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Clinical profile, antibiotic susceptibility pattern of bacterial isolates and factors associated with complications in culture-proven typhoid patients admitted to an urban hospital in Bangladesh

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Abstract

OBJECTIVES Typhoid fever is one of the major causes of morbidity and mortality in typhoid endemic countries like Bangladesh. However, data on the clinical and microbiological profile as well as factors associated with complications of typhoid in Bangladesh are scarce. We intended to characterise the clinical and microbiological profile of culture-proven typhoid fever and to identify factors associated with complications.

METHODOLOGY Retrospective analysis of clinical data from 431 patients with culture-confirmed typhoid fever admitted to Dhaka hospital of International Centre for Diarrhoeal Disease Research, Bangladesh, between January 2010 and December 2014. Clinical and microbiological profiles of the patients including age, sex, and duration of illness prior to hospital admission, haematological parameters and the antimicrobial resistance profile of the infecting isolate, duration of hospital stay and defervescence time were examined by logistic regression to identify the factors associated with complications.

RESULT About one of three patients were children under 5 years, and 21.5% of them were severely malnourished. During hospitalisation, 17.4% patients developed complications; mainly encephalopathy (6.7%), ileus (6.5%) and pneumonia (3.5%). Among culture-positive cases, 28.3% isolates showed multidrug resistant (MDR) and more than 90% of isolates were resistant to nalidixic acid and had intermediate sensitivity to ciprofloxacin. Five isolates were resistant to azithromycin; all isolates were sensitive to cefixime and ceftriaxone. Complication was independently associated with duration of fever before admission (adjusted odds ratio: 0.85; 95% CI: 0.074–0.97; $P < 0.05$), thrombocytopenia on admission (AOR: 2.84; 95% CI: 01.06–7.57; $P < 0.05$), duration of hospital stay (AOR: 1.34; 95% CI: 1.15–1.57; $P < 0.01$) and defervescence time (AOR: 0.83; 95% CI: 0.70–0.99; $P < 0.05$).

CONCLUSION The high prevalence of typhoid fever among under-five children and complications among hospitalised patients are matters of concern. Sensitivity of *Salmonella* Typhi to ceftriaxone and cefixime was better than to other conventional antibiotics. Shorter duration of fever and thrombocytopenia on admission can be considered as early signs of complications.

keywords typhoid fever, clinical profile of typhoid fever, antibiotic susceptibility pattern of *Salmonella* Typhi, complications of typhoid fever, factors associated with complications in typhoid fever, Dhaka, Bangladesh

Introduction

Typhoid fever is a systemic illness that mainly occurs due to Gram-negative bacteria such as *Salmonella enterica* serovar Typhi (*S.* Typhi) and less frequently with *Salmonella paratyphi* A, B and C [1]. Globally, typhoid fever is most prevalent in low resource setting regions that are overcrowded with poor access to sanitation [2, 3]. Transmission mostly takes place from human to human through consumption of food and water contaminated with *S.* Typhi [2]. In 2010, the estimated global burden of *S.* Typhi cases was approximately 27 million;

the highest morbidity occurred in the south and South-east Asia [4]. The incidence rate is high in children aged 1–15 years, and children under 5 years of age were reported as a vulnerable group in the highly endemic area [4–6]. Antibiotic use has changed the classical presentation of typhoid fever such as the gradual onset of sustained fever, chills, hepatosplenomegaly and abdominal pain [7]. Other aggravating symptoms are diarrhoea, vomiting, toxicity; complications such as encephalopathy and disseminated intravascular coagulation are infrequent but still prevalent [6, 7]. In early-onset typhoid fever (within 3 weeks of clinical manifestation), the most common complications are intestinal perforation and peritonitis, whereas in late-onset typhoid fever (after 3 weeks of clinical manifestation) encephalopathy, intestinal haemorrhage, hepatosplenomegaly are most prevalent [7, 8].

Severe typhoid fever with complications has been reported to be associated with age, sex, intermediate sensitivity to ciprofloxacin, abdominal pain, duration of illness before admission, systolic blood pressure <100 mm Hg, hypoalbuminaemia (<32 g/l) and thrombocytopenia [9–14]. Multidrug resistance was also proposed to be a factor associated with the complications of typhoid fever although there is a possibility of confounding the effect by late administration of an appropriate antibiotic [11, 12, 15].

As the introduction of chloramphenicol in treating typhoid fever, a radical reduction of case fatality was observed. However, random and indiscriminate use of this drug and acquisition of plasmid-mediated R factor hastened the emergence of resistance to chloramphenicol, amoxicillin and cotrimoxazole, resulting in multidrug resistance (MDR) of typhoid [16, 17]. Later, first- and second-generation fluoroquinolones such as nalidixic acid and ciprofloxacin were effective with increased minimum inhibitory concentration (MICs) [18]. Unfortunately, clinical failure of quinolones due to altered DNA gyrase has also been observed [18, 19]. Nowadays third-generation cephalosporins such as cefixime, ceftriaxone and macrolides including azithromycin are mostly used for the treatment of typhoid fever [1, 18–20].

Bangladesh is located in the region where typhoid fever is highly endemic [4, 18, 21]; however, there are few data on the clinical presentation and antibiotic sensitivity pattern of typhoid fever, as well as on associated risk factors of severe typhoid fever with/without complications in Bangladesh. Therefore, we intended to characterise the demographic, clinical and microbiological features, antimicrobial resistance pattern and clinical outcomes of patients admitted to an urban hospital in Bangladesh identified with *Salmonella enteric* serovar Typhi or *S. paratyphi* in blood culture.

Materials and Methods

Study setting and population

Retrospective data were retrieved from the hospital electronic medical record system of Dhaka Hospital of icddr, b located in Dhaka city, the capital of Bangladesh. This facility was established in 1962 and currently provides services free of cost to approximately 140 000 patients each year, most of whom present with diarrhoea and related diseases.

We identified patients admitted to Dhaka hospital from January 2010 to December 2014 and discharged with a clinical diagnosis of enteric fever. We further scrutinised for the cases that had *Salmonella* species isolated from blood cultures and considered these for analysis. Clinical and laboratory findings were extracted from the records for analysis. Complications were defined as typhoid with symptoms and signs of intestinal perforation and peritonitis, meningitis, encephalomyelitis, cranial or peripheral neuritis, psychosis, hepatitis, haemorrhage, myocarditis, pneumonia, disseminated intravascular coagulation and haemolytic uremic syndrome, hypoalbuminemia [22].

All patients suspected to be a case of typhoid fever on admission were admitted in the longer stay ward and severe cases were treated in the intensive care unit if required. After admission, history of illness was recorded and physical and laboratory examinations were performed. All patients with typhoid fever were treated with intravascular ceftriaxone 75 mg/kg/day, single dose once daily for 7–10 days in addition to supportive therapy. Patients were discharged after the body temperature was normal (<37.8 °C) for at least 24 hours.

Bacterial isolation and antibiotic susceptibility

The microbiologic culture of venous blood was performed in patients according to attending physicians' clinical judgement and prescription. Blood was collected directly into BacT/ALERT culture bottles and entered into the BacTAlert 3D system to detect bacteria.

Stool culture was performed for every 50th patient admitted in Dhaka hospital for surveillance and also for patients at the discretion of the attending physicians. The microbiologic culture of stool was performed by the standard method from a single fresh stool specimen collected from the patient.

Antibiotic susceptibility for a group of antibiotics was tested using Disc Diffusion Method. The detailed procedure of the method has been described elsewhere [23],

and the Clinical and Laboratory Standards Institute (CLSI) guideline was followed to interpret the susceptibility pattern [24].

Ethical considerations

This analysis used hospital record data of patients admitted to the LSU or ICU of Dhaka hospital of icddr, b. Data were retrieved anonymously and did not involve any interviews with patients or caregivers; therefore, no consent was taken. As these data have been used for improving the quality of patient care at Dhaka Hospital of icddr,b, the Ethical Review Committee (ERC) formally waived the requirement for institutional review board approval. The Director of Dhaka Hospital of icddr,b granted the permissions to access the medical records used in the study.

Case definitions

Severe sepsis	Sepsis associated with organ dysfunction, hypoperfusion or hypotension. Hypoperfusion and perfusion abnormalities may include but are not limited to lactic acidosis, oliguria or an acute alteration in mental status [41]
Fever	Axillary temperature >37.8 °C
Diarrhoea	The presence of loose or watery stool 3 times or more per day [27]
Severe dehydration in a child with diarrhea	The presence of diarrhea with any two of the following signs: lethargy, sunken eyes, very slow skin pinch and inability or poor dinking ability [28]
Suspected cases of typhoid fever	Patients with fever of at least 3 days with a positive serodiagnosis or antigen detection test but without *S.* Typhi isolation [22]; children presenting with fever and any of the following: constipation, vomiting, abdominal pain, headache, cough, transient rash, particularly if the fever had persisted for ≥7 days [22]
Confirmed cases of typhoid fever	Patients with fever of at least 3 days with laboratory-confirmed positive culture (blood, bone marrow, bowel fluid) of *S.* Typhi [22]
Severe acute malnutrition (SAM) for children under 5 years of age	Children with a weight-for-height Z score below −3 SD (based on the WHO reference) and/or the presence of bilateral pedal oedema
Leucopenia	WBC count less than the lower normal limit
Leucocytosis	WBC count higher than the upper normal limit according to age (0–1 month: 6000–36 000/cmm; 6 months to 3 years: 6000–17 500/cmm; 4 to 11 years: 5500–14 500/cmm; adult: 4000–11 000/cmm)
Hypokalemia	Serum potassium level below the reference lower value (3.5–5.3 mmol/L)
Hyponatremia	Serum sodium level below the reference lower value (135–146 mmol/L)
Hypocalcemia	Serum calcium level below the reference value (2.12–2.16 mmol/L)
Anaemia	Percentage of red blood cell on admission below the reference value adjusted for sex (males: 40–52, females: 35–47)
Thrombocytopenia	Decreased platelet count less than the lower limit of the reference value according to age (neonates: 80–400; adults: 150–450)
Thrombocytosis	Increased platelet count greater than upper limit of the reference value according to age (neonates: 80–400; adults: 150–450)

Data collection and statistical analysis

Anonymised data on clinical and laboratory findings were collected and analysed using STATA SE 13 version (College Station, TX: StataCorp LP). Demographic, clinical and microbiological features were described for the whole sample. Categorical variables were presented in proportion with 95% confidence interval, and continuous variables were presented as median and inter-quartile range (IQR). Simple logistic regression was performed to investigate the relationship between clinical and laboratory characteristics, and complications of typhoid fever. To determine the independent factors associated with complications, we entered age, sex, duration of illness prior to hospital admission, haematological parameters and the antimicrobial resistance profile of the infecting isolate, duration of hospital stay and defervescence time into the logistic regression model.

Results

During the study period (January 2010 to December 2014), a total of 702 patients were admitted to Dhaka hospital as clinically diagnosed cases of typhoid fever. Of these, 431 patients were found positive for *Salmonella* species, 395 had *S. typhi* and 36 had *S. paratyphi* A in blood or stool culture. Among 431 cases, 428 cases were found positive in blood culture. In another three cases,

no organism was found in blood culture but stool culture was positive. About one in three patients were children aged below 5 years, and 21.5% of them were severely malnourished. Median (IQR) age of the patients was 10 years (3.5, 18); 59.2% were male. On admission, the mean ± SD duration of fever and diarrhoea was 7.1 ± 3.6 days and 4.3 ± 3.2 days, respectively. The majority of the patients were admitted with diarrhoea (92.4%) and fever (91.2%); 36.7% also had a history of vomiting. About 44.3% presented with dehydration and 9.3% presented with severe dehydration (Table 1).

Laboratory findings revealed that 35.3% had leucopoenia and 8.5% had leucocytosis according to age-specific reference values. On admission, thrombocytopenia was observed in 62.5% patients while 8.5% had thrombocytosis. Hypokalemia (71.6%; 202/282), hypocalcemia (86.8%; 33/38) and hyponatremia (92.9%; 263/283) were also common at admission (Table 1]. Compared to patients with diarrhoea, significantly more patients with typhoid fever had low serum sodium and potassium (*P*-value = 0.000). However, there was no difference in calcium status in patients between the groups (*P*-value = 0.421).

Approximately 17% of patients had complications that included encephalopathy (6.7%), ileus (6.5%) and pneumonia (3.5%). Other complications were severe sepsis and hepatitis, and three patients had multiple complications (Table 2). One patient died in hospital due to severe acute malnutrition with severe pneumonia and septicemia. Median (IQR) time of defervescence defined as the time in days from the day of administration of antibiotic in the hospital to disappearance of the fever was 5 [4, 7] days. The median duration of patient's hospital stay was 7 days with an IQR of 5.0, 8.0.

The onset of diarrhoea in the majority (66%) of cases was within 4 days of fever onset (Figure 1). The results show that episodes of typhoid occur all year in Dhaka, with a slight increase in the pre-monsoon and early winter seasons. Although our study result on seasonality showed some bimodal increase post-monsoon, it may not be representative of the population-based scenario.

Table 1 Demographic, clinical and laboratory features of patients with typhoid fever (n = 431)

Sociodemographic characteristics	% (95% CI)
Male	59.2 (54.4–63.7)
Fever on admission	91.2 (88.1–93.5)
The presence of diarrhoea	92.3 (89.4–94.5)
The presence of vomiting	36.9 (32.4–41.6)
The presence of dehydration (some/severe)	44.3 (39.7–49.1)
Severe acute malnutrition among children <5 years (n = 144)	21.5 (15.5–29.1)
Age (median, IQR)	10 (3.5,18)
Temperature on admission (median, IQR)	39 (38.6,40)
Pulse rate on admission (median, IQR)	120 (108,136)
Respiratory rate on admission (median, IQR)	32 (26,40)
Systolic blood pressure (median, IQR)	100 (90,110)
Diastolic blood pressure	60 (50,70)
Duration of fever before admission (mean ± SD)	7.06 ± 3.64
Duration of diarrhoea before admission (mean ± SD)	4.28 ± 3.15
Laboratory investigations	**% (95% CI)**
Leucopenia	35.3 (30.1–40.8)
Leucocytosis	8.5 (5.8–12.2)
Raised serum creatinine	16.9 (12.7–22.3)
Hypokalemia	71.6 (66.1–76.6)
Hypocalcemia	86.8 (71.1–94.6)
Hyponatremia	92.9 (89.3–95.4)
Anaemia	81.4 (77.5–84.8)
Thrombocytosis	1.3 (0.5–3.5)
Thrombocytopenia	62.5 (56.9–67.8)
Treatment outcome	
Complications	17.4 (14.1–21.3)
Death	0.2 (0–1.7)
Hospital stay (median, IQR)	5 (7,8)
Defervescence time (median, IQR)	4 (5,7)

Antimicrobial susceptibility pattern

Among culture-positive cases (n = 431), the number of isolates resistant to ampicillin, chloramphenicol and co-trimoxazole was 96/335 (28.7%), 115/430 (26.7%) and 117/431 (27.1%), respectively, and 28.3% isolates were multidrug-resistant defined as resistant to ampicillin or amoxicillin; chloramphenicol and co-trimoxazole (Table 3). Moreover, 92.3% of isolates were resistant to nalidixic acid and had an intermediate sensitivity to

Table 2 Complications in typhoid fever (n = 431)

Type of complication	N (%)
Encephalopathy	29 (6.73)
Hepatitis	2 (0.46)
Ileus/intestinal obstruction/perforation/haemorrhage	28 (6.5)
Pneumonia	15 (3.48)
Sepsis	2 (0.46)
UTI, acute renal failure	2 (0.46)

ciprofloxacin. Seven isolates were resistant to azithromycin while all isolates were sensitive to cefixim and ceftriaxone. In 24.4% of patients, fever showed a delayed response of 7 or more days, even with 100% susceptibility to antibiotic treatment. The highest numbers of typhoid fever and MDR cases were admitted to the hospital in 2012 when the total number of hospital admissions was also high.

Factors associated with complications in typhoid fever

Logistic regression model revealed that complication in typhoid fever is significantly associated with duration of fever before admission, the presence of thrombocytopenia on admission, duration of hospital stay and defervescence time. Patients with shorter duration of fever before admission and those with thrombocytopenia on admission are more likely to develop complications (AOR: 0.85; 95% CI: 0.074–0.97; $P < 0.05$ and AOR: 2.84; 95% CI: 01.06–7.57; $P < 0.05$). Hospital stay was significantly longer in complicated patients (AOR: 1.34; 95% CI: 1.15–1.57; $P < 0.01$); however, the time to defervescence was significantly shorter (AOR: 0.83; 95% CI: 0.70–0.99; $P < 0.05$) in complicated cases especially patients with encephalopathy treated with dexamethasone in addition to antibiotics (Table 4). There was no association between age, sex, multidrug resistant isolates and disease severity (data not shown).

Discussion

Typhoid fever continues to be a major cause of morbidity and mortality worldwide, remarkably in central and south-east Asia [4, 18]. This study observed the clinical profile of typhoid fever with confirmed *Salmonella* species identified from blood or stool culture and the antibiotic susceptibility pattern of *S.* species over a period of 5 years (2010 to 2014) admitted in an urban hospital,

Table 3 Antibiotic susceptibility pattern of strains isolated from patients with *Salmonella typhi* and *Salmonella paratyphi* A

Antibiotics	*N*	Susceptibilities	% (95% CI)
Ampicillin	335	S	71.3 (66.2–76.0)
		I	0
		R	28.7 (24.0–33.8)
Amoxicillin	147	S	74.1 (66.4–80.6)
		I	0
		R	25.9 (19.4–33.6)
Chloramphenicol	430	S	73.3 (68.9–77.2)
		I	0
		R	26.7 (22.8–31.1)
Cotrimoxazole	431	S	72.9 (68.4–76.9)
		I	0
		R	27.1 (23.1–31.6)
Nalidixic acid	431	S	6.50 (4.50–9.30)
		I	0
		R	93.5 (90.7–95.5)
Ciprofloxacin	431	S	4.40 (2.80–6.80)
		I	94.4 (91.8–96.2)
		R	1.20 (0.50–2.80)
Ceftriaxone	431	S	100
		I	0
		R	0
Azithromycin	417	S	89.7 (86.4–92.3)
		I	8.60 (6.30–11.8)
		R	1.70 (0.80–3.50)
Cefixime	431	S	100
		I	0
		R	0
MDR	431	R	28.3 (24.2–32.8)

S, susceptible; I, intermediate susceptible; R, resistant; MDR, multidrug resistant (resistant to ampicillin or amoxicillin; chloramphenicol and co-trimoxazole).

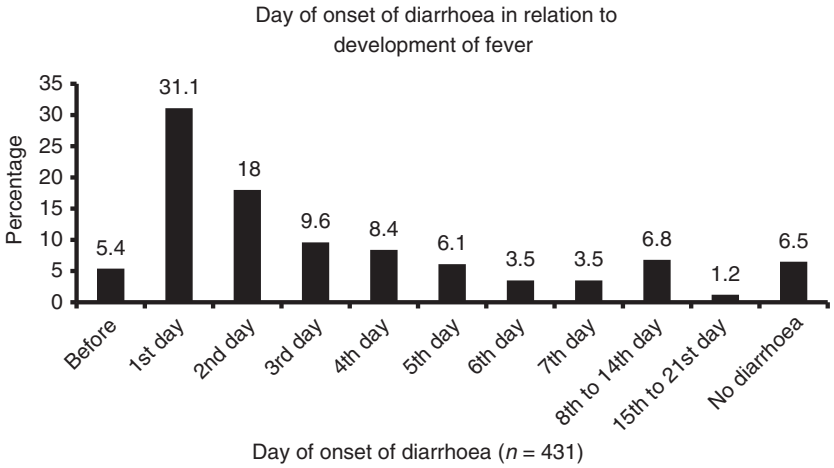

Figure 1 Day of onset of diarrhoea in relation to fever.

Dhaka, Bangladesh. We also developed a regression model to find the associating factors for complication in typhoid fever. Although an association between age and severity of disease was not observed in this study, findings from this study and other studies [5, 6, 25, 30] indicate that children under 5 years are the most common sufferers of typhoid fever. In a community surveillance study in Dhaka, under-fives were 12 times more often affected by typhoid than adults [21]. However, as this is a diarrheal disease hospital, findings from this study cannot be generalised for the population with typhoid.

Approximately one in six patients developed complications and the case fatality was 0.2%, comparable with other studies conducted in this area and neighbouring countries Pakistan, India, Nepal, Vietnam [11, 19, 29–32]. As only about 10% of the typhoid fever cases need hospitalisation in this region [21], this figure is less likely to represent the actual rate of complication in the community. The single fatal case in this study was an infant with severe malnutrition, pneumonia and septicemia – conditions which are identified risk factors of case fatality [22, 26, 28]. The high rate of complication in typhoid fever implies a need for early diagnosis at the community level and better management of typhoid fever.

Most of the patients had the common symptoms of typhoid fever such as high fever, diarrhoea and vomiting on admission while 66% cases developed diarrhoea within 1–4 days of onset of fever, which is an atypical feature in typhoid fever [8]. In this study, duration of fever before admission was independently associated with the complication. Multivariate analysis in a case–control study in Turkey also showed a significant association between shorter duration of symptoms and enteric perforation [10], while another retrospective cohort study from South Africa did not find any association with complications and duration of symptoms before admission to hospital [33].

Laboratory findings showed that a considerable number of patients had anaemia, leucopoenia and thrombocytopenia on admission and a high proportion with electrolyte imbalance, especially hypokalemia and hyponatremia. Thrombocytopenia, a well-known predictor of severe typhoid fever, was found to be an independent factor associated with the development of complications [9, 10]. Anaemia and leucopoenia have been observed to be risk factors for intestinal perforation and other complications in previous studies; however, this was not the case in this population [33].

Multidrug resistant (MDR) typhoid fever is widespread in Asian countries with evidence of the highest rate of MDR cases in Bangladesh [31, 34]. The 28.3% rate of MDR cases we found confirms results of other studies in Dhaka and neighbouring countries [5, 18, 21, 35]. In addition to MDR, close-to-universal resistance to nalidixic acid and reduced susceptibility to ciprofloxacin is causing difficulties in typhoid management [14]. In contrast, a changing trend of MDR has been observed by Misra *et al.*, who found a complete absence of MDR in *Salmonella* Typhi isolates with intermediate susceptibility to ciprofloxacin. Although we were unable to find any association of MDR and disease severity in this current study and in previous studies, the resistance to antibiotics including among young children is narrowing antimicrobial treatment options and management of typhoid fever is becoming more difficult [8, 11, 36, 37]. Ceftriaxone and cefixime remain the effective antimicrobial treatment options for this region [38, 39] even though several recent studies in India reported a high resistance to first, second, and third-generation cephalosporins of around 44%-100%. While other studies have shown a comparatively lower resistance, our all isolates were sensitive to cefixim and ceftriaxone [42]. Azithromycin might be an alternative option in low resource settings, although resistance and reduced sensitivity to azithromycin were also observed in some isolates [43]. A Cochrane review suggested azithromycin to be a better antibiotic for the treatment of uncomplicated typhoid fever and as effective for

Table 4 Factors associated with complications in typhoid fever: results of logistic regression

Variables	OR	95% CI	*P*-value	aOR	95% CI	*P*-value
Age	0.995	(0.97–1.02)	0.733	1.01	(0.97–1.06)	0.6
Sex	1.116	(0.67–1.86)	0.674	1.56	(0.73–3.33)	0.25
Duration of fever on admission	0.831	(0.75–0.92)	$P < 0.001$	0.85	(0.74–0.97)	0.02
The presence of severe dehydration	3.378	(1.6–7.13)	0.001	1.98	(0.59–6.6)	0.27
Presence of hypokelamia	2.338	(1.18–4.64)	0.015	1.78	(0.73–4.33)	0.21
Presence of thrombocytopenia	4.554	(2.07–10.02)	$P < 0.001$	2.84	(1.06–7.57)	0.04
Duration of hospital stay in days	1.191	(1.1–1.29)	$P < 0.001$	1.34	(1.15–1.57)	$P < 0.01$
Time to defervesence in days	1.066	(0.97–1.18)	0.203	0.83	(0.7–0.99)	0.04

OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.

MDR strains [20]. A noteworthy observation was a delay in defervescence compared to the standard time of <5 days despite an adequate dose of sensitive antibiotics. The reason behind this is unclear and needs more research.

The outcome of the treatment in terms of hospital stay and defervescence time differs in complicated cases. Total hospital stay was significantly longer in patients with complications which is also evident from a previous study [13]. However, time to defervescence was significantly lower in complicated cases. This might due to the use of dexamethasone in complicated cases with encephalopathy which was common in this group. Although treatment outcome of administration of dexamethasone varied in different studies, some studies suggested a lower mortality rate among patients who received high-dose dexamethasone [37, 40, 41]. Another potential bias of this finding might be the lack of information on the use of prior antibiotics before admission in the hospital. The availability of the antibiotics without a prescription and irrational use in the community is high, which undoubtedly biases the findings in hospitalised cases.

This study has a number of limitations. We used retrospective data from hospital records where missing information could not be retrieved. This analysis was conducted among only hospitalised cases which prevented the observation of a pattern in most uncomplicated patients.

Conclusion

Our findings suggest that typhoid fever in under-five children remains a major public health problem in Dhaka. A substantial number of patients develop serious and occasionally fatal complications. We found an independent association between duration of fever before admission, thrombocytopenia on admission and complication in typhoid fever. There was no significant association observed between age, sex, MDR strain and development of complications in hospitalised typhoid cases. Hospital stay was significantly longer in patients with complications; however, time to defervescence was shorter in this group. The high rate of MDR, as well as almost universal resistance to nalidixic acid and reduced sensitivity to ciprofloxacin of the bacterial strains during this study period, limits treatment choices to third-generation cephalosporins (ceftriaxone and cefixime) and azithromycin.

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