present	Absent	> 10 per HPF	180
Study 2										
Patient 1	4	Male	RMS	Induction	7	> 10	Absent	Absent	Normal	790
Patient 2	5	Female	PNET	Induction	0	6-9	Present	Present	Pus cells	20
Patient 3	2.5	Male	ALL	Induction	22	6-9	Present	Absent	Normal	40

[1]Days in hospital prior to the onset of diarrhoea. ALL: Acute lymphoblastic leukaemia; ANC: Absolute neutrophil count per μL; HPF: High power field; NHL: Non-Hodgkin's lymphoma; PNET: Primitive neuroectodermal tumour; RMS: Rhabdomyosarcoma.

positive for *C. difficile* in their stool with an absence of toxin positivity based on EIA; while in the second study 5.1% (only in 39 subjects tested) were positive for *C. difficile* (none were toxin positive). In comparison, among Dutch immunocompromised children admitted to a tertiary hospital, the prevalence of *C. difficile* detected by culture and cytotoxin tissue culture assay was 27.4%, with over half toxin-positive[19]. In contrast, the prevalence of toxigenic *C. difficile* among symptomatic paediatric oncology patients was found to be 8.7% in a prospective Australian study (based on culture and EIA for toxin A and cytopathic assay for toxin B), with an additional 4% with non-toxigenic *C. difficile*[20]. Interestingly, in this study, the prevalence of toxigenic and non-toxigenic *C. difficile* was higher among asymptomatic children (19% and 6.7% respectively) indicating that toxigenic *C. difficile* may be part of children's indigenous gastrointestinal flora, particularly in young infants, as observed in other studies[20,21]. The prevalence of toxigenic *C. difficile* colonisation may also be higher in children with underlying malignancy. The colonisation rate of *C. difficile* among asymptomatic Iranian children with cancer was 25% by stool culture, 92% of which were toxicogenic based on cytopathic effect on HeLa cells[22]. Although no studies of Bangladeshi children with malignancy exist, among otherwise healthy Bangladeshi children hospitalised with diarrhoea, 1.6% were infected with *C. difficile* diagnosed by cell cytotoxin assay in 1993-1994[23].

Despite high rates of colonisation, with even toxigenic strains of *C. difficile* among asymptomatic children with malignancy, it is important to have an accurate estimate of the prevalence in our population since it has been shown that colonisation with a toxigenic strain is predictive of subsequent *C. difficile* infection[24]. Further studies using PCR to detect presence of *C. difficile* toxins would be useful given the limited sensitivity of EIAs used in the current studies.

There were several limitations to these studies. First, the sample sizes were small, the study methodologies were different across the two studies, diagnostic tools used were not uniform, the age groups differed, and in the second study *C. difficile* was tested in only a small subset of patients; hence the findings are not generalisable. However, despite these shortfalls, these two are the first ever studies in Bangladeshi children with cancer to provide data on the infectious aetiologies of diarrhoea in this population and inspire further research. In conclusion, this study confirms that parasites constitute a significant burden in Bangladeshi children with malignancy who present with diarrhoea. While molecular diagnostic tools detect an array of stool pathogens with greater sensitivity, conventional laboratory diagnostic methods are also useful.

ARTICLE HIGHLIGHTS

Research background

Diarrhoea is a frequently occurring symptom among children with cancer. In a large proportion of cases, the aetiology of diarrhoea remains unknown but often multiple pathogens are

attributed.

Research motivation
There is little or no information about pathogens responsible for diarrhoea among children with cancer in Bangladesh, a country where diarrhoeal diseases are endemic.

Research objectives
To describe pathogens causing diarrhoea in Bangladeshi children with cancer.

Research methods
Two cross-sectional pilot studies were carried out involving hospitalised paediatric oncology patients with diarrhoea. Stool samples were tested by conventional microscopy and culture techniques and by polymerase chain reaction for parasites and bacteria, as well as immunoassays for *Clostridium difficile*, and enzyme-linked immunosorbent assay for *Cryptosporidium* antigen.

Research results
In the first study *Giardia lamblia* was detected in around 69% of samples, *Entamoeba histolytica* in 13%, *Cryptosporidium* in 6%, non-toxigenic *C. difficile* in 22% and other bacteria in 5%. In the second study, *Entamoeba histolytica* was detected in 10% of samples, *Cryptosporidium* in 4%, *G. lamblia* in 1%, non-toxigenic *C. difficile* in 5% and other bacteria in 6% of samples.

Research conclusions
These pilot data suggest that parasites are important aetiologies of diarrhoea among Bangladeshi children with malignancy.

Research perspectives
In a resource poor setting such as Bangladesh, while molecular diagnostic tools allow detection of an array of stool pathogens with greater frequency, conventional laboratory diagnostic methods are still useful.

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