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Clinical risk factors, bacterial aetiology, and outcome of urinary tract infection in children hospitalized with diarrhoea in Bangladesh

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SUMMARY

Urinary tract infection (UTI) is common in children aged <5 years with diarrhoea, but little is known about risk factors, aetiology and outcome of such children. We aimed to evaluate these knowledge gaps of UTI in children aged <5 years with diarrhoea. We enrolled all children aged <5 years with diarrhoea admitted to Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh, between May 2011 and April 2013, who had history of fever ($\geqslant$38 °C) and obtained a urine sample for culture. Diarrhoea with UTI (confirmed by culture) constituted cases ($n = 26$) and those without UTI constituted controls ($n = 78$). Threefold controls were randomly selected. The case-fatality rate was comparable in cases and controls (4% *vs.* 1%, $P = 0{\cdot}439$). *Escherichia coli* (69%) and *Klebsiella* (15%) were the most commonly isolated pathogens. Persistent diarrhoea, pneumonia and prior antibiotics use were identified as risk factors for UTI in logistic regression analysis ($P < 0{\cdot}05$ for all). Thus, children with diarrhoea presenting with persistent diarrhoea, pneumonia, and prior antibiotic use should be investigated for UTI for their prompt management that may reduce morbidity.

Key words: Antibiotic use prior to admission, urinary tract infection, persistent diarrhoea, pneumonia.

INTRODUCTION

Urinary tract infection (UTI) is one of the most common serious bacterial illnesses in children, especially in infants and young children [1] and is often associated with high morbidity and mortality [2]. The reported incidence of UTI is 7% in girls and 2% in boys during the first 6 years of life [3]. Studies conducted in the UK [4], Sweden [5], Finland [6], and The Netherlands [7] reported incidence rates ranging from 0·17 to 18/1000 person-years for boys and from 0·4 to 66/1000 person-years for girls. Due to overt clinical features, diagnosis of UTI is often delayed, which increases the risk of renal damage-related morbidity [8]. Although non-specific symptoms including vomiting, poor feeding, and diarrhoea have been postulated as signs of UTI in young children, this association has not been verified [9]. In recent studies conducted in Kingdom of Saudi Arabia and Western Iran, *Escherichia coli* (44·5%), *Klebsiella* spp. (18·6%), *Enterobacter* spp. (15%) and *Staphylococcus* spp.

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(12·7%) have been identified as the most common pathogens for UTI [10, 11]. Of these pathogens *E. coli* is the most common responsible for UTI [12]. Studies from Ethiopia and Colombia suggest that antibiotic resistance of urinary tract pathogens is known to increase worldwide, especially to commonly used antimicrobials [13, 14]. The increasing antibiotic resistance trends are likely to have important clinical implications for the empirical use of antibiotics [15]. Most recent studies, particularly in developing countries like Jordan and Iran, on the antimicrobial susceptibility of bacterial pathogens causing UTI in children have shown high levels of antibiotic resistance in clinical settings [16, 17].

Dhaka Hospital of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b) has cared for a number of children with diarrhoea that also have UTI but does not have any data on the burden, risk factors, bacterial aetiology and the susceptibility to antibiotics, and outcome of UTI in these children. Our aim was to evaluate the above factors in children with diarrhoea aged <5 years presenting with UTI.

MATERIALS AND METHODS

Study design

This was a retrospective chart review that was conducted at the Dhaka Hospital of icddr,b using the electronic database of the hospital (SHEBA). We used an unmatched case-control design and enrolled all children with diarrhoea of both sexes, aged 0–59 months, who were admitted to the intensive care unit, high-dependency unit, or longer stay ward of the hospital from May 2011 to April 2013 with history of fever (⩾38 °C) and who had a urine culture been performed. Children with diarrhoea with UTI constituted cases and randomly selected children with diarrhoea without UTI constituted controls. Controls were randomly selected by computer randomization using SPSS v. 17.0 (SPSS Inc., Chicago) from a computerized data source of icddr,b. We used a 1:3 unmatched case-control ratio to increase the statistical power of our analyses.

Study site

The study was conducted at Dhaka Hospital of icddr, b. The description of this hospital has been given elsewhere [18].

Patient management

Children with diarrhoea and a UTI received levofloxacin/ciprofloxacin; associated other comorbidities, i.e. management of pneumonia, sepsis, severe cholera, dysentery, severe malnutrition, and other bacterial infections was performed following the hospital's guidelines [19, 20].

Definitions

UTI. We defined UTI in a child as the presence of significant bacteriuria [21] from a single sample of urine culture reported by the microbiology laboratory of icddr,b. Only clean-catch urine samples were collected for both cases and controls before administration of any antibiotic at hospital. Urine specimens were collected into a sterile container. Bacterial growth $<10^5$ c.f.u./ml from the collected urine sample were regarded as contaminants and disregarded [21].

Diarrhoea. Passage of ⩾3 abnormally loose or watery stools/24 h, and status of dehydration was defined by 'Dhaka Methods' of assessment of dehydration that is almost similar to the WHO method and approved by WHO [22].

Nosocomial infection (NI). If evidence of new infection was identified at least 48 h after admission, patients were categorized as NI. Evidence of new infection was categorized clinically as the development of new clinical features in hospitalized children [23, 24].

Sepsis. Presence or presumed presence of infection with hypothermia (⩽35·0 °C) or hyperthermia (⩾38·5 °C), tachycardia, tachypnoea, and abnormal white blood cell count (WBC) (>11 × 10^9/l or <4 × 10^9/l or band and neutrophil ratio ⩾0·10) [25, 26].

Pneumonia. Initial diagnosis of pneumonia was done clinically following the WHO recommended classification of pneumonia [20, 27] and confirmed with radiological evidence of consolidation or patchy opacities [28] by attending hospital physicians.

Severe acute malnutrition (SAM). SAM in a child was defined if the child had severe wasting (weight for height/length Z score <−3 of median of the WHO growth standard), or nutritional oedema.

Persistent diarrhoea (PD). PD was defined as children having acute diarrhoea lasting ⩾14 days [29].

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Procedure. In the laboratory, each collected urine specimen was plated onto blood agar medium along with a selective and differential agar such as MacConkey agar for Gram-negative organisms [30]. Urine specimens were plated, using a 0·001 ml calibrated loop. Plates were incubated at 35 °C aerobically and examined at 18–24 h, they were further incubated for another 24 h before a negative report was issued. Cultures were quantitated, and those microorganisms isolated in the range of $\geqslant 10^5$ c.f.u./ml were identified. 'Significant' bacteriuria is defined as a clean-catch, midstream specimen containing a bacterial count of $\geqslant 10^5$ c.f.u./ml. Bacterial identifications were performed with the API 20E system (Analytab Products, USA) [31]. The agar diffusion technique was used for antibiotic susceptibility testing. Five colonies of the test organisms were streaked on agar plates using a sterile inoculating wire loop. The appropriate multidisc, depending on whether the test organism plated will be Gram negative or Gram positive, was then placed firmly onto the surface of the dried plates, using sterile forceps. The plates were left at room temperature for 1 h to allow diffusion of the different antibiotics from the disk into the medium. The plates were further incubated at 37 °C for 18–24 h. Susceptibility pattern was interpreted using the zone sizes according to Clinical and Laboratory Standards Institute (CLSI) guidelines [32].

The identification of blood isolates was performed following standard microbiological laboratory procedure in the Dhaka Hospital, icddr,b [33].

Analysis

Case report forms were developed, pre-tested, and finalized for data acquisition. Characteristics analysed included socio-demographics (age, gender, height and weight, low socioeconomic status, source of drinking water, formula feeding, vaccination status), history of vomiting and pre-admission antibiotic use, duration of fever, clinical signs, infection indices including: WBC and immature polymorph (B), renal function by serum creatinine level, isolated uropathogens and their sensitivity, microscopic urine analysis, clinical diagnoses (sepsis, pneumonia, SAM, PD, NI) and outcome.

All data were entered into SPSS for Windows v. 17.0 and Epi-Info v. 6.0 (USD Inc., USA). Differences in proportions were compared by χ^2 test. In normally distributed data differences of means were compared by Student's t test and Mann–Whitney test was used for comparison of data that were not normally distributed. A probability of <0·05 was considered statistically significant. Strength of association was determined by a calculating odds ratio (OR) and 95% confidence intervals (CI). We have these statistics both in our univariate analyses and logistic regression. Initially, we performed univariate analyses of the relevant characteristics (Table 1) to identify factors that were significantly associated with UTI and finally, we performed logistic regression analysis to identify the independently associated factors of UTI in children aged <5 years with diarrhoea. In the logistic regression model UTI was the dependent variable and the characteristics that were significantly associated with UTI in the univariate model were considered as independent variables.

Ethical standards

Our research did not involve any interviews with patients or caregivers and it was solely a chart analysis. The data were anonymized before being received by us.

RESULTS

A total of 365 children were enrolled with study criteria. There were 26 cases and 78 controls. Thus, the prevalence of culture-proven UTI in diarrhoeal children who presented with history of fever was 7% (26/365). In all the bacterial isolates of UTI in our study, 18 (69%) were *E. coli,* four (15%) were *Klebsiella*, one each was *Acinetobacter, Enterococcus*, and group B streptococcus. The sensitivity of *E. coli* was 100% for meropenem, 93% amikacin, 79% ceftazidime, 57% levofloxacin, 20% ceftriaxone and cotrimoxazole, and 0% for ampicillin.

Cases more often received antibiotics prior to admission, presented with younger age, and pneumonia, and less often presented with documented fever on admission compared to controls (Table 1). In logistic regression analysis after adjusting for potential confounders such as younger age (6 months), severe acute malnutrition, and NI, cases more often had PD, pneumonia and received antibiotics prior to admission (Table 2). Death was comparable in cases and controls (Table 1). Other variables were also comparable in the groups (Table 1).

DISCUSSION

This study, although limited by small sample size, was able to describe our experience with the patients

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Table 1. *Characteristics of cases and controls admitted to Dhaka Hospital, icddr,b.*

Characteristics	Cases ($n = 26$)	Controls ($n = 78$)	OR (95% CI) (unadjusted)	P value
Male sex	13 (50)	48 (61·5)	0·63 (0·23–1·67)	0·421
Age, months (median, IQR)	6·0 (4·8–9·3)	9·0 (4·0–18·0)	–	0·041
Poor socioeconomic status	17 (65)	57 (75)	0·63 (0·22–1·83)	0·488
Source of drinking water (tube well)	2 (8)	26 (33)	0·27 (0·04–1·44)	0·117
Formula feeding	3 (12)	7 (9)	2·14 (0·28–16·34)	0·394
Vaccination	13 (50)	63 (81)	0·36 (0·08–1·74)	0·214
Documented fever on admission (⩾38 °C)	15 (58)	62 (80)	0·35 (0·12–1·01)	0·053
Vomiting	18 (69)	54 (69)	1·00 (0·35–2·92)	0·806
Dehydrating diarrhoea	19 (73)	42 (54)	2·36 (0·80–6·93)	0·135
Antibiotic use prior to admission	7 (27)	8 (10)	3·22 (0·91–11·51)	0·052
Persistent diarrhoea	10 (39)	16 (21)	2·42 (0·83–7·05)	0·067
Pneumonia	10 (39)	14 (18)	2·86 (1·00–8·50)	0·032
SAM	18 (69)	38 (49)	2·37 (0·84–6·79)	0·069
Sepsis	5 (19)	11 (14)	1·45 (0·39–5·25)	0·539
Nosocomial infection	10 (39)	21 (27)	1·70 (0·60–4·76)	0·386
White blood cell count (no./mm^3) (mean ± S.D.)	14373·1 ± 5652·9	14131·3 ± 6736·1	–	0·858
Immature polymorph (no./mm^3) (mean ± S.D.)	0·3 ± 1·2	1·3 ± 4	–	0·433
Serum creatinine level (μmol/l) (median, IQR)	26·6 (21·8–31·7)	26·6 (18·5–43·5)	–	0·962
WBC in urine microscopy, per HPF (median, IQR)	5·5 (2·0–10·5)	8·0 (4·0–20·0)	–	0·072
Outcome (died)	1 (4)	1 (1)	3·08 (0·0–117·91)	0·439

OR, odds ratio; CI, confidence interval; IQR, interquartile range; SAM, severe acute malnutrition; S.D., standard deviation; HPF, high-power field.
Values given are n (%) unless indicated otherwise.

Table 2. *Results of logistic regression in exploring the independent predictors of UTI in children aged <5 years with diarrhoea*

Characteristics	aOR	95% CI	P value
Age (6 months)	1·043	0·980–1·110	0·181
Antibiotic use prior to admission	4·208	1·216–14·556	0·023
Severe acute malnutrition	1·644	0·584–4·629	0·347
Persistent diarrhoea	3·364	1·163–9·732	0·025
Pneumonia	3·302	1·148–9·497	0·027
Nosocomial infection	1·023	0·336–3·114	0·968

aOR, Adjusted odds ratio; CI, confidence interval

admitted for treatment of diarrhoea and UTI. We are able to identify different risk factors of UTI in children aged 0–59 months with diarrhoea. The observation of this study indicates that UTI is common in hospitalized children with diarrhoea tested for UTI. Their median age was 6 months which is consistent to our earlier observation in children without diarrhoea [34–37].

As expected, *E. coli* was the most common uropathogen in our study, as reported previously in a number of studies [10, 16, 20, 34]. One of the important observations of this study is the association of UTI with PD. Most of the cases of PD are associated with non-gastrointestinal infections particularly UTI and acute respiratory tract infection (ARI). Those may be missed on clinical examination unless efforts are made to investigate these children [38, 39]. However, frequent association of PD has been observed with UTI or ARI or both [40]. Although we failed to identify any stool pathogen in PD cases, a previous study from Bangladesh revealed that the most common pathogen causing PD was *E. coli* [38]. In our study, PD developed during hospitalization and stool culture of all PD patients was performed after the

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development of PD. Initiation of antibiotics in all patients with UTI and PD might have an impact on no growth in stool culture. As these patients simultaneously presented with UTI and acute watery diarrhoea (and developed PD during hospitalization), we do not know whether diarrhoea could either be the cause or the consequence of UTI. However, a prospective study with large sample may answer this question.

Our observation that children with UTI were more likely to have received antibiotics prior to hospital admission compared to those without UTI is also consistent with other studies [41, 42]. The use of antibiotics pre-admission might have an impact for development of increased resistance bacteria [41] causing UTI or diarrhoea in our study children. However, we do not have any data that suggest the administration of antibiotics prior to hospital admission in children with diarrhoea and UTI is directly related to UTI, or that UTI is a consequence of the prior antibiotic treatment.

We observed that a higher proportion of children with diarrhoea (39%) and UTI were associated with pneumonia than those without UTI. In our study children, both UTI and pneumonia were present simultaneously during hospitalization. We can speculate that it might be due to translocation of bacteria such as *E. coli* through transcellular and paracellular pathways of vulnerable gut in diarrhoeal children, and this might occur prior to hospitalization. This finding of our study is consistent with an earlier observation [43].

UTI in febrile children has been widely studied in different parts of the world [13, 14, 21]. An 11% prevalence in febrile children aged <5 years was reported by researchers in Nigeria [21]. In our study, children with diarrhoea and UTI presented less often with documented fever compared to those without UTI as most of them received antibiotics prior to hospital admission, which is consistent with previous observations [9].

Our observation of a lack of association of low socioeconomic status, source of drinking water (tube well), formula feeding, vomiting, dehydrating diarrhoea, sepsis, NI during hospitalization with UTI in diarrhoeal patients might be due to small sample size.

Our study has some limitations, including the method of urine collection. We used clean-catch urine, rather than supra-pubic aspiration, which, especially in young children, is more likely to avoid contamination of urine with stool. Second, the retrospective design of the study potentially created a selection bias as we relied on records for enrolment criteria. Third, the same design limited the sample size and probably prevented identification of subtle differences between groups for further relevant clinical risk factors of UTI in such children. Fourth, the results could only be applicable in children with diarrhoea presenting with history of fever, but could not be generalized in all diarrhoeal children.

In conclusion, our data showed that the prevalence of UTI in children aged <5 years with diarrhoea was 7%. PD, pneumonia and history of receiving antibiotics prior to admission were independently associated with UTI in children aged <5 years with diarrhoea. Commonly isolated uropathogens found were *E. coli* and *Klebsiella* leading to UTI. Thus, identification of these simple clinical predictors of UTI may help clinicians for early diagnosis and prompt treatment with antibiotics in order to reduce morbidity in such populations.

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DECLARATION OF INTEREST

None.

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