COMPARE THE CLINICAL EFFICACY OF AZITHROMYCIN WITH CIPROFLOXACIN IN TREATMENT OF TYPHOID FEVER IN CHILDREN

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ABSTRACT

Objective: To compare the clinical efficacy of Azithromycin with ciprofloxacin in treatment of typhoid fever in children.

Setting: The study was conducted in Paediatric department Lahore General Hospital/PGMI Lahore from 11-12-2012 to 11-02-2012

Methodology: After permission from hospital ethical committee and informed written consent taken from attendants of patients of inclusion criteria, data was collected on data collection Performa. Patients fulfilling the criteria were admitted in Paediatric department, Lahore General Hospital. Patients were divided by lottery method into two groups A and B. Group A was given ciprofloxacin 15mg/kg/dose BD orally for 7 days. Group B was given azithromycin 10mg/kg/dose OD orally for 7 days. Both groups were kept under close observation for 7 days. Monitoring of patient during stay was done by researcher. The cost of medicine was beard by hospital.

Results: In our study, 65%(n=65) in Group-A and 52%(n=52) in Group-B were between 3-8 years of age while 35%(n=35) in Group-A and 48%(n=48) in Group-B were between 9-14 years of age, mean+sd was calculated as 7.07+3.25 and 8.27+3.03 years respectively, 48%(n=48) in Group-A and 55%(n=55) in Group-B were male while 52%(n=52) in Group-A and 45%(n=45) in Group-B were females. Comparison of efficacy of oral azithromycin versus Ciprofloxacin in children with enteric fever shows that 72%(n=72) in Group-A and 85%(n=85) in Group-B were treated effectively, p value was calculated as 0.02 showing a significant difference.

Conclusion: We concluded that the clinical efficacy of Azithromycin is significantly higher when compared with ciprofloxacin in treatment of typhoid fever in children.

Keywords: Children, Typhoid fever, treatment, Azithromycin, ciprofloxacin.

INTRODUCTION

Typhoid fever is caused by Salmonella Typhi. It is a major cause of human infections all over the world.[1] Mean age of occurrence is 5-19 year all over the world, however in certain areas it is common below five years age group.[2] It is mainly transmitted by faeco-oral route. Important initial symptoms are nausea, fever, malaise anorexia, pain in abdomen, headache. Among all 5-15% get complications.[2]

There are approximately 21 million cases of typhoid fever annually with more than 210,000 deaths all over the world.[3] In 2006, WHO estimated case fatality rate between 1.5-3.8%.South Asia has 80% of the global cases and since 1996-2005, incidence of typhoid fever in south Asia is 110 cases/100,000 population. So South Asia is considered to be on the top of acquisition of typhoid fever. An estimate in 2003 indicates that there are annual 250,000 deaths due to water borne infections in Pakistan. Typhoid fever is the leading cause among these.[4]

Multidrug resistant typhoid fever (MDRTF) is defined as typhoid fever caused by Salmonella enterica serovar (a strain of Salmonella Typhi) which is resistant to the first- line recommended drugs for treatment such as ampicillin, chloramphenicol and trimethoprim-sulphamethoxazole.[5] This resistant strain spread through Indian subcontinent in 1980s and resulted in increased morbidity and mortality, especially in affected children below five years of age.[5] From this time fluoroquinolones (ciprofloxacin, ofloxacin) and nalidixic acid became the treatment of choice for typhoid fever.[6] This extensive antibiotic usage resulted in selection of single point mutation in DNA Gyrase A of S.Typhi, causing resistance to nalidixic acid and decreased susceptibility to fluoroquinolones.[7] This resistance resulted in poor clinical response with ofloxacin and ciprofloxacin (fluoroquinolones) also proved by accumulated data.[8,9] According to current WHO recommendation third generation cephalosporins (cefotaxime, ceftriaxone), macrolides (azithromycin) and fluoroquinolones(ciprofloxacin, ofloxacin) can be used in treatment of typhoid fever.[10]

Azithromycin, an azalid antibiotic has excellent clinical response in treatment of multidrug resistant

typhoid fever.[9] According to a study in clinical research unit of Oxford University Chi Minn City Vietnam, the clinical cure rate in terms of resolution of fever was 82% with only azithromycin and 64% with ofloxacin.The resistance strains are better treated with 7 days course of azithromycin.[11] A study conducted in Shoukat Khanum Hospital in May 2011 to determine the mean inhibitory concentration of salmonella typhi and paratyphi with azithromycin also suggests that azithromycin can be effectively used for treatment of typhoid fever. Salmonella

Typhi, Salmonella Paratyphi A and Salmonella Paratyphi C isolates mean inhibitory concentration(MIC) of 2-12 mg/l against azithromycin, suggesting antibiotic could be used for therapeutic purposes.[12]

A study conducted in 2009 suggests that fluoroquinolones(ciprofloxacin,ofloxacin) and azithromycin are almost equal in clinical efficacy in treatment of typhoid fever.[6]

However a study conducted in 2011 suggests that fluoroquinolones are found to be superior than other recent antibiotics(azithromycin,cephalosporins).[13]

Due to this controversy in literature and non conductance of study in last 5 years in Lahore (as resistance against antibiotics changes day by day), my aim of study is to compare the clinical efficacy of azithromycin and ciprofloxacin in local population.

MATERIALS AND METHODS

Sample size of 200 cases (100 in each group) is calculated with 80% power of test, 5% level of significance and taking expected percentages of efficacy in both groups i.e.82% in azithromycin group vs 64% in ciprofloxacin group in treatment of typhoid fever in children.[11]

Consecutive non probability sampling technique

Children of both sexes between 3-14 years of age having typhoid fever presenting within first four weeks of fever were included in the study.All children having fever other than typhoid fever or having current history of oral or intravenous antibiotics were excluded from study.After permission from hospital ethical committee and informed written consent taken from attendants of patients of inclusion criteria, data was collected on data collection Performa. Patients fulfilling the criteria were admitted in Paediatric department, Lahore General Hospital. Patients were divided by lottery method into two groups A and B. Group A was given ciprofloxacin 15mg/kg/dose BD orally for 7 days.Group B was given azithromycin 10mg/kg/dose OD orally for 7 days. Both groups were kept under close observation for 7 days. Monitoring of patient during stay was done by researcher. The cost of medicine was beard by hospital. Efficacy was labeled as per operational definition. All the data was entered on pre designed performa.Data was analysed by SPSS version 10. Quantitative variables i.e. age was presented in mean and standard deviation. Qualitative variables i.e. gender and efficacy of both treatment groups was presented in frequencies and percentages. P value less than 0.05 was considered significant. Chi square test was used to compare the frequency of efficacy in both groups. Data was stratified for gender, duration of fever, age and BMI. Post stratification chi square test was applied.

RESULTS

A total of 200 patients (100 in each group) fulfilling inclusion/exclusion criteria were enrolled to compare the clinical efficacy of Azithromycin with ciprofloxacin in treatment of typhoid fever in children.

Age distribution of the patients was done showing that 65%(n=65) in Group-A and 52%(n=52) in Group-B were between 3-8 years of age while 35%(n=35) in Group-A and 48%(n=48) in Group-B were between 9-14 years of age, mean+sd was calculated as 7.07+3.25 and 8.27+3.03 years respectively. (Table No. 1)

Patients were distributed according to gender showing that 48%(n=48) in Group-A and 55%(n=55) in Group-B were male while 52%(n=52) in Group-A and 45%(n=45) in Group-B were females. (Table No. 2)

Comparison of efficacy of oral azithromycin versus Ciprofloxacin in children with enteric fever shows that 72%(n=72) in Group-A and 85%(n=85) in Group-B were treated effectively while 28%(n=28) in Group-A and 15%(n=15) in Group-B were not treated effectively, p value was calculated as 0.02 showing a significant difference. (Table No. 3)

Table 1: Age Distribution (n=200)

Age (in years)	Group-A (n=100)		Group-B (n=100)	
	No. of patients	%	No. of patients	%
3-8	65	65	52	52
9-14	35	35	48	48
Total	100	100	100	100
Mean+sd	7.07+3.25		8.27+3.03	

Table 2: Gender Distribution (n=200)

Gender	Group-A (n=100)		Group-B (n=100)	
	No. of patients	%	No. of patients	%
Male	48	48	55	55
Female	52	52	45	45
Total	100	100	100	100

Table 3: Comparison Of Efficacy Of Oral Azithromycin Versus Ciprofloxacin In Children With Enteric Fever (n=200)

Efficacy	Group-A (n=100)		Group-B (n=100)	
	No. of patients	%	No. of patients	%
Yes	72	72	85	85
No	28	28	15	15
Total	100	100	100	100

P value: 0.02

Table 4: Stratification Of Efficacy In Both Groups With Regards To Age Age: 3-8YRS

Group	Efficacy		P value
	Yes	No	
A	44	21	0.01
B	45	7	

AGE: 9-14 years

Group	Efficacy		P value
	Yes	No	
A	28	7	0.69
B	40	8	

Table 5: Stratification Of Efficacy In Both Groups With Regards To Gender

Male

Group	Efficacy		P value
	Yes	No	
A	35	13	0.39
B	44	11	

Female

Group	Efficacy		P value
	Yes	No	
A	37	15	0.69
B	41	4	

Table 6: Stratification Of Efficacy In Both Groups With Regards To Duration Of Fever

2-5 days

Group	Efficacy		P value
	Yes	No	
A	42	18	0.02
B	48	7	

>5 days

Group	Efficacy		P value
	Yes	No	
A	30	10	0.41
B	37	8	

The Data was stratified for gender, duration of fever, age and BMI. Post stratification chi square test was applied. (Table No. 4-7)

Table 7: Stratification Of Efficacy In Both Groups With Regards To Bmi Bmi: <30

Group	Efficacy		P value
	Yes	No	
A	47	10	0.31
B	56	7	

BMI>30

Group	Efficacy		P value
	Yes	No	
A	25	18	0.05
B	29	8	

DISCUSSION

Typhoid fever, a common and sometimes fatal infection of children that causes bacteremia and inflammatory destruction of the intestine and other organs, is endemic in most countries, especially throughout Asia and Africa. Chloramphenicol has been the treatment of choice for typhoid fever for 40 years, but the widespread emergence of multidrug-resistant (MDR) Salmonella typhi (resistant to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole) has necessitated the search for other therapeutic options. In our country, the cumulative prevalence of Multiple Drug Resistant Salmonella typhi (MDRST) was recorded in 67.2%. Only 32.8% of isolated Salmonella typhi were susceptible to chloramphenicol and amoxicillin.[69] In vitro, azithromycin has an MIC range of 4 to 16 μg/ml against S. typhi, suggesting that the drug has limited utility for the treatment of typhoid fever.

Due to the controversy in literature and non-conductance of study in last 5 years in Lahore (as resistance against antibiotics changes day by day), we aimed to compare the clinical efficacy of azithromycin and ciprofloxacin in local population.

In our study, 65%(n=65) in Group-A and 52%(n=52) in Group-B were between 3-8 years of age while 35%(n=35) in Group-A and 48%(n=48) in Group-B were between 9-14 years of age, mean+sd was calculated as 7.07+3.25 and 8.27+3.03 years respectively, 48%(n=48) in Group-A and 55%(n=55) in Group-B were male while 52%(n=52) in Group-A and 45%(n=45) in Group-B were females. Comparison of efficacy of oral azithromycin versus Ciprofloxacin in children with enteric fever shows that 72%(n=72) in Group-A and 85%(n=85) in Group-B were treated

effectively, p value was calculated as 0.02 showing a significant difference.

We compared our results with a study in clinical research unit of Oxford University Chi Minn City Vietnam, the clinical cure rate in terms of resolution of fever was 82% with only azithromycin and 64% with ofloxacin.The resistance strains are better treated with 7 days course of azithromycin.[11] Another study conducted in Shoukat Khanum Hospital in May 2011 to determine the mean inhibitory concentration of salmonella typhi and paratyphi with azithromycin also suggests that azithromycin can be effectively used for treatment of typhoid fever. Salmonella.

Typhi, Salmonella Paratyphi A and Salmonella Paratyphi C isolates mean inhibitory concentration(MIC) of 2-12 mg/l against azithromycin, suggesting antibiotic could be used for therapeutic purposes.[12]

A study conducted in 2009 suggests that fluoroquinolones (ciprofloxacin, ofloxacin) and azithromycin are almost equal in clinical efficacy in treatment of typhoid fever.[6]

NA Trivedi and others[73] planned to determine the strength of evidence supporting use of azithromycin over the alternate drugs available for treatment of uncomplicated typhoid fever and recorded that azithromycin is marginally better in reducing the chance of CF with RR 0.46 (95% CI 0.25-0.82), while in comparison to ceftriaxone, it significantly reduced the chance of relapse with RR 0.1 (95% CI 0.01- 0.76). There were no serious adverse events reported in any of the trials, they concluded that azithromycin can be recommended as a second-line drug in MDR typhoid fever, however, large trials involving pediatric age group patients are recommended to arrive at a definite conclusion.

Miron et al studied the efficacy of oral azithromycin as an alternative to nalidixic acid for children with Shigella gastroenteritis.[65] All of the 61 children studied initially received nalidixic acid (55 mg/kg/day), but 25 were switched to azithromycin (10 mg/kg/day) because of persistent diarrhea. All of the azithromycin-treated patients had resolution of diarrhea within 48 hours of initiation of therapy, versus 65% of the nalidixic acid-only group.

However, in light of our results and other studies, the hypothesis of our study that “there is difference in clinical efficacy of azithromycin and ciprofloxacin in treatment of typhoid fever in children” is justified.

CONCLUSION

We concluded that the clinical efficacy of Azithromycin is significantly higher when compared with ciprofloxacin in treatment of typhoid fever in children.

REFERENCES

1. Leukinman, Nakari U, Lilmatainen A, Sitonen. Genomic diversity within phage type of salmonella enterica serotypes. Enteriditis and Typhimurium foodborne pathog Dis 2006;3:97-105.
2. Effa EE, Bukirwa. Azithromycin for treating uncomplicated Typhoid and paratyphoid fever. Cochrane database Syst Rev 2008;4:CDOO6083.
3. BhuttaZA.Current concepts in treatment of typhoid fever.Bmj 2006;(333):78-82.
4. Farooqui A, Khan A, Kazmi SU. Investigation of community outbreak of typhoid fever associated with drinking water. BMC Public Health 2009;9:476.
5. Zaki SA, Karande S. Multidrug resistant typhoid fever.J Infect Dev Ctries 2011;5(5):324-37.
6. Anita K, Julia C, Asma A, Zufiqar A.A comparison of fluoroquinolones versus other antibiotics for treating enteric fever.BMJ 2009;338:b1865.
7. Chall TT, Comphell JI, Galindo CM,Van Minh Hoang N, Diep JS,etal. Antimicrobial drug resistance of salmonella enteric serovar Typhi in Asia and molecular mechanism of reduced susceptibility to the fluoroquinolones. Antimicrob agent chemother 2007;51:4315-23.
8. Weil FX. Facing the challenge of resistant strains in typhoid fever. MedSci (Paris) 2010;26(11):969-75.
9. Capoor M, Nair D, Walia N, Routella R. Molecular analysis of high level ciprofloxacin resistance in salmonella enterica serovar typhi and paratyphi. Epidemiology and infection 2009;137(06):871-78.
10. Capoor MR, Nair. Quinolone and cephalosporin resistance in enteric fever.J Globe Infect Dis 2010;2(3):258-62
11. Parry CM,HoVA, Phuong le T, Bay PV, Lanh MN, Tungle T. A Randomized controlled comparison of ofloxacin, Azithromycin, and an Ofloxacin Azithromycin combination for treatment of multidrug resistant and nalidixic acid resistant typhoid fever. Antimicrobe Agent Chemother 2007;51(3):819-25
12. Butt F, SultanF. Invitro activity of Azithromycin in salmonella isolates from Pakistan. J Infect Dev Ctries 2011;5(5):391-5.
13. Effa E, Lassi ZS, Critchley JA, Bhutta ZA. Fluoroquinolones for treating typjoid and paratyphoid fever.Cochrane database sys review 2011;(10):CDOO4530.
14. Crump JA, Luby SP & Mintz ED. The global burden of typhoid fever. Bull World Health Organ. 2004 May;82(5):346-53.

15. Bhan MK, Bahl R & Bhatnagar S. Typhoid and paratyphoid fever. Lancet 2005;366(9487):749-62.
16. Chau TT, Campbell JI, Galindo CM, Van Minh Hoang N, Diep TS, Nga TT, Van Vinh Chau N, and Tuan PQ. Antimicrobial drug resistance of Salmonella enterica serovar Typhi in asia and molecular mechanism of reduced susceptibility to the fluoroquinolones. Antimicrob Agents Chemother. 2007 Dec;51(12):4315-23.
17. Whitaker JA, Franco-Paredes C, del Rio C & Edupuganti S. Rethinking typhoid fever vaccines: implications for travelers and people living in highly endemic areas. J Travel Med. 2009;16(1):46-52.
18. Baker S, Favorov M & Dougan G. Searching for the elusive typhoid diagnostic. BMC Infect Dis. 2010 Mar 5;10:45.
19. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ 2004;82:346-53
20. Ochiai RL, Wang X, von Seidlein L, Yang J, Bhutta ZA, Bhattacharya SK. Salmonella paratyphi A rates, Asia. Emerg Infect Dis 2005;11:1764-6.
21. Shirakawa T, Acharya B, Kinoshita S, Kumagai S, Gotoh A, Kawabata M. Decreased susceptibility to fluoroquinolones and gyrA gene mutation in the Salmonella enterica serovar Typhi and Paratyphi A isolated in Kathmandu, Nepal, in 2003. Diagn Microbiol Infect Dis 2006;54:299-303.
22. Luxemburger C, Chau MC, Mai NL. Risk factors for Typhoid fever in the Mekong Delta, southern Vietnam: a case-control study. Trans Roy Soc Trop Med Hyg 2001;95:19-23.
23. Parkhill J, Dougan G, James KD. Complete genome sequence of a multiple drug resistant Salmonella enterica serovar typhi CT18 provides insight into the evolution of host restriction and antibiotic resistance. Nature 2001;413:848-52.
24. Chiu CH, Chuang CH, Chiu S. Salmonella enterica serotype Choleraesuis infections in pediatric patients. Pediatrics. 2006;117(6):e1193-6.
25. Reller ME. Salmonella Species. Long A, Pickering, L, Prober C (Editors). Principles and Practices of Pediatric Infectious Diseases Elsevier, Inc. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone 2012;814-19.
26. Ramsden AE, Mota LJ, Münter S, Shorte SL, Holden DW. The SPI-2 type III secretion system restricts motility of Salmonella-containing vacuoles. Cell Microbiol. 2007;9(10):2517-29.
27. Gonzalez-Escobedo G, Gunn JS. Gallbladder epithelium as a niche for chronic Salmonella carriage. Infect Immun. 2013;81(8):2920-30.
28. Franco A, Gonzalez C, Levine OS. Further consideration of the clonal nature of Salmonella typhi: evaluation of molecular and clinical characteristics of strains from Indonesia and Peru. J Clin Microbiol 1992;30:2187.
29. Thong KL, Passey M, Clegg A. Molecular analysis of isolates of Salmonella typhi obtained from patients with fatal and nonfatal typhoid fever. J Clin Microbiol 1996;34:1029.
30. Blaser MJ, Newman LS. A review of human salmonellosis: I. Infective dose. Rev Infect Dis 1982;4:1096.
31. McCormick BA, Miller SI, Carnes D, Madara JL. Transepithelial signaling to neutrophils by salmonellae: a novel virulence mechanism for gastroenteritis. Infect Immun 1995;63:2302.
32. Raffatellu M, Chessa D, Wilson RP. The Vi capsular antigen of Salmonella enterica serotype Typhi reduces Toll-like receptor-dependent interleukin-8 expression in the intestinal mucosa. Infect Immun 2005;73:3367.
33. van de Vosse E, de Visser AW, Al-Attar S. Distribution of CFTR variations in an Indonesian enteric fever cohort. Clin Infect Dis 2010;50:1231.
34. Hoffman SL, Punjabi NH, Kumala S. Reduction of mortality in chloramphenicol-treated severe typhoid fever by high-dose dexamethasone. N Engl J Med 1984;310:82.
35. Rubin FA, McWhirter PD, Burr D. Rapid diagnosis of typhoid fever through identification of Salmonella typhi within 18 hours of specimen acquisition by culture of the mononuclear cell-platelet fraction of blood. J Clin Microbiol 1990;28:825.
36. Nix RN, Altschuler SE, Henson PM, Detweiler CS. Hemophagocytic macrophages harbor Salmonella enterica during persistent infection. PLoS Pathog 2007;3:e193.
37. Moalem S, Weinberg ED, Percy ME. Hemochromatosis and the enigma of misplaced iron: implications for infectious disease and survival. Biometals 2004;17:135.
38. Christie AB. Anonymous Infectious Diseases: Epidemiology and Clinical Practice. 3rd ed. Edinburgh: Churchill Livingstone;Typhoid and paratyphoid fevers. 1984;47-102.
39. Richens J, Smith T, Mylius T, Spooner V. An algorithm for the clinical differentiation of malaria and typhoid: a preliminary communication. PNG Med J 1992;35:298-302.

40. Sharma AM, Sharma OP. Pulmonary manifestations of typhoid fever. Chest 1992;101:1144-6.
41. Zafar J, Abbas S, Qayyum A, Ahmed N, Hussain S, Qazi RA. Typhoid orchitis. JPMA J Pak Med Assoc 1995;45:106-7.
42. Sitprija V, Pipantanagul V, Boonpucknavig V, Boonpucknavig S. Glomerulitis in typhoid fever. Ann Intern Med 1974;81:210-3.
43. Parry C, Hien TT, Dougan G, White NJ, Farrar J. Current concepts;typhoid fever. N Engl J Med, 2002, in press.
44. Yang HH, Gong J, Zhang J, Wang ML, Yang J. An outbreak of Salmonella Paratyphi A in a boarding school: a community-acquired enteric fever and carriage investigation. Epidemiol Infect. 2010;138(12):1765-74.
45. Bhutta ZA. Current concepts in the diagnosis and treatment of typhoid fever. BMJ 2006;333(7558):78-82.
46. Kundu R, Ganguly N, Ghosh TK, Yewale VN, Shah RC & Shah NK. IAP Task Force. IAP Task Force Report: diagnosis of enteric fever in children. Indian Pediatr. 2006;43(10):875-83.
47. Wain J & Hosoglu S. The laboratory diagnosis of enteric fever. J Infect Dev Ctries. 2008;2(6):421-5.
48. Parry CM, Hien TT, Dougan G, White NJ & Farrar JJ. Typhoid fever. N Engl J Med. 2002;347(22):1770-82.
49. World Health Organization. Background document: The diagnosis, treatment and prevention of typhoid fever. WHO/V&B/03.07.Geneva: World Health Organization, 2003.
50. Zhou L & Pollard AJ. A fast and highly sensitive blood culture PCR method for clinical detection of Salmonella enterica serovar Typhi. Ann Clin Microbiol Antimicrob. 2010;9:14.
51. Widal FM. Serodiagnostic de la fiévre typhoide a-propos d'uve modification par MMC Nicoll. Halipie. Bull Soc Med Hop Paris, 1896;13:561–6.
52. Olsen SJ, Pruckler J Bibb W, Nguyen TM, Tran MT & Nguyen TM. Evaluation of rapid diagnostic tests for typhoid fever. J Clin Microbiol. 2004;42(5):1885-9.
53. Begum Z, Hossain MA, Musa AK, Shamsuzzaman AK, Mahmud MC & Ahsan MM. Comparison between DOT EIA IgM and Widal Test as early diagnosis of typhoid fever. Mymensingh Med J. 2009;18(1):13-7.
54. Narayanappa D, Sripathi R, Jagdishkumar K & Rajani HS. Comparative study of dot enzyme immunoassay (Typhidot-M) and Widal test in the diagnosis of typhoid fever.Indian Pediatr. 2010;47(4):331-3.
55. Dutta S, Sur D, Manna B, Sen B, Deb AK, Deen JL, Wain J & Von Seidlein L. Evaluation of new-generation serologic tests for the diagnosis of typhoid fever: data from a community-base surveillance in Calcutta, India. Diagn Microbiol Infect Dis. 2006;56(4):359-65.
56. Oracz G, Feleszko W, Golicka D, Maksymiuk J, Klonowska A & Szajewska H. Rapid diagnosis of acute Salmonella gastrointestinal infection. Clin Infect Dis. 2003;36(1):112-5.
57. Ley B, Thriemer K, Ame SM, Mtove GM, von Seidlein L & Amos B. Assessment and comparative analysis of a rapid diagnostic test (Tubex®) for the diagnosis oftyphoid fever among hospitalized children in rural Tanzania. BMC Infect Dis. 2011;11:147.
58. Nandagopal B, Sankar S, Lingesan K, Appu KC, Padmini B, Sridharan G & Gopinath AK. Prevalence of Salmonella Typhi among patients with febrile illness in rural and peri-urban populations of Vellore district, as determined by nested PCR targeting the flagellin gene. Mol Diagn Ther. 2010;14(2):107-12.
59. Nakhla I, El Mohammady H, Mansour A, Klena JD, Hassan K, Sultan Y, Pastoor R, Abdoel TH & Smits H. Validation of the Dri-Dot Latex agglutination and IgM lateral flow assays for the diagnosis of typhoid fever in an Egyptian population. Diagn Microbiol Infect Dis. 2011;70(4):435-41.
60. Smith SI, Bamidele M, Fowora M, Goodluck HT, Omonigbehin EA, Akinsinde KA, Fesobi T, Pastoor R, Abdoel TH & Smits HL. Application of a point-ofcare test for the serodiagnosis of typhoid fever in Nigeria and the need for improved diagnostics. J Infect Dev Ctries. 2011;5(7):520-6.
61. American Academy of Pediatrics. Salmonella infections. In: Red Book: 2015 Report of the Committee on Infectious Diseases, 30th, Kimberlin DW, Brady MT, Jackson MA, Long SS (Eds), American Academy of Pediatrics, Elk Grove Village, IL 2015;695.
62. Zithromax® prescribing information. Pfizer Inc., January 2004.
63. Dunne MW, Khurana C, Mohs AA. Efficacy of single-dose azithromycin in treatment of acute otitis media in children after a baseline tympanocentesis. Antimicrob Agent Chemother 2003;47:2663-5.
64. Kogan R, Martinez MA, Rubilar L. Comparative randomized trial of azithromycin versus erythromycin and amoxicillin for treatment of community-acquired pneumonia in children. Pediatr Pulmonol 2003;35:91-8.

65. Miron D, Torem M, Merom R. Azithromycin as an alternative to nalidixic acid in the therapy of childhood shigellosis. Pediatr Infect Dis J 2004;23:367-8.
66. Acobs RF, Maples HD, Aranda JV. Pharmacokinetics of intravenously administered azithromycin in pediatric patients. Pediatr Infec Dis J 2005;24:34-9.
67. Imre S, Dogaru MT, Vari CE, Muntean T, Kelemen L. Validation of an HPLC method for the determination of ciprofloxacin in human plasma. J Pharm Biomed Anal 2003;33:125–30.
68. Trivedi NA, Shah PC. A meta-analysis comparing the safety and efficacy of azithromycin over the alternate drugs used for treatment of uncomplicated enteric fever. JPGM 2012;58:112-8.
69. Hazir T, Qazi SA, Abbas KA, Khan MA. Therapeutic Re-appraisal of Multiple Drug Resistant Salmonella Typhi (MDRST) in Pakistani Children. JPMA 2002;52:123.