Original Article

Comparing the Efficacy of Amoxicillin and Ceftriaxone in Clinical Management of Uncomplicated Enteric Fever in Children: A Cost-effective Approach in Bangladesh

*Md. Abdul Hye[1], Syeda Afroza[2], ARM Luthful Kabir[3], Md. Rahat Bin Habib[4], Most. Eleza Khanom[5]

Abstract:

Background: Enteric fever (EF) is a systemic and often a fatal infection caused by Salmonella enteric serotype typhi. EF poses a significant public health challenge in Bangladesh. Uncomplicated susceptibility to EF can be defined as a clinical diagnosis of typhoid or paratyphoid fever without excessive toxemia, gastrointestinal hemorrhage or perforation, shock, or neuropsychiatric complications. S. typhi, characterized by resistance to 3 (three) primary antibiotics used in typhoid treatment: chloramphenicol, ampicillin, and cotrimoxazole necessitated the search for a suitable alternative typhi susceptibility to amoxicillin, which could be a safe, cost-effective and suitable drug.

Objective: We evaluated the efficacy of amoxicillin and ceftriaxone to compare the treatment status against uncomplicated-**EF** in children thus to guide in selectivity, safety, effectiveness, readily available alternate, better therapeutic measure and potentially reduced overall treatment cost.

Methodology: In this cross-sectionally designed comparative study, we enrolled 96 children with clinically diagnosed uncomplicated-**EF** admitted at the department of Pediatrics, SSMCH. Of total 96 children, 48 were placed in the amoxicillin Group (Gp-A) and another **48** in ceftriaxone Group (Gp-B). Age, sex and socioeconomic condition of child's households/families were recorded to compare findings between A and B Group of children. Period of defervescence, hospital stay, treatment outcome, adverse effects, and cost of drugs were compared between these two Groups (A and B).

Results: Slight male preponderance was observed. Most children came from families of a low socio-economic class. A shorter defervescence period, duration of treatment and hospital stay was noted in the Ceftriaxone Group. The mean period of defervescence was 5.11 ± 1.90 days in Group A, while in the other Group it was 5.55±0.45 days - which is not statistically significant (P>0.05). In the Amoxicillin Group, the duration of treatment was 12.80 ± 1.20 days and the mean hospital stay was 12.20±1.8 days. Whereas, in the Ceftriaxone Group children received treatment for 8.70± 1.30 days on average and were inpatients for 9.13±0.87 days. Both the findings for treatment duration and hospital stay were statistically significant (p<0.05). 73% of patients receiving Amoxicillin were cured but 100% of those in Group B were cured. Treatment with Amoxicillin is significantly more cost-effective than Ceftriaxone. 63.83% and 2.13% of the isolates were resistant to Amoxicillin and Ceftriaxone respectively. No serious adverse effects were noted.

Conclusion: Ceftriaxone showed better efficacy (100% clinical sure rate) shorter defervescence period and shorter hospital stay, though no major difference was revealed. Amoxicillin remained comparable to that of ceftriaxone in treating uncomplicated EF in children yielding a high cure rate being comparable to that of ceftriaxone. Furthermore, amoxicillin appeared to be a safe choice including total treatment cost (~81% lower than that of Ceftriaxone).

Key words: Amoxicillin, Ceftriaxone, Uncomplicated Typhoid Fever, Cost-effectiveness, Bangladesh.

1. Assistant Professor, Department of Pediatrics, Rajshahi Medical College, Bangladesh.
2. Ex-Head, Department of Pediatrics, Sir Salimullah Medical College and Mitford Hospital, Bangladesh.
3. Prof., Dept. of Pediatrics, Ad-din Women's Medical College and Hospital, Bangladesh.
4. Assistant Professor, Department of Pediatrics, Syed Nazrul Islam Medical College, Kishoreganj, Bangladesh.
5. Jr. Consultant (Gynae, Unit-1), Rajshahi Medical College, Bangladesh.

Correspondence: Dr. Md. Abdul Hye, Asstt. Prof., Dept. of Pediatrics, Rajshahi Medical College (RMC), E-mail: dr_abdulhai@hotmail.com Tel/Cell: +880-1714-363809

Received Date : 10 January, 2023
Accepted Date : 15 March, 2023

Introduction

Enteric fever (**EF**) is a systemic infection, primarily caused by the bacterium *Salmonella enterica serotype Typhi,* a gram-negative bacillus.[1] It poses a significant public health challenge in the Indian subcontinent, particularly in Bangladesh[2-3] where the annual incidence rate reaches a substantial 252 cases per 100,000 people.[4] Uncomplicated-EF can be defined as a clinical diagnosis of typhoid or paratyphoid fever without overwhelming toxemia, gastro-intestinal hemorrhage or perforation, shock, or neuropsychiatric complications at the onset of treatment.

According to UK based National Health Service (NHS), the clinical features of EF range from prolonged high

fever, constipation, diarrhea and headache to severe complications, like gastrointestinal perforation, neuro-psychiatric complications and even death particularly among the vulnerable children with compromised immune systems.[5]

In 1948, the treatment landscape for typhoid fever underwent a remarkable transformation with the introduction of chloramphenicol by Theodore E. Woodward.[6] This heralded the era of modern treatment of typhoid fever, effectively transforming a once-debilitating and often fatal disease into a readily treatable one. Thus, chloramphenicol, amoxicillin, ampicillin, and cotrimoxazole emerged as the key treatment modalities for most Typhoid cases.[7] As a consequence, in 1940s, the mortality rate from EF plummeted from 26% to a mere 1%.[1] However, in 1950, Chloramphenicol-resistant *S. typhi* was reported for the first time and nearly 30 years later, the same resistance pattern was documented in Bangladesh as well.[8]

The widespread emergence of Chloramphenicol-resistant *S. typhi* and rise of multi-drug resistant (MDR) *S. typhi*, resistant to 3 three-primary antibiotics being used in typhoid treatment- *chloramphenicol, ampicillin*, and *cotrimoxazole* that posed a significant setback in the clinical management of typhoid fever (EF). So, this situation necessitated to search for a suitable alternative drug, the 3rd-generation cephalosporin (ceftriaxone). This emerged as an effective antibiotic against MDR *S. typhi.* [9-11] But, this has a big drawback: ceftriaxone is very costly and it requires parenteral administration.

Recent studies have reported a shift in the antibiotic susceptibility patterns, indicating the re-emergence of susceptibility of *S. typhi* to drugs used decades before such as chloramphenicol and amoxicillin,[12-13] where amoxicillin stands out as a safe and suitable drug and remain cost-effectiveness and suitable a drug for treating uncomplicated EF in LMICs-countries.

The promising results with amoxicillin prompted us to undertake this study to compare its efficacy against ceftriaxone in the treatment of uncomplicated EF in children. The outcome of this study may guide us in selecting a safe, effective, and readily available alternative for EF treatment, potentially reducing overall treatment costs compared to other available drugs.

Material and methods:

Study type : Cross-sectionally designed clinico-epidemiological study

Research design : Comparative study among 96 hospital admitted children with clinically diagnosed uncomplicated enteric fever-**EF**.

Study place : Department of Pediatrics, SSMCH

Study duration : 12 months (July 2013 through June 2014).

Total sample size : 96 admitted children with EF

Random distributed study Groups: 48 of total 96 randomly selected clinically diagnosed EF cases in **group-A** who received treatment with **inj. amoxicillin** and the rest **48** belonged to **group-B** who had been treated with **inj. Ceftriaxone**.

Variables studied : Age, sex and socioeconomic condition of all 96 children's households/families **Clinico-epidemiological variables**: Period of defervescence, hospital stay, treatment outcome, adverse effects, and cost of drugs were compared between these two Groups (A and B).

Data management : All double-checked data were entered into an IBM-PC using SPSS/Win.V.22.0

Data Analysis : Data of all variables (taken from filled in respective questionnaire) was analyzed using required statistical lines: Following a frequency distribution tables to yield dispersions of data to get the percentage of each variables of interest. A p-value (0.05) was taken as statistically significant, all through the analysis.

Results:

Table-I

Distribution of socio-demographic characteristics in the children (n=96)

Characteristics	Number of Patients	Percentage
Age (Years)		
2-5	46	47.92%
6-8	96	34.37%
9-12	17	17.71%
Sex		
Male	51	53.12%
Female	45	46.80%

(Male : Female = 1.13:1)

Out of the 96 cases, the majority of the patients were from the age Group of 2- 5 years (47.92%), followed by 6-8 years (34.37%). A little predominance was observed among male with female ratio of 1.13:1.

The incidence of enteric fever among the study children in relation to their monthly family income (n=96) was analyzed. More than half of patients 58 (56.25%) came from lower socio-economic households with a monthly income of less than 10,000/- BDT .

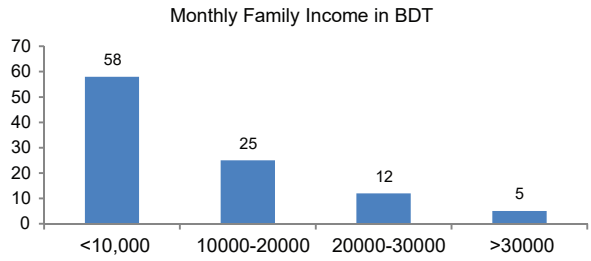

Figure-1 : *Monthly Family Income In Studied Children (n=96)*

Table-II

Distribution children with EF by physical findings (n=96)

Physical examination	Group A n (%) (n=48)	Group B n (%) (n=48)	Proportion of G-A (nA/48)	Proportion of G-B (nB/48)	p-value
Coated tongue [83 (86.5%)]	40(41.7)	43 (44.8)	0.83	0.90	0.15
Hepatomegaly [65 (67.7%)]	32(33.3)	33 (34.4)	0.67	0.69	0.41
Splenomegaly [36 (37.5%)]	17(17.7)	19 (19.8)	0.35	0.40	0.30
Toxic look [63 (65.6%)]	30(31.2)	33 (34.4)	0.63	0.69	0.26
Dehydration [17 (17.7%)]	08 (8.3)	09 (9.4)	0.17	0.19	0.39
Abd. Tenderness [74 (77.1%)]	39(40.6)	35 (36.5)	0.81	0.73	0.17
Abd. Distention [45 (46.9%)]	23 (24)	22 (22.9)	0.48	0.46	0.42
Caecal gurgling [15 (15.6%)]	09 (9.4)	05 (5.2)	0.19	0.10	0.10

On comparing all the physical examinations, like: coated tongue in 83 (86.5%), hepatomegaly in 65 (67.7%), splenomegaly in 36 (37.5%), toxic look in 63 (65.6), dehydration in 17 (17.7%), abdominal tenderness in 74 (77.1%), abdominal distention in 45 (46.9%), caecal gurgling in 15 (14.6%) among groups of A and B receiving amoxicillin and ceftriaxone respectively, but it did not differ, p-values significantly. (Table-II)[8]

Table-III

Comparison of sensitivity pattern of amoxicillin VS ceftriaxone (n=47)

	Sensitive (S) n (%)	Resistant (R) n (%)	P-value between Group A and Group B
Group A (Amoxicillin)	17 (36.2)	30 (63.8)	p<0.001
Group B (Ceftriaxone)	46 (97.9)	1 (2.1)	

The blood cultures yielded *S. typhi* spp and it's anitimicrobial sensitivity testing (AST) revealed a comparative state of both drugs (amoxicillin vs. ceftriaxone) in terms of their sensitivity 'S' and resistant 'R' pattern. While much higher percentage of 'Sensitivity' was yielded by ceftriaxone (group-B) by 98% than amoxicillin (group-A) 36%; the resistant pattern was just inversed more for amoxicillin (group-A) being more resistant to amoxicillin (64%) than that of ceftriaxone (2%), yielding a statistically valid difference in AST of *S. typhi* isolated from children with EF, (p<0.01). (Table-III)

Table-IV

Duration of treatment and clinical response to children with EF (n=96)

Clinical parameter compared (between Group-A vs. Group-B) children suffering from EF	Amoxicillin (Group- A) (Mean ± SD days)	Ceftriaxone (Group- B) (Mean ± SD days)	χ^2 test p-value
Defervescence from the day of starting antibiotics	5.55 ± 1.9	5.11 ± 0.45	0.57
Duration of treatment required	12.80 ± 1.20	8.70±1.30	<0.001
Total hospital stay	12.20 ± 1.80	9.13 ± 0.87	<0.003

P<0.05, statistically significant

Mean period of defervescence was 5.11±1.9 days for group-A children receiving amoxicillin and 5.55±0.45 days for group-B receiving ceftriaxone, which did not differ significantly (p=0.56). Contrarily, the two other clinical parameters: treatment duration and hospital stay yielded highly significant differences between the two groups: children with EF amoxicillin (group A) required 12.80±1.20 day to recover while children of ceftriaxone (group B) took 8.70±1.30 days, (p<0.01). Similarly, the mean hospital stay varied significantly: 12.20±1.80 days claimed for group-A children Inj. amoxicillin than 9.13±0.87 days for group-B (Inj. ceftriaxone) (p < 0.05). Thus, it is evident that children with EF who received ceftriaxone had a shorter treatment duration and they also had to stay in the hospital for less days, though period of defervescence between the two treatment groups (A and B) remained comparable. (Table-IV)

Table-V

Comparison in the clinical improvement (in mean days) between Group-A and Group-B suffering from EF receiving Inj. Amoxicillin vs. Inj. Ceftriaxone

Clinical Presentation	Clinical improvement in mean days of sickness		X2 test (p-value)
	Group A children of EF receiving Inj. Amoxicillin	Group B children of EF receiving Inj. Ceftriaxone	
Fever	5.19 ± 1.90	5.0 ± 0.45	0.004**
Abdominal Pain	3.15 ± 1.25	2.90 ± 0.50	0.037*
Appetite	6.30 ± 1.60	5.80 ± 1.22	0.003**
Weakness	8.30 ± 1.20	7.80 ± 1.11	0.002**
Headache	4.60 ± 1.70	3.90 ± 1.11	0.002**
Abdominal Tenderness	4.40 ± 1.20	4.06 ± 0.9	0.038*
Toxic Look	5.01 ± 1.11	4.90 ± 1.19	0.038*
Vomiting	3.10 ± 0.45	3.05 ± 0.15	0.039**
Diarrhoea	2.90 ± 1.10	2.70 ± 1.12	0.033

***Highly significant, *Moderately significant

Findings of table-V all the type of clinical improvement (in mean day) among the children suffering from EF between group-A receiving Inj. Amoxicillin and group-B receiving Inj. ceftriaxone when compared in regards to all clinical signs.

Thus all the clinical signs and symptoms, like fever, abdominal pain, appetite, weakness, headache, abdominal tenderness, toxic look, vomiting, and diarrhoea differed statistically between children of group A and group B are statistically significant (p<0.004, p<0.037, p<0.003, p<0.002, p<0.002, p<0.038, p<0.038, p<0.039, p<0.033) (Table-V).

Table-VI

Comparison of treatment outcome of studied children (n=96)

Study Group	Treatment outcome		P-Value
	Cured	Not Cured	
A (Amoxicillin) (n= 48)	35 (72.92%)	13 (27.08%)	0.03
B (Ceftriaxone) (n= 48)	48 (100%)	0 (0%)	0.14
Total	83	13	

Among the 48 cases in group A, 13 patients receiving Inj. amoxicillin did not get cured, resulting in a cure rate of 35 patients (72.92%). This difference was statistically significant ($p < 0.03$). In contrast, the Ceftriaxone group which yielded among all the children a 100% cure rate in group-B children ($p<0.14$).

Table-VII

Cost comparison between amoxicillin & ceftriaxone in treating of a patients weighing 20 kg

Drug name	Do se	Daily cost in BDT	Duration	Total cost in BDT	Proportions (total cost /8066)	p-value, z-score ***
Amoxicillin (Group A)	100 mg/ kg/ day 8 Hourly	94	14 days	1316	0.16	P<0.05
Ceftriaxone (Group B)	75 mg/ kg/ day 12 Hourly	675	10 days	6750	0.84	

As indicated in table -VII, children with EF administered with Inj. ceftriaxone group B incurred an average cost of 6,750 BDT, in contrast to Inj. amoxicillin group A spending only 1,316 BDT. Thus treatment with amoxicillin demonstrated significantly cost-effectiveness compared to that of for ceftriaxone (6750 BDT), resulting in a potential savings of approximately 5,000 BDT. Hence, treatment with amoxicillin remained 81% less costly than full treatment with ceftriaxone in children sufferinfg from complicated EF.

*** This p-value was calculated using two proportion test of unequal size using Google calculator utilizing a 1-tailed analysis. The alternative or claimed hypothesis was: Proportion of Amoxicillin≥ Proportion of Ceftriaxone. Thus, this one-tailed test was performed to prove our claim of which drug remains more effective.

Discussion:

Enteric Fever poses a significant challenge to public health in Bangladesh, often being a potentially fatal multi systemic infection. However, the 3rd generation cephalosporin (i.e. ceftriaxone) remains a costly drug with a high efficacy rate, which often evidences as potential high disease-burden in an low-middle-income country's (LMICs) like Bangladesh.[1] The wide-spread emergence of multi-drug resistant (MDR) strains has compelled us to search for an effective antibiotic.[2,3] It is spread predominantly by gram negative bacillus *Salmonella enterica serotype typhi* and less commonly Salmonella enterica serotype and para typhi A, B, and C.[1]

We evaluated and compared the efficacy of amoxicillin with ceftriaxone in the treatment of uncomplicated enteric fever (EF) among 96 admitted children at Sir Salimullah Medical College and Hospital (SSMCH). We particularly tried to determine the efficacy and cost-effectiveness between these two drugs used to match with low social economic status communities >65% of total population in Bangladesh.

Our findings yielded a little male preponderance (male to female ratio 1.13:1). Similar to that of several other studies,14 most of our children suffering from EF came out of low socio-economic strata. Half of the children's (56.25%) families had a per capita income of 10,000 BDT/month. 8,14

On clinical assessment, the common symptoms among these EF children were weakness (84.4%), followed by anorexia and/or nausea (72%) and headache and abdominal pain ranged between 61-64%, which is similarly reported by Ayamn et al from India.[13] Physical

findings in most of the children with EF showed coated tongue (86.5%), and a toxic look (65.5%)-a finding that remains consistent with that of Lakhotia M et al. from India.[15]

We observed hepatomegaly in 68% children while splenomegaly was noted in more than half of them (38%). This findings were similar to that of an Indian study[16], but it contrasted findings of Lakhotia M et al. [15] where it was 50% and 32% respectively, similar to that of Hosoglu S et al., who reported it by 42% and 20% respectively.[17]

Similar to a report from Pakistan,[18] our findings of blood culture yielded 48.9% as positive. Our finding on high yield blood culture positive cases may be due to the fact that the child having EF was brought to the hospital earlier in first week of illness and did not receive any antibiotic like amoxicillin, cotrimoxazole and chloramphenicol earlier. Blood culture of *S. typhi* isolate was sensitive to amoxicillin by 36% and ceftriaxone by 98%. The mean bacteriological R-pattern findings remain almost similar to that of another study from icddr,b, Bangaldesh,[19] and, the WHO report-2003.[20]

Based on clinical outcome the mean defervescence period was 5.55±1.9 days among group-A children receiving amoxicillin, against 5.11±0.45 days for ceftriaxone (group-B) though did not differ significantly, (p=0.57).

Efficacy of drugs was assessed, based on: i) defervescence period, ii) hospital stay and, iii) clinical cure rate, to determine the rate of "clinically cured" cases as study children started showing a positive clinical response evidenced by alleviation of clinical signs &/or symptoms. However, a study in Germany[21] contrasts our findings of mean defervescence (5.55±1.9) vs. 5.11±0.45. Their findings were 3.9±1.0 days vs 4.1±1.1 days in cases of amoxicillin and ceftriaxone, respectively.

While the duration of treatment with Inj. amoxicillin was 12.80±1.20 days, it was significantly less (8.70±1.30) days at a dose of 75 mg/kg/day for 10 days for Inj. Ceftriaxone received group B (p=0.01).

Mean duration of hospital stay of our EF children was 12.20±1.80 days who received Inj. amoxicillin (Group-A), was much less (9.13±0.87) days, who received Inj. ceftriaxone (Group-B), differing significantly, (p<0.05).

Thus, the mean period of defervescence revealed as 5.55 ± 1.90 days in group A, and 5.01±0.45 days group B yielded no statistical significant (P=0.57) difference. In the children with EF from amoxicillin group, the treatment duration was 12.80±01.20 days with a mean hospital stay of 12.20±1.8 days, in comparison to children receiving Inj. ceftriaxone (8.70± 1.3 days) on an average and, with a mean hospital stay of 9.13±0.87 days. Though findings of both the duration of treatment and hospital stay yielded a statistically significant difference (p<0.05 each), notably children receiving Inj. ceftriaxone (group-B) got faster than those receiving Inj. amoxicillin (group-A). And, children from Group-B were discharged earlier than that of Group-A.

Though the cure rate of children with EF receiving amo xicillin was good (73% cure rate), 100% children got cured who received Inj. ceftriaxone.[22] Children who did not respond to Inj. amoxicillin, even after 7 days, were then switched to receiving Inj. ceftriaxone. However, all the 96 children revealed a mean defervescence period after 5 days in both groups.

To evaluate the cost-effectiveness of these two injectable drugs in treating uncomplicated EF, we considered various factors: i) Opted for the cheapest drugs readily available in the market, ii) Per unit price of each drug was multiplied by the duration of treatment in order to account for dosing variation, iii) The mean weight of the EF children was read (~20 kg) thus, estimating the patients were cost administering Inj. ceftriaxone were projected to incur an ~cost of 6,750 BDT- while those in the Inj. Amoxicillin group it was 1,316 BDT. This evidences that treatment with Inj. amoxicillin is significantly less costly than that of with ceftriaxone. We calculated that a patient can save ~5,000 BDT. Treatment with amoxicillin is 81% less costly than treatment with ceftriaxone for complicated EF. Given that 56.25% of children with EF originated from households with family earning of <10,000 BDT/month, in the context of low- and middle-income countries (LMICs). Hence, it is reasonable that affordable treatment to treat EF children with amoxicillin will not only reduce the financial stress but also enhance treatment compliance and proper adherence among patients.

Finally, of 96 blood samples cultured from the children with EF, ~64% were resistant to amoxicillin and ~2% to ceftriaxone, respectively. With the re- emergence of sensitivity to amoxicillin against *S. typhi* and decreased

plasmid- mediated resistances, administration of Inj. amoxicillin may be effective approach of treatment as earlier data revealed.[23,24] Notably, no serious adverse drug reaction was noted in amoxicillin except slight nausea and vomiting, treating childhood EF with amoxicillin remain quite a logical and effective way to treat.

Conclusion

Though ceftriaxone showed better efficacy, shorter defervescence period and shorter hospital stay, we deduce that use of amoxicillin in treating uncomplicated children with EF may be considered as a logical option due to its high cure rate and being clinically effective when compared with ceftriaxone. Furthermore, Inj. amoxicillin appears to be a safe choice, in terms of antibiotic-related adverse effects and most notably, the cost of treatment using Inj. amoxicillin remain 81% less than that of the Inj. Ceftriaxone. This is particularly a cost-effective, safer, and, a potent antibiotic to cure children with EF, particularly in LMICs, like Bangladesh.

Limitations

1. Since this study was conducted among a relatively small sample size, we sincerely recommend further research among larger samples in multiple hospitals before refuting or accepting our findings.

2. The evaluation of cost-effectiveness should ideally include hospitalization costs, especially considering the varying hospital stay durations for the two drugs. Additionally, inpatient costs can differ based on the specific hospital where a patient is admitted. Future studies should take these factors into account to provide a more comprehensive cost analysis.

3. An essential consideration that Inj. Amoxicillin may not be suitable for children infected with EF due to probable resistance that needs to be revealed by blood culture reports.

Conflict of Interest (**COI**): None declared.

References

1. Salman, Y., Asim, H., Hashmi, N., Islam, Z., Essar, M. Y., and Haque, M. A. (2022). Typhoid in Bangladesh: Challenges, efforts, and recommendations. Annals of Medicine and Surgery (2012), 80, 104261. https://doi.org/10.1016/j.amsu.2022.104261
2. Abdool Gaffar, M. S., Seedt, Y. K., and Coovadia, Y. M. (1992). The white cell count in typhoid fever. Tropical Geographical Medicine, 44, 23-27.
3. Alam, M. N., Haq, S. A., Das, K. K., Mazed, M. N., Siddique, R. U., Hasan, Z., et al. (1992). Multidrug-resistant enteric fever in Bangladesh. Bangladesh Journal of Medicine, 3, 38-41.
4. Forster, D. P., and Leder, K. (2021). Typhoid fever in travellers: estimating the risk of acquisition by country. Journal of Travel Medicine, 28(8), taab150. https://doi.org/10.1093/jtm/taab150
5. Habib Tharwani, Z., Salman, Y., Islam, Z., Ahmad, S., Essar, M. Y., Essar, M. Y., et al. (2022). Typhoid in Pakistan: Challenges, Efforts, and Recommendations. https://doi.org/10.2147/ IDR. S365220. Published online
6. Afroza, S. (2003). Typhoid fever in children: An update (Review Article). Journal of the Bangladesh College of Physicians and Surgeons, 21, 141-148.
7. Kalra, S. P., Naithani, N., Mehta, S. R., and Swamy, A. J. (2003). Current trends in the management of typhoid fever. Medical Journal, Armed Forces India, 59(2), 130.
8. Rahman, M. N. (1995). Clinical efficiency of ciprofloxacin in the treatment of childhood typhoid fever. Bangladesh Journal of Child Health, 19(3), 76-80.
9. Kabra, S. K. (2000). Multidrug-resistant typhoid fever. Tropical Doctor, 30(4), 195–197.
10. Bhutta, Z. A., Khan, I. A., and Molla, A. M. (1994). Therapy of multidrug-resistant typhoid fever with oral cefixime vs. intravenous ceftriaxone. Pediatric Infectious Disease Journal, 13, 990-994.
11. Crump, J. A., and Mintz, E. D. (2010). Global trends in typhoid and paratyphoid fever. Clinical Infectious Diseases, 50, 241–246.
12. Antony, T. J., Palwari, A. K., Anand, V. K., and Pillai, P. K. (1994). Duodenal string test in typhoid fever. Indian Pediatrics, 30, 643-47.
13. Ayana, N., and Surekha, K. (2008). Antimicrobial susceptibility pattern and characterization of ciprofloxacin-resistant Salmonella enteric serovar Typhi isolates in Kerala, South India. Research Journal of Microbiology, 3, 654-660.
14. Malla, T., Malla, K. K., Thapalial, A., and Shaw, C. (2007). Enteric fever: a retrospective 6-year analysis

of 82 paediatric cases in a teaching hospital. Kathmandu University medical journal (KUMJ), 5(2), 181–187.

15. Lakhotia M, Gehlot RS, Jain P, Sharma S, Bhargava A. Neurological manifestations of enteric fever. J Indian Acad Clin Med. 2003 Jul;4(3):196-9.
16. Verma S, Thakur S, Kanga A, Singh G, Gupta P. Emerging Salmonella Paratyphi A enteric fever and changing trends in antimicrobial resistance pattern of salmonella in Shimla. Indian journal of medical microbiology. 2010 Jan 1;28(1):51-3.
17. Hosoglu S, Aldemir M, Akalin S, Geyik MF, Tacyildiz IH, Loeb M. Risk factors for enteric perforation in patients with typhoid fever. American journal of epidemiology. 2004 Jul 1;160(1):46-50.
18. Farooqui BJ, Khurshid M, Ashfaq MK, Khan MA. Comparative yield of Salmonella typhi from blood and bone marrow cultures in patients with fever of unknown origin. Journal of clinical pathology. 1991 Mar 1;44(3):258-9.
19. Brooks WA, Hossain A, Goswami D, Sharmeen AT, Nahar K, Alam K et al . (2005). Bacterimic Typhoid fever in children in an Urban Slum , Bangladesh. Emerging infectious Diseases ; 11
20. World Health Organization. Background document: the diagnosis, treatment and prevention of typhoid fever. World health organization; 2003.
21. Muehlen M, Frank C, Rabsch W, Fruth A, Suckau M, Moeller I, Gronemann B, Prager R, Ruf BR, Grünewald T, Ammon A. Outbreak of domestically acquired typhoid fever in Leipzig, Germany, June 2004. Eurosurveillance. 2007 Feb 1;12(2):7-8.
22. Bhutta, Z. A. (1996). Current concepts in the diagnosis and treatment of typhoid fever: Clinical review. BMJ, 333, 78-82.
23. Butler, T., Palomino, C., Johnson, R. B., and Hopkins, S. J. (1992). Efficacy of Azithromycin for the treatment of typhoid fever. In Programme and Abstracts of the thirty-second Interscience Conference on Antimicrobial Agents and Chemotherapy, Anaheim, CA. Abstract 1579, American Society for Microbiology. Washington.
24. Butler, T., and Girard, A. E. (1993). Comparative efficacies of Azithromycin and Ciprofloxacin against experimental Salmonella typhimurium infection in mice. Journal of Antimicrobial Chemotherapy, 31, 313-319