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Original Article

Enteric Fever: A retrospective 6-year analysis of 82 paediatric cases in a teaching hospital

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Abstract

Objective: To evaluate the clinical and laboratory properties, to see the response to therapy, incidence of antimicrobial resistance and complications of Enteric Fever in children.

Methods: This is a retrospective study of 82 cases of enteric fever admitted in department of pediatrics, Manipal Teaching hospital, Pokhara, Nepal .Study period was six years from (Jan 2000 to Dec 2005).

Results: Total of 82 cases of Salmonella infections were admitted .There were 50 (60%) males and 32 (40%) females. Most of the patients were above the age of five. The leading clinical feature were Fever (100%) , GI symptoms (73%), followed by splenomegaly (60%), hepatomegaly (58%) , chills & rigor (41%), headache(33%),coated tongue(17%), lymphadenopathy (13%), Respiratory signs (13%) , toxic look (7%). The laboratory reports revealed leucopenia in 26% and leukocytosis in 16%. Widal test was positive in 83%, Blood culture was positive in 37 %.Bone marrow was done in 8 cases, out of which 5(62.5%) were culture positive. Out of 35 culture positive cases 32 were Salmonella typhi and 3 were Salmonella paratyphi A. Regarding the treatment 55% were treated with ciprofloxacin, 29 % with ceftriaxone , 7% with ampicillin , 6% with cefotaxime and 2.4 % with chloramphenicol . Response to therapy was assessed by day of defervescence after antibiotics. Best response was observed with ciprofloxacin (4.7 days) followed by ceftriaxone (5days), ampicillin (5.5 days), cefotaximee (6.4 days), chloramphenicol (10 days) respectively. In the antibiogram resistance was 43% with chloramphenicol, 37% with ampicillin, 31% with trimethoprim- sulfamethoxazole, 5.7%with ciprofloxacin and 4% with cefotaxime .Resistance was 0% with ceftriaxone, cefuroxime, and ofloxacin. Gentamycin was found to show high sensitivity (91%). The complications observed were anemia in 10%, 5% had neurologic signs like clouding of consciousness and 3.7% had CNS irritability.

Conclusion: It is important to include Enteric fever in the differential diagnosis of febrile patients with abdominal symptoms. Though blood culture is the definite test, Widal test plays supportive role in diagnosis of enteric fever, especially when patients come after a course of antibiotics. Sometimes when both blood culture and Widal tests are negative Bone marrow can be the diagnostic tool for the diagnosis. Based on this analysis ciprofloxacin is still a good drug for the treatment of Enteric Fever. Ceftriaxone, Cefuroxime and Ofloxacin can be considered as first line treatment for Enteric fever since resistance was nil with these drugs on culture reports.

Key words: Enteric fever, salmonella infections

Enteric fever is still a common health problem in many countries, especially in children. Typhoid fever is a systemic infectious disease characterized by an acute illness, the first typical manifestations of which are fever, headache, abdominal pain, relative bradycardia, splenomegaly, and leucopenia [1, 2.] Typhoid fever is an important cause of morbidity in many regions of the world, with an estimated 12 to 33 million cases occurring annually.[3] Cases are more likely to be seen in areas with rapid population growth, increased urbanization, and limited safe water, infrastructure, and health systems. With the above background, enteric fever is endemic in Pokhara thus this retrospective analysis was undertaken.

Materials and methods

Case records of children admitted with Enteric Fever during the period 1st January 2000 to 31st December 2005 were studied retrospectively with special attention to the clinical features, laboratory findings, treatment outcome, antimicrobial resistance patterns and complications.

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The inclusion criteria were the presence of clinical features compatible with enteric fever , isolation of Salmonella typhi , paratyphi A, B, or C from blood , stool cultures or any other sites, and positive Widal test either on admission or later. The children were between age 1- 15 yrs.

Results

There were total 82 cases over 6 years period : 20 cases in 2000, 23 cases in 2001, 14 cases in 2002 , 13 in 2003, 5 in 2004, and 7 in 2005 (Fig.1). There were 50 (60%) males and 32 (40%) females (Fig 2). Their mean age was 6.5 years (range 1 year to 15 years-(Fig 3).

The most common complaints were fever (82/82). The average duration of fever before diagnosis was 14.1 days (range 5-30days). Other features were GI symptoms (60/ 82), splenomegaly (49/82), hepatomegaly (48/82), chills & rigor (34/82), headache (27/82), coated tongue (14/82), lymphadenopathy (11/82), respiratory signs (11/82), toxic look (6/82) (Table1).

Coming to laboratory findings, leucopenia was present in 27% and leukocytosis in 16% of the cases. Blood culture was positive in 36.6%, negative in 46% and it was not done in 17% (Table- 2).In these 17% cases, Widal test was positive (Table -3). Widal test was positive in 83%, negative in 9.7 % and it was not done in 7% (Table 2). Bone marrow was done in 8 cases out of which 5/8 (62.5 %) were culture positive and 3/8 (37.5%) were culture negative (Fig 4).

There were 24 (29%) cases who were both blood culture and Widal test positive (Table-3). In 30 (37%) cases blood culture was negative but Widal test was positive. In 17% cases blood culture was not done as they already received antibiotics from outside. In these 17% cases Widal test was positive. In 6 cases Widal test was not done as blood culture was positive (Table 3).

Response to therapy

Empirically, injectable antibiotic was started in all cases before culture reports were available. Response to therapy was seen with the empirically used antibiotic during treatment course. Switching over to other antibiotics after culture report was not required as the empirically used antibiotic was found to be sensitive. Switching over to oral form during discharge was not considered. Out of 82 cases, 45 were treated with Ciprofloxacin (55%), 24 with Ceftriaxone (29%), 6 with Ampicillin (7%), 5 with Cefotaxime (6 %), 2 with Chloramphenicol (2.4%). Best response was observed with Ciprofloxacin with the child being afebrile in a mean of 4.7 days after therapy followed by Ceftriaxone (mean 5 days), Ampicillin (mean 5.5 days), Cefotaxime (mean 6.4 days) and Chloramphenicol (mean10 days) respectively.

The antimicrobial resistance was observed with chloramphenicol 43 %, ampicillin 37%, and cotrimoxazole 31%, gentamycin 9% ciprofloxacin 6%, cefotaxime 4% (Table 5).The complications observed were anemia in 10%, 5% had clouding of consciousness, 3.7 % had CNS irritability.

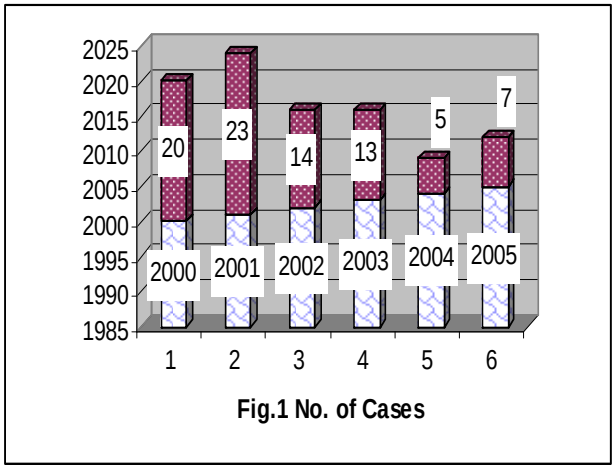

Fig 1: No. of cases

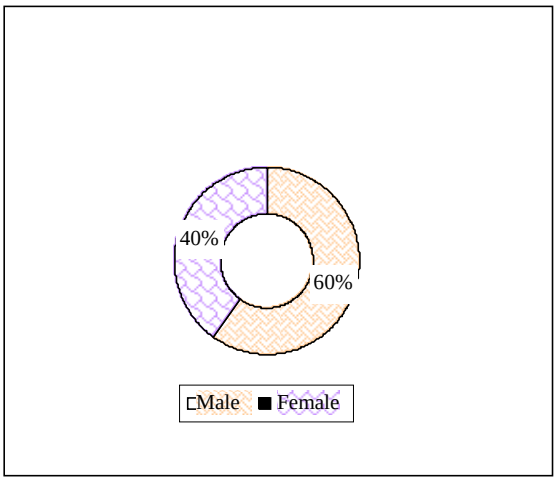

Fig 2: Distribution of sex

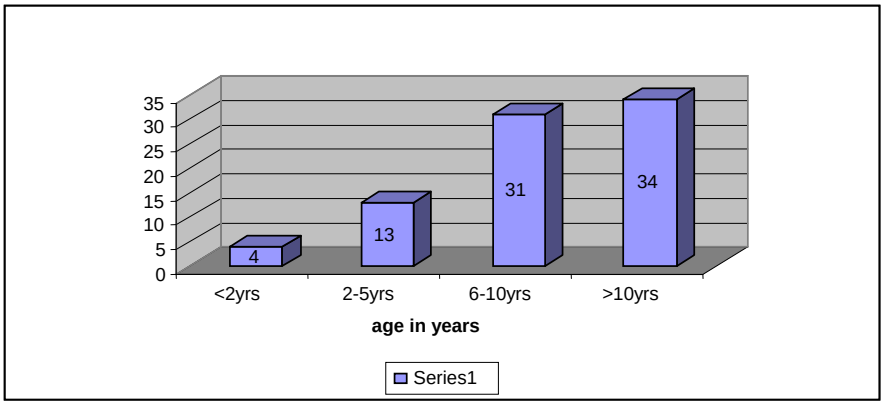

Fig 3: Age distribution of cases

Table 1: Clinical presentations

Clinical Picture	Yes		No		Total
	No	%	No	%	
Fever	82	100	0	0	82
GI symptoms	60	73	22	27	
Splenomegaly	49	60	33	40	
Hepatomegaly	48	58	34	42	
Chills/Rigor	34	41	48	59	
Headache	27	33	54	67	
Coated tongue	14	17	68	83	
Lymphadenopathy	11	13	70	87	
Resp symptoms	11	13	75	87	
Anemia	8	10	73	90	
Toxic look	6	8.5	75	91.5	
Clouding of consciousness	4	5	77	95	
CNS irritability	3	3.7	78	96.3	

Table 2: Blood culture, Widal test and Bone marrow Culture of 82 cases

N = 82	Positive		Negative		Not done	
	No.	%	No.	%	No.	%
Blood culture	30	37%	38	46%	14	17%
Widal test	68	83%	8	9.7%	6	7.3%
Bone marrow culture	5	6%	3	4%	74	90%

Table 3: Relation of Blood culture and Widal test

	Blood C/S (+) Widal test (+)	Blood C/S(–) Widal test (+)	Widal test (+) Blood C/S ND	Blood C/S(+) Widal test ND
Number (n=82)	24	30	14	6
Percentage	29%	36.6%	17%	7.3%

(+) Positive (-) Negative ND= not done

*** In 8 cases where both blood culture and Widal test was negative, bone marrow culture was done*

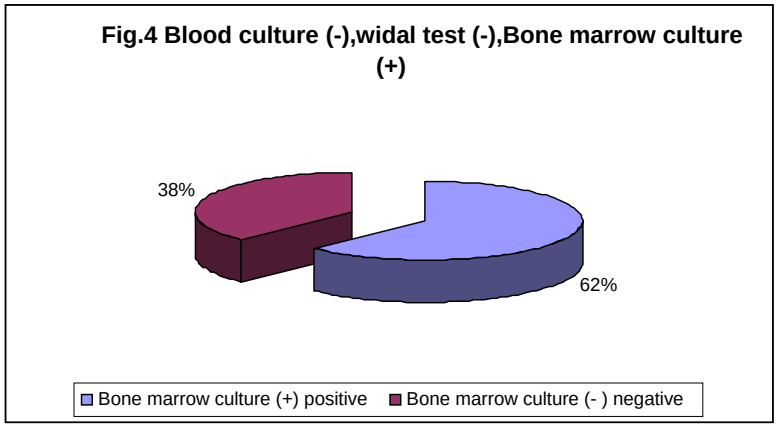

Table 4. Treatment and response to therapy

Antibiotic	Number (n=82) (%)	Afebrile day after antibiotic Mean (Range) days
Ciprofloxacin	45 55%	4.7 (1-13 days)
Ceftriaxone	24 29%	5 (2-10 days)
Cefotaxime	5 6%	6.4 (4-9 days)
Ampicillin	6 7%	5.5 (3-11 days)
Chloramphenicol	2 2.4%	10 (10 days)

Table 5: Antibiogram of culture positive (blood bone marrow) cases (n=35)

Antibiotic	Sensitivity tested	Sensitivity not tested	Sensitive No %	Inter sensit No %	Resistant No. %
Ciprofloxacin	35	0	32 91	1 3	2 6
Ampicillin	35	0	22 63	0 0	13 37
Chloramphenicol	21	14	12 57	0 0	9 43
Co-trimoxazole	29	6	20 69	0 0	9 31
Cefotaxime	25	10	24 96	0 0	1 4
Ceftriaxone	15	20	15 100	0 0	0 0
Cefuroxime	10	25	9 90	1 10	0 0
Ofloxacin	6	29	6 100	0 0	0 0
Cefazoline	3	32	3 100	0 0	0 0
Carbenecillin	2	33	2 100	0 0	0 0
Gentamycin	23	12	21 91	0 0	2 9
Amikacin	4	31	4 100	0 0	0 0
Amoxyclav	2	33	2 100	0 0	0 0

Discussion

Enteric fever remains a major cause of fever in many parts of the world including Nepal. It is an important cause of morbidity in many regions of the world, [4] with an estimated 13 million cases occurring annually in Asia alone.[4] In recent years, cases have been reported from Eastern Europe.[5] In this hospital based study there were total 82 cases over a period of 6 years. Unlike this study, incidence of enteric fever was high in other studies. According to records of the Health Ministry in Turkey, about 20,000 cases have been seen each year .[6] From July 1, 1995 to 2000, the bacteriology laboratory of a French pediatric hospital had identified 215 patients aged between 1 month and 15 years with positive blood or stools for

Salmonella sp.[7] Out of 82 children male to female ratio was 1.5:1 (Fig 2). Their mean age was 6.5 years (range1 - 15 yrs).Some other auther[8] had reported 21.7% children aged less than 5 years and 6.1% less than 2 years .The signs and symptoms of uncomplicated typhoid fever are nonspecific, and an accurate diagnosis on clinical grounds alone is difficult. The most consistant complaint in this study was fever (82/82) .The average duration of fever before diagnosis was 14.1 days. Caumes E, Ehya N, Nguyen J, Bricaire F. reported [9] fever and headache in more than 80% patients as the only signs in Enteric Fever .While in another study by Nasrallah SM, Nassar VH [10] , they found fever and bradycardia as the leading clinical signs followed by splenomegaly, hepatomegaly and rose spots. Rose spots were conspicuous by their absence in our study. Other features noted were GI symptoms, splenomegaly, hepatomegaly, chills & rigor, headache, coated tongue, lymphadenopathy, respiratory signs and toxic look. The complications observed were anemia in 10%, clouding of consciousness in 5% and CNS irritability in 3.7%.The principal complications observed in some other studies, [10] included anemia, typhoid hepatitis, and relapse and bleeding. Evidence of typhoid hepatitis was present in 30% of the patient's tested.[10]

The diagnosis of typhoid fever on clinical grounds is difficult, as the presenting symptoms are diverse and similar to those observed with other febrile illnesses. A definitive diagnosis can be made by isolation of Salmonella typhi from blood or bone marrow.[11] but, cultures of stool, urine, gastric and intestinal secretions can all be useful for diagnosis. In developing countries like ours bacterial culture facilities are often unavailable and many times the Widal test is the only supportive diagnostic tool available. In health centers with limited facilities, the Widal test 1/200 titer may be helpful for its high specificity .[12]

The laboratory tests done in this study were Complete Blood Count, Widal test, and Blood Culture. In 8 cases where both Blood Culture and Widal test was negative bone marrow was done. It was observed that leucopenia was present in 27% and leukocytosis in 16% cases. No reference article were available in this relation in pediatric casesd.There is a report in adult cases of Enteric Fever by K.C. Mathura, Chaudhary D, Simkhada R et.al[3] They found leukocytosis in 8.7% and leucopenia in 2.2% cases. Widal tests was positive in 83%, negative in 9.7 %.It was not done in 7% as culture was already positive in these cases. In a study by Caumes E, Ehya N, Nguyen J, Bricaire F,[9] The Widal test at inclusion was positive in 27%, and a second serological test was found to be positive in 50% of evaluated cases.

Although the isolation of Salmonella from blood remains the method of choice for the laboratory diagnosis. But, Blood cultures can be negative when patients have received prior antibiotic therapy. Bone marrow culturing has a higher sensitivity than blood culturing, [14, 15] but is a more invasive procedure. Bacteria can be isolated from blood in 73 to 97% of cases before antibiotic use [2]. However, many times to do blood culture may not be possible since (i) patients often receive antibiotics prior to medical diagnosis, (ii) bacteria can be isolated from the blood cultures in only 40 to 60% of the cases ,[16,17,18] and (iii) culture facilities may not be available. In this study 37 % were Blood culture positive, 46% Blood culture negative. In 17% cases Blood culture was not done. They were either partially treated by wide range of antibiotics by other pediatricians outside or were cases with positive Widal test on admission. They preferred to change hospital as defevescence was not attained. In these 17% cases Widal test was positive (Table-III). Su CP, Chen YC, Chang SC[19] isolated Salmonella typhi from Blood culture in 20 cases, from stool culture in 3 cases, and from bone marrow culture in 1 case. Yet in another study Salmonella spp were isolated in blood and stool cultures in 4 cases and in urine in 1 case.[9] In this study in 30 cases Salmonella was isolated in blood culture and 5 in bone marrow culture (Table-III). In a study , of 377 blood culture-positive cases, 80.6% were Salmonella typhi and 19.4% Salmonella paratyphi A, [8] While in this study ,out of 35 culture positive cases 32 (91.5 %) were Salmonella typhi and 3(8.5%) were Salmonella paratyphi A .Bone marrow was done in 8 cases where both blood culture and Widal test were negative. Out of these 5 (62.5%) were culture positive and 3(37.5%) were culture negative for Salmonella (Fig 4).Usually antibiotic is empirically started when a case of Enteric Fever is suspected. The empirically used antibiotics in this study were Ciprofloxacin in 55%, Ceftriaxone in 29%, ampicillin in 7%, cefotaxime in 6 %, and chloramphenicol in 2.4% (Table IV). Response to therapy with these with these first used antibiotics was seen. Best response was observed with ciprofloxacin, followed by ceftriaxone, ampicillin, cefotaxime, chloramphenicol respectively (Table IV). In another study, out of 98 children with enteric fever 72 children treated (67 with ceftriaxone and 5 with amoxicillin) for 5 or 7 days showed rapid improvement: Apyrexia was obtained in 1.5 day after the start of treatment with ceftriaxone.[7] But the remaining 26 (24 treated with ceftriaxone and 2 with amoxicillin) were clinically

ineffective, despite good in vitro activity, and was switch for oral ciprofloxacin .[7] Clinical improvement with ciprofloxacin was obtained in less than 48 h in these cases. [7] None of the patient treated with ciprofloxacin had side effects either early or late. In this study, Chloramphenicol had a significantly longer duration before defervescence time (10days).
Emergence of drug resistance in enteric fever is a major concern for the clinician. The last two decades have seen a change in the pattern of enteric fever with the emergence of multidrug-resistant strains (MDRS). The emergence of antimicrobial resistance during the last six years were also observed in this study .It was 43 % with chloramphenicol, 37% with ampicillin ,31% with trimethoprime-sulfamethoxazole ,6% with ciprofloxacin,4% with cefotaxime .There was nil resistance with ceftriaxone, cefuroxime , cfloxacin and gentamycin. The sensitivity was 100% with Ceftriaxone in another study in Nepal.[13]

Study by Gupta A, Swarnkar NK, Choudhary SP[20]revealed significant resistance to ciprofloxacin (55.5 %) and early evidence of emerging drug resistance to ceftriaxone (4.4 %). In another study out of 110 strains (including 4 S. typhi, 51 S. typhimurium, 25 S. enteritidis, 6 S. hadar and 5 S. heidelberg) none were resistant to Ceftriaxone or Ciprofloxacin.[9] In this study also none were resistant to Ceftriaxone, Cefuroxime and Ofloxacin. In a study by Walia M, Gaind R, Mehta R, Paul P, Aggarwal P, Kalaivani M , Resistance to ciprofloxacin was detected in only two isolates, both Salmonella paratyphi.[8]

An interesting finding in this study is 91% sensitivity to aminoglycosides like gentamycin which is bactericidal against gram negative organisms. This is to be kept in mind for further emergence of resistance to cephalosporin or fluroquinolones.

Conclusion

In conclusion, the diagnosis of typhoid fever is often challenging due to non-specific symptoms and lack of an immediate confirmatory test. In making the diagnosis, the isolation of bacteria from blood or bone marrow is the "gold standard," but widespread uncontrolled use of antibiotics leads to negative culture results. Again the culture facilities for isolation from bone marrow or blood are limited outside teaching hospitals. So, in these situations, Widal test plays a supportive role in diagnosis of Enteric Fever. Sometimes when both blood culture and Widal tests are negative bone marrow can be the diagnostic tool. Although the sample size is small in this study and has its own limitations, it can be concluded from above findings that ciprofloxacin is still a good drug for the treatment of Enteric Fever. But keeping in mind the potential toxicity of ciprofloxacin over cartilage growth, ceftriaxone, cefuroxime and ofloxacin with 100% sensitivity can be considered as first line drugs in the treatment of enteric fever. Gentamycin can be kept as reserve drug.

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