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Original Contribution

- 418 Effects of Nebulized Budesonide as an Adjunct to Standard Treatment of Asthma Exacerbations: A Randomized, Double-Blind, Placebo-Controlled Trial
Akhtaruzzaman M, Ahmed SU, Hoque MA, Choudhury AM, Hossain MA, Islam MN, Begum B, Dhar SK, Maniruzzaman M, Rashid FB, Kabir A, Hasan MM, Chowdhury B, Khan AH
- 426 Detection of Giardia lamblia and Cryptosporidium parvum by Direct Immunofluorescence Assay in Stool Specimen
Rahman MM, Hossain MA, Paul SK, Ahmed S, Islam A, Ehsan MA, Alam MM, Kabir MR, Sarkar SR
- 430 Serum Albumin and Creatinine Clearance Rate among Smear Positive Pulmonary Tuberculosis Patients in Bangladesh
Hoque MR, Chakraborty PK, Paul UK, Sarkar S, Akhter S, Shahidullah SM, Gautam B, Sultana S, Ferdous N, Samsunnahar M
- 435 Socio-Demographic Characteristics, Types and Slit Skin Smear (SSS) of the Leprosy Patients: A Hospital Based Study
Sarker UK, Mohammad QD, Uddin MJ, Chowdhury RN, Bhattacharjee M, Mondol G, Roy N
- 441 Comparison between Azithromycin and Cefixime in the Treatment of Typhoid Fever in Children
Begum B, Haque MA, Ahmed MS, Islam MN, Ahsan MM, Khan AH, Hasan MM, Akhtaruzzaman M, Hossain MA, Khaleque MA, Choudhury AM, Khatun AA
- 449 Multiplex Polymerase Chain Reaction for Detection of Campylobacter from Stool Specimen
Sarkar SR, Ray NC, Hossain MA, Paul SK, Sarkar S, Kobayashi N
- 456 Comparative Efficacy of Pregabalin and Therapeutic Ultrasound versus Therapeutic Ultrasound Alone On Patients with Post Stroke Shoulder Pain
Rahman MS, Uddin MT
- 461 Evaluation of the Outcome of Replacement Hemiarthroplasty by Uncemented Bipolar Prosthesis in Displaced Fracture Neck Femur
Rahman MG, Choudhury AI, Sakeb N, Islam KM, Karim R, Ali MY, Yiasmeen S
- 471 Transforaminal Lumbar Interbody Fusion in symptomatic Low-Grade Isthmic Spondylolisthesis
Ahsan MK, Sakeb N, Rahman MG, Zaman N, Karim R, Jannat SN
- 480 Hyperglycemia is a Predictor of Mortality and Morbidity in Low Birth Weight Newborn
Banik SK, Baki MA, Sarker S, Rahat F, Akhter S, Nahar N
- 485 Chronic Calcific Pancreatitis and Pancreatic Cancer
Billah MM, Chowdhury MM, Das BC, Shampa NN, Khan ZR
- 489 Penicillamine Challenge Test in the Diagnosis of Wilson's Disease
Mazumder MW, Karim MB, Rukunuzzaman M
- 496 Role of Crush Smear Cytology in the Diagnosis of Gastrointestinal Malignancy
Saha M, Hossain A, Bhuiyan SH, Islam MN, Chowdhury MS, Kumar SU

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Content continued on
inside front cover

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Comparison between Azithromycin and Cefixime in the Treatment of Typhoid Fever in Children

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An intervention study was carried out in the department of paediatrics of Mymensingh Medical College Hospital, Mymensingh to compare the clinical efficacy of Azithromycin in the treatment of childhood typhoid fever with that of cefixime for a period of one year from January 2011 to December 2011. A total of 60 cases of typhoid fever were enrolled in to a randomized clinical trial and was divided into two groups. The inclusion criteria of the cases were: Documented fever for more than 4 days plus two or more of the following clinical features: toxic physical appearance, intestinal complaints, coated tongue, ceacal gurgling, hepatomegaly and splenomegaly, diarrhoea and constipation plus positive Widal test and/or blood culture positivity. Patients who had complication like GIT heamorrhage; intestinal perforaion and/or shock were excluded from the study. Data were collected in a structured questionnaire. Azithromycin was given at a dose of 10mg/kg/day for a period of 07 days Cefixime was given at a dose of 20mg/kg/day in two divided dose for 14 days. The mean time of defervesence was 4.05+1.14 days with azithromycin and 3.41+0.95 with cefixime respectively. The minimum defervesence time was 02 days and maximum defervesence time was 07 days. Clinical cure rate was 87% in azithromycin group and 93% in cefixime group. No serious adverse effect was noted related to azithromycin and cefixime therapy except nausea, vomiting, diarrhoea and jaundice. It was found that azithromycin is almost as effective as cefixime in the treatment of typhoid fever.

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Key words: Typhoid fever, Azithromycin, Cefixime, Effectiveness

Introduction

Typhoid Fever is a global health problem and major cause of morbidity and mortality word wide¹. The disease is endemic in the Indian subcontinent including Bangladesh, South-East and Far-East Asia, the Middle East, Africa, Central and south America^{2,3}. Incidence of typhoid fever has been estimated as approximately 22 million cases with at least 200,000 deaths occurring annyally⁴. In Bangladesh, the overall incidence of typhoid fever is 390 cases per 100, 000 populations per year⁵. Peak incidence is reported to occur among the children during 5-15 years of age; however, in highly endemic region, the highest incidence of infection occurs among the children <5 years of age⁶.

Clinical presentation of typhoid fever is widely variable; atypical presentation is not uncommon. Some of the severe manifestations like disorientations, delirium, seizure and coma known as typhoid state, gastrointestinal bleeding, sub-acute intestinal obstruction, intestinal perforation, jaundice, bronchitis and hypotension pose a diagnostic problem in endemic areas⁷.

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For decades chloramphenicol has been highly effective against *S. typhi*⁸. However wide spread emergence of multi-drug resistant (MDR) *S. typhi* has necessitated the search for other therapeutic options⁹. The recent reports of multi-drug resistant (MDR) *S. typhi* from Bangladesh¹⁰ and Eastern India have introduced uncertainty on the optimal choice of antibiotics in typhoid fever. MDR *Salmonella typhi* were reported to be 89.7% in Calcutta in 1989¹¹ 40% in Pakistan in 1990¹² and 80% in China in 1989¹³. The first case from Bangladesh of *S. typhi* resistant to chloramphenicol was reported in 1982¹⁴ few years later MDR strains were reported in Bangladesh¹⁰. In ICDDR'B in 1992, 44.1% strains of *S. typhi* were found resistant to three first line drug VIZ. Ampicillin, chloramphenicol and cotrimoxazole¹⁵. Two separate intervention studies carried out at the Institute of Postgraduate Medicine and Research (IPGM & R) Dhaka in 1992-1993 reported that 39%¹⁶, 86%¹⁷ strains of *Salmonella* were resistant to multiple drugs.

In face of emergence of MDR strain highly promising results have been obtained using newer quinolones was found to be effective with high cure rate and no relapse¹⁵ but quinolones resistant strain of *S. typhi* has been reported¹⁸. Ciprofloxacin-resistant strains have already begun to emerge^{19,20} and this will further limit the therapeutic options. Ciprofloxacin is no more drugs for empirical therapy for the treatment of enteric fever in almost all countries of the world unless complete ciprofloxacin susceptibility is proved²¹.

Resistance to azithromycin and ceftriaxone is rarely reported and this is why they can be used as empirical therapy in enteric fever^{22,23}.

Ceftriaxone, the third generation cephalosporin is highly effective against *S. typhi* and has become the standard of cure for the treatment of typhoid fever in many parts of the world⁹. But the recent report of an isolates of *S. typhi* from Bangladesh high level of resistance to ceftriaxone means that untreatable typhoid becomes a reality²⁴ Because of high cost and need for parenteral administration of ceftriaxone, the antibiotic is less than ideal treatment alternative²⁵.

Cefixime, oral third generation cephalosporin has been effective in treating multi-drug resistant enteric fever in children and now clinically well practiced in Bangladesh²⁶. Few reports suggest that

oral cefixime; a third generation can be used as effectively as parenterally administered ceftriaxone in children²⁷. Cefixime is widely used in India due to its oral route of administration.

The recent availability of azalide class of antibiotics has provided another potential option for the treatment to of typhoid fever²⁵. Azithromycin is the first drug of this class, which contain a nitrogen atom in the macrolide a glycon ring²⁸. Azithromycin has an MIC of 4-16mg/L against isolates of *S. typhi*. Rapid movement of azithromycin from blood into tissue results in significantly higher azithromycin concentrations in tissue than in plasma after oral administration. Serum concentration of Azithromycin decline in a polyphasic pattern, resulting in an average half-life of 68 hours²⁹ several studies showed that the clinical and bacteriological cure rate is higher with Azithromycin as its intracellular concentration >100-fold compared with serum^{30,25}. A few studies have been done in Bangladesh to compare the efficacy of azithromycin with cefixime. So this study is designed to compare the efficacy of azithromycin with cefixime in patients suffering from typhoid fever in children.

Methods

An intervention study was carried out in the Department of Paediatrics of Mymensingh Medical College Hospital, Mymensingh to determine the efficacy of Azithromycin versus cefixime in the treatment of typhoid fever in children for a period of one year from January 2011 to December 2011. A total of 60 cases of typhoid fever were enrolled in this study and was divided into two groups. The inclusion criteria of the cases were: Documented fever for more than 4 days plus two or more of the following clinical features: toxic physical appearance, intestinal complaints, coated tongue, ceacal gurgling, hepatomegaly and splenomegaly, diarrhoea and constipation plus positive Widal test and/or blood culture positivity. Patients who had complication like GIT heamorrhage; intestinal perforation and/or shock were excluded from the study. Typhoid fever was diagnosed by clinical presentation supported by widal test positivity (*Salmonella Typhi* O agglutinin >1:160) and or blood culture positivity before initiation of antibiotic therapy samples of blood were taken for complete blood count, widal test & blood culture.

Other investigations e.g. blood for MP and urine for routine microscopic examination was done to exclude other causes. Most of the investigation was done in the department of pathology, microbiology of Mymensingh Medical College. Blood culture was done by lytic method using polyenethol sulphate available commercially As Aibact Duppon's tube and Widal test was done by slide agglutination tube method using commercial kit.

Drug intervention

Patients who had fulfilled the diagnostic criteria were enrolled in the study and sample was collected by random selection method every odd number patient was treated with azithromycin suspension, tablet or capsule (10mg/kg/day) administered once daily for 7 days and even number patient was treated with cefixime (20mg/kg/day) in two divided doses for 14 days. Azithromycin and cefixime was given in a patient orally or by nasogastric tube when needed. If patient vomited within 30 minutes after ingestion of drug, same does was given again by adding a sweetening agent (honey, sugar etc). Despite that if vomiting continues for second time drug was given by nasogastric tube.

Those who were not responded to azithromycin or cefixime after 05 days of treatment or developed intolerance to drugs patient was Hospitalized and switch over to injection ceftriaxone. Responses to treatment were classified as clinical cure or failure. Clinical cure was defined as resolution of all typhoid related symptoms or signs by the end of

seven days of therapy. Clinical failure was defined either as persistence of >1 typhoid related symptoms or signs present at study entry, or development of a typhoid related complications after seven days of treatment. Axillary temperature was recorded every 8 hourly for 7 days and was plotted in a temperature chart, especially to find out the effervescence time. All indoor patients was examined thrice daily by investigator herself. All the guardians of out door patient were educated to record the temperature 8 hourly. Temperature chart was provided to the guardians for recording the temperature.

Results

Clinical presentations, laboratory data, response to treatment were studied in 60 cases. Majority of the patients were seen in the age group of 3-<6 years. Lowest age was 1 year and highest age was 12 year. Mean age was 7.91 ± 2.62 years in Azithromycin group and 6.35 ± 2.27 years in Cefixime group (Table I). Male to female ratio was 1.2:1. A greater number of urban patients (62.07%) than the rural (37.93%) was enrolled in this study. Fever was universal and was present in 100% patients in both groups (Table II). Other symptoms were anorexia (61.67%) vomiting (41.67%), diarrhoea (31.67%), constipation (18.33%), and abdominal pain (53.33%); important clinical signs were toxic appearance (65%), Hepatomegaly (55%), Splenomegaly (45%) and Coated Tongue (41.67%).

Table I: Distribution of age of the patients

Age group in years	No. of Patients	%	Azithromycin (n=30)		Cefixime (n=30)	
			Number	%	Number	%
0-<3	06	10.00	03	10.00	03	10.00
3-<6	29	48.33	15	50.00	14	46.67
6-<9	14	23.33	07	23.33	07	23.33
9-12	11	18.33	05	16.67	06	20.00
Mean±SD	6.17±2.46		7.91±2.62		6.35±2.27	
P value					0.0044	
Level of Significance					**	

Chi-square test; ** means significant at (p<0.01)

Table II: Symptom of the patients (fever) (n=60)

Symptom	Duration	No. of patients	%
Fever	7 days	09	15.00
	>7-14 days	37	61.67
	>14-21 days	11	18.33
	>21 days	03	05.00
Mean±SD		8.52±4.15	

Table III: Baseline laboratory investigations

Lab test	No. of Patient	%	Azithromycin (n=30)		Cefixime (n=30)	
			Number	%	Number	%
Widal Test	60	100	30	100	30	100
<i>Blood</i>						
Culture	07	11.67	03	10.00	04	13.33
TC of WBC						
<4000	04	06.66	02	6.66	02	06.66
4000-7000	44	73.33	21	70.00	23	76.67
>7000						
10000	08	13.33	03	10.00	05	16.67
>10000						
13000	04	06.66	01	3.33	03	10.00
Mean±SD	9000.00±1700		8000.00±1900		7000.00±1100	
P value	-			0.0037		
Level of significance	-			**		

Chi-square test; **means significant (p<0.01)

Widal test was positive in all the cases (100%). Blood culture was positive in 07 out of 60 cases (Table III). Clinical response (defervescence) was observed 4.05±1.14 days with azithromycin and 3.41±0.95 for cefixime respectively (Table IV) adverse effects related to azithromycin and cefixime were observed in 7 and 5 patients respectively. Among the azithromycin treated patients 4 had vomiting, 2 had nausea and 1 had jaundice. On the other 3 had diarrhoea, 1 had vomiting and 1 had nausea of the cefixime group patients (Table V). Clinical cure rate was 93.33% in cefixime group and azithromycin group was 86.67% (Table VI). Four patients did not improve by 07 days treatment with azithromycin and two patients with cefixime. These cases were treated with parenteral ceftriaxone. Response was almost similar with both drugs in most of the cases. There was no difference with regards to defervescence time (p<0.01).

Table IV: Time of defervescence (n=60)

Time of defervescence	No. of patients	%	Azithromycin (n=30)		Cefixime (n=30)	
			Number	%	Number	%
1-3 days	14	23.33	7	23.33	07	23.33
>3-5 days	20	33.33	9	30.00	11	36.66
>5-7 days	12	20.00	6	20.00	06	20.00
>7 days	08	13.33	4	13.33	04	13.33
not improve	06	10.00	4	13.33	02	6.66
Mean±SD	4.25±1.22		4.05±1.14		3.41±0.95	
P value	-		0.0109			
Level of significance	-		**			

Chi-square test; ** means significant (p<0.01)

Table V: Adverse effect of drugs in patients

Symptoms	Azithromycin (n=7)		Cefixime (n=5)	
	Number	Percentage	Number	Percentage
Diarrhoea	0	00.00	3	60.00
Vomiting	4	57.14	1	20.00
Nausea	2	28.57	1	20.00
Jaundice	1	14.29	0	00.00
Mean±SD	2.12±0.52		1.55±0.09	
P value			0.5280	
Level of significance			NS	

Chi-square test; NS means not significant at (p>0.05)

Table VI: Clinical response of 2 drugs

Responses	Azithromycin (n=30)		Cefixime (n=30)	
	Number	Percentage	Number	Percentage
Clinically cure	26	0.87	28	0.93
Clinically failure	04	0.13	02	0.07
P value			0.0028	
Level of significance			**	

Chi-square test; ** means significant at (p<0.01)

Discussions

In this study an attempt was made to evaluate efficacy of azithromycin and cefixime in the treatment of typhoid fever in children. Typhoid

fever may occur at any age, but it is reported rare in infancy²⁶. In this study the highest prevalence (48.33%) was found age group of 3 to 6 years. This study results are similar to that of Islam et al. Saha

et al. and Sinha et al.^{22,31,32}. There is no significant difference in proportion between the sexes³³. This study showed male preponderance. Similar observation was also observed in a number of studies conducted at home and abroad³⁴. A greater number of urban patients (62.07%) than the rural (37.93%) were enrolled in this study.

Hematological investigations are not helpful in suggesting diagnosis of typhoid fever^{27,35}. Total leucocyte counts are generally low in relation to the fever and toxicity. In our experience leucopenia was observed only in 6.66% cases which was less than the findings of Islam et al. and Thisyakorn K^{22,36}.

The efficacy of the drugs was assessed in terms of defervescence time as well as clinical wellbeing. The time of defervescence in the majority of the cases (30%) was >3-5 days, 23.33% was 1-3 days, 20.00% was >5-7 days and 13.33% was >7 days in azithromycin group. While 36.66% was >3-5 days, 23.33% was 1-3 days, 20% was >5-7 days and 13.33% was >7 days in cefixime group. Four patients and two patients did not improve in azithromycin and cefixime group respectively which were treated later with parenteral ceftriaxone. So the minimum duration was 02 days and maximum was 07 days. The mean time of defervescence was 4.05 ± 1.14 days with azithromycin and 3.41 ± 0.95 for cefixime respectively. The time of defervescence in the majority of cases (33.33%) was >3-5 days for the both cases. The mean time of defervescence was 4.25 ± 1.22 days, which is similar to observation made by other workers^{25,37}.

No serious adverse effect was noted in both this drugs except diarrhoea, vomiting, nausea and jaundice after taking the drugs.

From this above discussion it can be said that azithromycin is more acceptable, convenient and low cost therapy for a patient suffering from Typhoid fever.

Cefixime is effective in most of the cases and clinical cure rate is 93.33% on the other hand cure rate is 86.67% with azithromycin which is almost equal to cefixime. No patient died or developed complications in this study. This result is almost similar to other workers^{25,38}. The absence of mortality & morbidity in this study may be due to early diagnosis, and prompt administration of effective drugs.

Conclusion

Diagnosis of Typhoid fever is mainly clinical. Confirmation needs isolation of organism which is not always possible every where. Both Azithromycin & Cefixime the drugs are equally effective in the treatment of childhood typhoid fever & no serious adverse effect was noted with these drugs in this study.

References

- Olsen SJ, Pruckler J, Bibb W, Thanh NTM, Trinh, TM, Minh NT et al. Evaluation of rapid diagnostic tests for typhoid fever. JCM. 2004;42:1885-9.
- Gillespie S. Salmonella infection. In: Cook Go, Zumla A. Eds. Manson's Tropical Diseases. 21st ed. London, UK: Elsevier Science, Health Science Division; 2003. p.937-47.
- Saha SK, Ruhulamin M, Hanif M, Islam M, Khan WA. Interpretation of the Widal test in the diagnosis of typhoid fever in Bangladeshi children. Ann Trop Pead. 1996;16:75-8.
- Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ. 2004;82:1-24.
- ICDDR, B 6th international conference on Typhoid fever and other Salmonellosis, Guilin, China. 2005. p.122-4.
- Brooks AW, Hossain A, Brooks AW, Hossain A, Goswami D, Sharmin AT, Nahar K, Alam K et al. Bacteremic Typhoid Fever in Children in an Urban Slum, Bangladesh. Emerging Infectious Diseases. 2005/2001;11:326-7.
- Ahsan HAMN, Rafiquddin AKM, Chowdhury MAJ, Azhar MA, Ara M, Farazi MA. Complications of Typhoid Fever encountered in Medical wards. Journal of Dhaka Medical College. 1993;2:32-3.
- Islam A, Butler T, Kabir L, Alam NH. Treatment of typhoid fever with ceftriaxone for 5 days of chloramphenicol for 14 days: a randomized clinical trial. Antimicrob Agents Chemother. 1993;37:1572-5.
- Mirza SH, Beeching NJ, Hart CA. Multi-drug resistant typhoid fever, a global problem. J Med Microbiol. 1996;44:317-9.
- Albert MD, Haider K Nahar S et al. Multi drug resistant salmonella typhi in Bangladesh. J Antimicrob Chemother. 1991;27:554.

11. Anand AC, Katana VK, Singh W et al. Epidemic multi drug resistant enteric fever in Eastern India. *Lancet*. 1990;335:357.
12. Mandal BK. Modern Treatment of typhoid fever. *Infection*. 1991;22:1-7.
13. Wang F, Gu ZJ, Zahng M et al. Treatment of typhoid fever with ofloxacin. *J Antimicrob Chemother*. 1989;23:785-93.
14. Huq MI, Samad AR. Chloramphenicol resistant *Salmonella typhi* VI phage type A isolated from patient in Bangladesh (letter). *Lancet*. 1982;1:1125.
15. Hoque SS, Alam AN, Islam MR. Recent advances in the treatment of typhoid fever; with special emphasis on multidrug resistant *salmonella typhi* in Bangladesh. *Bangladesh J Child Health*. 1992;16(1/2):15-9.
16. Alam MN, Haq SA, Majid MN et al. Multi-drug resistant typhoid fever in Bangladesh. *Bangladesh J Med*. 1992;3:36-41.
17. Islam MN, Afroza A, Hasan Z et al. Recent antibiogram Pattern and clinical profile of typhoid fever in children- a study of 36 cases. *Bangladesh J Child Health*. 1993;17(3):93-6.
18. Threlfall EJ et al. Resistance to ciprofloxacin in Pathogenic enterobacteriaceae in England and Wales. *J Clin Pathol*. 1997;50:1027-8.
19. Murdoch DA, Banatvala NA, Bone BL et al. Epidemic ciprofloxacin-resistant *Salmonella typhi* in Tajikistan. *Lancet*. 1998;351:339.
20. Rahman AKMM, Ahmad M, Begum RS, Ghosh AK, Hossain MZ. Multidrug Resistant Typhoid Fever in Children: A Review. *J Dhaka Med Coll*. 2008;17(2):121-6.
21. Rahman M. Treatment of enteric fever. *Orion Med J*. 2009;32(3):674.
22. Islam MN, Rahman ME, Rouf MA, Islam MN, Khaleque MA, Siddika M, Hossain MA. Efficacy of azithromycin in the treatment of childhood typhoid fever. *Mymensingh Med J*. 2007;16(2):149-53.
23. William W. Hay Jr Anthony R. Haywood, Myron J. Levin, Judith M. Sondheimur, *Current Paediatric Diagnosis and Treatment*. 15th ed. Lange Medical Book/ McGraw-Hill: 2001. p.541-2.
24. Shah SK, Talukder MI, Shaha SA. Highly Ceftriaxone resistant *salmonella typhi* in Bangladesh. *Pediatr infect Dis J*. 1999;18:387.
25. Frenck RW, Isabella Jr N, Sultan Y et al. Azithromycin versus ceftriaxone for the treatment of uncomplicated typhoid fever in children. *Clinical Infectious Disease*. 2000; 31:1134-8.
26. Huckstep RL. Editor. *Typhoid fever and other Salmonella infections*. Edinburg, Churchill-Livingstone Ltd; 1962. p.51-8.
27. Bhutta ZA. Impact of age and drug resistance on mortality in typhoid fever. *Arch Dis Child*. 1996;75:214-7.
28. Rowe B, Ward LR, Threlfall EJ. Multi-drug resistant *salmonella typhi*: world wide epidemic. *Clin Infect Dis*. 1997;24(Suppl 1):S106-9.
29. Parry C, Wain J, Chinh NT et al. Quinolone resistant *Salmonella Typhi* in Vietnam. *Lancet*. 1998;35:1289.
30. Butler T, Sridhar CB, Daga MK et al. Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multi-center Multi-drug Resistant Typhoid Fever in Children: A Review Rahman AKMM et al. trial in India. *J Antimicrob Chemother*. 1999;18:245-8.
31. Shaha SK, Talukder SY, Islam M, Shaha S. A highly ceftriaxone-resistat *salmonella typhi* in Bangladesh. *Pediatr. Infect Dis J*. 1999;18: 387.
32. Singh S. Symposium: Typhoid fever- Pathogenesis and Laboratory Diagnosis. *Journal, Indian Academy of Clinical Medicine*. 2001;2:17-20.
33. Mulligan TO. Typhoid fever in young children. *Br Med J*. 1971;4:665-7.
34. Akbar MS, Khan N, Shaha SK. Evaluation of chloramphenicol and cotrimoxazole in the treatment of enteric fever. *Bangladesh J of Child Health*. 1986;10:11-4.
35. Bhutta ZA, Mansurali N. Rapid serologic diagnosis of pediatric typhoid fever in an endemic area: A prospective comparative evaluation of two dot-enzyme immunoassays and the Widal test. *Am J Trop Med Hyg*. 1999;61:654-7.
36. Thisyakorn K, Tailor DN. Typhoid and paratyphoid fever in 192 hospitalized children in Thailand. *Asian J Dis Child*. 1987;141:862-5.