

Enteric Fever in Children - Clinical Profile, Sensitivity Patterns and Response to Antimicrobials

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Abstract :

Aims : Enteric fever is endemic in Ahmedabad and its diagnosis and treatment poses certain problems. The aim of the study was to study the clinical and hematological profile, culture positivity rate, sensitivity patterns of *Salmonella enterica* and response to antimicrobial therapy. **Materials and Methods :** This was a prospective study of all the patients who were clinically suspected and had either positive blood culture or Widal test with significantly raised titre in a tertiary care private hospital in Ahmedabad over the period from January to December 2012. **Results :** Culture positivity rate in our study was 49.35 %. Of the total isolates, 89.5 % were *Salmonella typhi* and 10.5% were *Salmonella paratyphi A*. All the isolates were sensitive to third generation cephalosporins and fluoroquinolones. The mean time to defervescence, when ceftriaxone was used as a single drug was 3.9 and 5.9 days, in those who received prior antibiotics and those who did not, respectively. **Conclusions :** High culture positivity despite prior antibiotics was seen. Also, low prevalence of resistance to ampicillin, amoxicillin and chloramphenicol and 100 % sensitivity to nalidixic acid and third generation cephalosporins was seen. Ceftriaxone was used as a monotherapy and was found to be highly efficacious.

Introduction :

Enteric fever is a systemic infection caused by *Salmonella enterica serotype typhi* or *paratyphi A* or *B*. It occurs in all parts of the world where water supplies and sanitation are substandard. Enteric fever is endemic in India. Reported data for the year 2009 shows 1.03 million cases and 421 deaths worldwide occurred due to enteric fever.⁽¹⁾

Clinical as well as laboratory diagnosis of enteric fever poses problems. Symptoms and signs of enteric fever resemble other febrile illnesses. Blood culture is considered the "gold standard" for diagnosis as not only it identifies the organism but also gives its antibiotic sensitivity. However, lack of awareness among health care professionals, use of empirical antibiotics, lack of facility for blood culture, as well as cost factor has led to a decreased use of this investigation for diagnostic purpose. The Widal test as a diagnostic modality has suboptimal sensitivity and specificity and also requires careful interpretation.^(2, 3) Since 1990s, *Salmonella typhi* has developed resistance simultaneously to all the

drugs used in first line treatment (chloramphenicol, cotrimoxazole and ampicillin). Fluoroquinolones were widely regarded as the most effective drug for the treatment of typhoid fever.⁽⁴⁾ But unfortunately, some strains of *S. typhi* have shown reduced susceptibility to fluoroquinolones.^(5,6) Also there is high rate of clinical failure seen with fluoroquinolones. At present third generation cephalosporins are used in treatment but there are sporadic reports of resistance to these antibiotics.⁽⁷⁾ Recently, azithromycin is being used as an alternative agent in uncomplicated enteric fever. It has been found that it reduces the clinical failure rate and duration of hospital stay in comparison to fluoroquinolones and relapse rate in comparison to ceftriaxone, when used in the treatment of multidrug resistant typhoid fever. However, experience with it is still limited.⁽⁸⁾ Aztreonam and imipenem are also potential third line drugs which are being used recently.⁽⁹⁾

Thus enteric fever raises several questions; particularly use of blood culture sensitivity as an important tool for diagnosis in clinically suspected cases as well as treatment, particularly choice and efficacy of antibiotics. Resistance pattern of *Salmonella* has been found to be different in different countries and regions of same country. Hence, a prospective study was

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undertaken in our hospital to study current scenario of enteric fever in our region.

The primary aim of the study was to study the culture positivity rate in clinically suspected enteric fever, sensitivity patterns of *Salmonella enterica* and response to antimicrobial therapy. The secondary aims were to study the clinical and laboratory profile of patients of enteric fever proven either by positive blood culture or Widal test with significant titre.

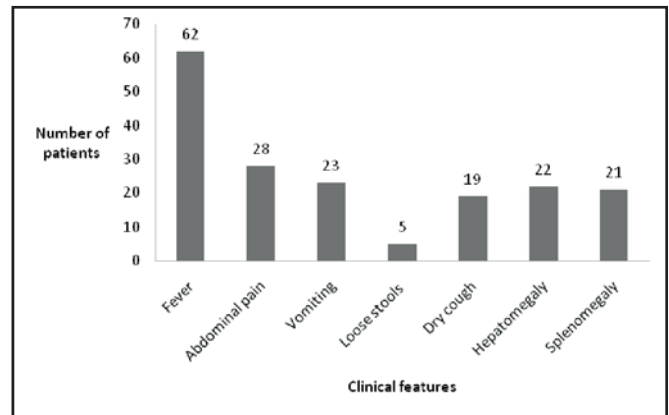
Materials and methods :

This was a prospective study carried out in the department of pediatrics at a tertiary care private hospital in Ahmedabad, India, from January to December 2012. All pediatric patients with clinically suspected enteric fever, as defined by the case definition and proven either by positive blood culture or Widal test with significant titre (level of both H and O antibodies of 1 in 160 dilution (four fold rises) or more by tube method) were enrolled in the study.⁽¹⁰⁾ Others who were clinically diagnosed as enteric fever but had less than significant titre or negative Widal test and Blood culture were excluded from the study. Clinical, laboratory and treatment informations were taken on a detailed proforma and analyzed. The approval of Ethics Committee of the hospital was obtained.

Results :

A total of 77 patients were admitted with clinically suspected enteric fever during the period January 2012 to December 2012. Out of these, 62 were diagnosed as enteric fever either by positive blood culture or Widal test with significant titre and were included in the study. Thirty four of the 62 study patients were male and 28 were female. The age ranged from 2 to 14 years, the mean age being 7.62 years. All patients had fever prior to admission; the median duration of fever prior to admission was 7 days, the range being 2 to 30 days. Abdominal pain, vomiting, loose stools and dry cough were the most common associated symptoms seen in 45.2%, 37.1%, 8.1% and 30.6% patients, respectively. None of the patients had relative bradycardia. Hepatosplenomegaly was seen in 22.5% patients. Only hepatomegaly was seen in 35.4% while only splenomegaly was seen in 33.8% patients.

Figure 1 Clinical features of enteric fever in children



The mean white blood cell (WBC) count was 8455 cells/cumm with a range from 2600 cells/cumm to 21,400 cells/cumm. Seventy four percent patients had the WBC count within the normal range (4000 – 11000 cells/cumm) while 9.6 % patients had leucopenia (WBC count < 4000 cells/cumm). Leucocytosis (WBC count > 11000 cells/cumm) was seen in 16.2 % patients. Absolute eosinopenia (<40 cells/cumm eosinophils) was found in 72.5 % of the patients. The mean platelet count of the study patients was 2, 61,000/ cumm (range 85,000 to 5, 66,000). Thrombocytopenia (platelet count < 1.5 lacs/ cumm) was seen in 11.2 % of the patients. Hyperbilirubinemia (>1 mg/dl) was seen in 28.7% while the ALT was elevated (> 60 IU/ml) in 25.7% patients. Serum C reactive protein (CRP) was positive in 50 % patients. Widal test was positive in 33 of 62 patients (53.2 %). Thirty eight were culture proven cases of enteric fever. The culture positivity rate was 49.35%. The blood culture of 34 of the 62 study patients (89.5%) were positive for *Salmonella typhi* and 4 (10.5%) were positive for *Salmonella paratyphi A*.

Table 1 : Sensitivity patterns of Salmonella enterica isolates

Sr. no.	Antibiotic	Salmonella typhi N =34 (%)	Salmonella paratyphiA N=4 (%)
1.	S to Chloramphenicol	32(95.11%)	4(100%)
2.	S to Ampicillin	33(97.04%)	4(100%)
3.	S to Amoxicillin	33(97.04%)	4(100%)
4.	S to Nalidixic acid	34(100%)	4(100%)
5.	S to Ciprofloxacin	34(100%)	4(100%)
6.	S to Ofloxacin	34(100%)	4(100%)
7.	S to Cefotaxime	34(100%)	4(100%)
8.	S to Ceftriaxone	34(100%)	4(100%)
9.	S to Cefixime	34(100%)	4(100%)
10.	S to Azithromycin	33(97.04%)	4(100%)

Table 1 shows the sensitivity pattern of the isolates. There is no significant difference between the antimicrobial susceptibility patterns of that of *S typhi* and *S paratyphi A*. Twenty nine percent patients received antibiotics before being admitted to the hospital. Culture positivity rate in those who received antibiotics was 61.1% and those who did not was 58.33%. (p value 0.81 - not significant)

As per current recommendations, ceftriaxone was used to treat all the patients diagnosed with enteric fever. In those patients who were discharged before 14 days, therapy was completed with cefixime. The mean duration of receipt of ceftriaxone after hospitalization was 9 days. The mean time to defervescence defined as time period in days from the day of onset of the antibiotic therapy in the hospital to the disappearance of fever was calculated for various patient groups. The mean time to defervescence in the group of patients who had received antibiotics prior to admission was 3.9 days (95% CI 2.8, 4.9 days)(CI – confidence interval) while in the patients who did not receive prior antibiotics was 5.7 days (95% CI 4.3, 7.0 days) , p <0.05 (significant). (One sample t test)

The mean time to defervescence differed significantly between those who had received prior antibiotics and those who did not (3.9 days versus 5.7 days respectively). Complications noticed during hospitalization were bronchitis in two, hepatitis in two and myocarditis in three patients. All the study patients were discharged and mean duration of hospitalization was 10 days.

Discussion :

This study is a large prospective study on enteric fever in pediatric population. Fever was the common clinical presentation seen in all (100%) our cases which is similar to the studies done by other authors.^(10, 11, 12, 13) The clinical features of typhoid fever seen in our series in comparison with other published studies are shown in Table 2.^(11, 13, 14)

Table 2 Prominent clinical features of enteric fever in various studies

Clinical features	Series in current study	Ganesh et al(11)	Jog et al(13)	Chowta et al(14)
Fever	100%	100%	100%	100%
Vomiting	37.1%	49%	42%	20.4%
Diarrhea	8.1%	29%	31%	20.4%
Abdominal pain	45.2 %	-	15.9%	18%
Hepatomegaly	35.4%	71%	7.5%	34%
Splenomegaly	33.8%	34%	33.6%	11.3%

The total white blood cell count was normal in most of our patients which is similar to earlier studies.^(11, 13) Absolute eosinopenia was seen in 72.5% of our patients which is consistent with other studies (70-80%).⁽¹⁰⁾ Absolute eosinopenia can be used as a pointer to the diagnosis of enteric fever.^(10, 13) Thrombocytopenia in our study is reported in 11.2% of cases which is also consistent with most of the studies (10-15%).⁽¹⁰⁾ Elevation of serum aminotransferases was seen in 25.7% of our cases which is lower when compared to other studies.^(11, 13)

There was no significant difference in the culture positivity rate between those who received prior antibiotics and those who did not. The high yield from blood cultures despite antibiotics being given could have been as a result of processing of blood cultures by the BACTEC method and also the fact that *Salmonella* is the easiest organism to isolate in laboratory. Also, these results could be due to small sample size. The usual perception is that culture positivity falls dramatically with prior use of antibiotics, which often prevents clinicians from sending blood cultures in patients with pyrexia.^(15, 16) However, results of our study suggest that blood cultures should be sent in suspected enteric fever cases even if the patient is on antibiotics.

From the total isolates, 10.5% were *Salmonella paratyphi A* whereas the remaining was *Salmonella typhi*. The reported rate of isolation of *Salmonella paratyphi A* in literature is 20%.⁽¹⁷⁾ All the isolates of *Salmonella typhi* were sensitive to nalidixic acid, ciprofloxacin, ofloxacin and the commonly used cephalosporins including ceftriaxone, cefotaxime and cefixime. One isolate was resistant to ampicillin (2.94%), amoxicillin (2.94%), two isolates were

resistant to chloramphenicol (5.88%) and one isolate was resistant to azithromycin (2.94%). All the isolates of *Salmonella paratyphi A* were sensitive to above mentioned antibiotics. Resistance to cephalosporins was not seen in our study as in conjunction with other studies.^(11, 13, 14, 18) Also, there was no resistance to nalidixic acid and fluoroquinolones in our study as compared to studies by Ganesh et al⁽¹¹⁾ and Walia et al⁽¹⁸⁾ which showed a resistance of 73% and 88.9%. These results suggest that nalidixic acid and fluoroquinolone resistance is still not high in this part of India.

According to the guidelines given by IAP national task force, all the patients were treated with ceftriaxone.⁽⁹⁾ The mean time of defervescence was 3.9 days in those who received prior antibiotics and 5.9 days in those who did not, which is statistically significant. The mean time of defervescence when ceftriaxone is used as a single therapy in studies reported by Jog et al, Chowta et al and Parry et al is 4.2, 6 and 6.1 days respectively.^(4, 13, 14) Complications are seen in about 10-15 % of the patients of enteric fever which include gastrointestinal bleeding and perforation, hepatitis, myocarditis, osteomyelitis, splenic abscess, acute pancreatitis, cutaneous vasculitis and neuropsychiatric manifestations.⁽⁹⁾ Complication rate in our study was 11.2 % commonest being myocarditis, hepatitis and bronchitis.

Conclusion :

Enteric fever continues to be a major health problem in children. Fever and abdominal pain are the commonest presenting symptoms. Normal leukocyte count, absolute eosinopenia, thrombocytopenia, elevated AST and CRP levels help to suspect the diagnosis. The other conclusions which can be drawn from our study is the high culture positivity despite the receipt of prior antibiotics, low prevalence of resistance to ampicillin, amoxicillin and chloramphenicol and 100 % sensitivity to nalidixic acid, ciprofloxacin, ofloxacin and third generation cephalosporins in this part of India. Also, ceftriaxone was found to be highly efficacious when used as a monotherapy.

References :

1. K. Park. Park's textbook of preventive and social medicine. 21st ed. Banarsidas Bhanot Publishers; 2011. pp 212-216.
2. Olopoenia LA, King AL. Widal agglutination test-100 years later: Still plagued by controversy. Postgrad Med J 2000; 76: 80-84.
3. Rodrigues C. The Widal test more than 100 years old: abused but still used. J Assoc Physicians India 2003; 51: 7-8.
4. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. N Engl J Med 2002; 347:1770-82.
5. Gupta A, Swarnkar NK, Choudhary SP. Changing antibiotic sensitivity in enteric fever. J Trop Ped 2001; 47: 369-371.
6. Dutta P, Mitra U, Dutta S, De A, Chatterjee M K, Bhattacharya SK. Ceftriaxone therapy in ciprofloxacin treatment failure typhoid fever in children. Indian J Med Res 2001; 113: 210-213.
7. Saha SK, Talukder SY, Islam M. Saha S. A highly Ceftriaxone resistant *Salmonella typhi* in Bangladesh. Pediatr Infect Dis J 1999; 18: 297-303.
8. Dheeraj Shah. Role of Azithromycin in enteric fever. Cochrane collection. Indian Pediatrics 2009; 46: 51-52.
9. Kundu R, Ganguly N, Ghosh TK, Yewale VN, Shah RC, Shah NK; IAP Task Force. IAP Task Force Report: Management of enteric fever in children. Indian Pediatr 2006; 43: 884-887.
10. 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: 875-883.
11. Ganesh R, Janakiraman L, Thiruvengadam V, Sathiyasekeran M. Profile of typhoid fever in children from a tertiary care hospital in Chennai - South India. Indian J Pediatrics (2010) 77:1089-1092.
12. Walia M, Gaiind R, Paul P, Mehta R, Aggarwal P, Kalaivani M. Age related clinical and microbiological characteristics of enteric fever in India. Trans R Soc Trop Med Hyg. 2006 Oct; 100(10):942-8.
13. S Jog, R Soman, T Singhal, C Rodrigues, A Mehta, FD Dastur. Enteric fever in Mumbai - Clinical Profile, Sensitivity Patterns and Response to Antimicrobials. Journal of Association of Physicians of India 2008 April; 65: 237-40.
14. Chowta MN, Chowta NK. Study of clinical profile and antibiotic response in typhoid fever. Indian Journal of Medical Microbiology (2005) 23 (2):125-127.
15. Kadhivaran T, Wig N, Kapil A, Kabra SK, Renuka K, Misra A. Clinical outcomes in typhoid fever: Adverse impact of infection with nalidixic acid - resistant *Salmonella typhi*. BMC Infectious diseases 2005; 5:37.
16. Ananthanarayan R, Paniker CKJ. Textbook of Microbiology, 6th edition. Publishers- Orient Longman Private Ltd., Hyderabad, India; 2000:267-80.
17. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ 2004; 82:346-353.
18. Walia M, Gaiind R, Paul P, Mehta R, Aggarwal P, Kalaivani M. Current perspectives of enteric fever: a hospital based study from India. Ann Trop Paediatrics. 2005 Sep; 25(3):161-74.