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***Research Article***

# STUDY OF CLINICAL AND LABORATORY PROFILE OF ENTERIC FEVER IN PEDIATRIC AGE GROUP

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## ABSTRACT
Objective was to study the clinical profile, laboratory parameters and antibiotic sensitivity pattern in culture positive enteric fever cases in paediatric age group in Bangalore. The study was designed as prospective observational study and conducted at Department of Pediatrics, Command Hospital Air Force, and Tertiary care hospital in Bangalore. Study was done from Nov 2008 to Apr 2010. All children presenting in the OPD with fever of ≥ 5 days with or without organomegaly during the study period were included in the study. Data of culture positive enteric fever cases was analysed for the objective of the present study. A total of 727 children were screened for enteric fever, out of which 104 cases were diagnosed as enteric fever based on widal titers and/or positive blood cultures. 52 cases of blood culture positive enteric fever were included in the study. 43(82.7%) of the culture positive cases of enteric fever were caused by Salmonella typhi (S.Typhi) and 9 (17.3%) were caused by *Salmonella Paratyphi A* (*S. Paratyphi A*). Mean age of presentation was 6.6 ± 3 years. Common clinical features were anorexia 25 (47.1%), cough 21 (39.6%), diarrhoea 14 (26.4%), headache 13 (24.5%), hepatosplenomegaly 24 (46%), isolated hepatomegaly 11 (21.1%), isolated splenomegaly 9 (17.3%). Leukopenia, eosinopenia and mildly elevated liver enzymes were the common laboratory findings. The sensitivity and specificity of Widal test taking titres TO and TH≥ 1:120 as cut off were found to be 84.61% and 54.4% respectively. Percentage of S.Typhi strains found to be sensitive to chloramphenicol, amoxicillin and injectable cephalosporins is 90.7%, 78.6% and 88.6% respectively. 76.9% strains of S.Typhi were resistant to nalidixic acid and 5.8% were multidrug resistant. In paratyphoid fever, 100% were sensitive to Chloramphenicol. Resistance to nalidixic acid, co-trimoxazole and ampicillin was seen in 66.7%, 11.1% and 11.1% respectively. Fever with anorexia, cough, diarrhoea, headache, hepatosplenomegaly with mildly elevated liver enzymes were the common clinical findings in culture positive enteric fever. There is re-emergence of strains fully susceptible to first line antibiotics (choramphenicol, ampicillin and co-trimoxazole) except nalidixic acid for which 77% of the isolated strains were resistant. In view of increased resistance to nalidixic acid, indiscriminate use of quinolones should be avoided.

***Key Words****: S. typhi, S. paratyphi A, Enteric Fever, Widal Titers*

## INTRODUCTION
Assessment of a child presenting with fever is always a challenge to most paediatricians. To determine the aetiology and plan the management in the first few days is always difficult. In view of the anxiety of the parents most paediatricians have the tendency to start some antibiotics before any real clue about the aetiology. Most of these fevers might just be of viral aetiology unnecessarily managed with antibiotics. In enteric fever this initial antibiotic might modify the course of the disease and pose significant difficulty in interpretation of lab investigations.

Enteric fever is one of the common causes of fever in children with varied presentation and significant difference in the signs and symptoms compared to adults. It is a common infectious disease presenting as acute multisystem febrile illness caused by *S. typhi* and *S. paratyphi*. It is a major public health problem in developing countries including India where patients report throughout the year with monsoon clustering patterns. Low standards of living are the main reasons behind the higher endemicity in India. The matter is further worsened by the fact that etiological diagnosis for cases of pyrexia is available in

relatively few centers. This might lead to improper therapy and worsen the drug resistance among Salmonella isolates. The clinical profile, laboratory features, antibiotic sensitivity pattern of the organism and the clinical response of the illness to the antibiotics differ from country to country and within the same country. Widal test in India continues to be important in the work up of patient with fever despite its variable sensitivity and specificity. It is important to define a simple and easily available test in a particular set up to plan management. Since 1990's *S. typhi* has developed resistance simultaneously to all the drugs used in first line treatment (chloramphenicol, co-trimoxazole and ampicillin) and are known as MDRTF. There are some reports of reemergence of fully susceptible strain to first line drugs (Sood *et al.,* 1999). But these reports are few and unless antibiotic sensitivity testing shows the organisms to be fully susceptible to first line drugs they are not advocated for empirical therapy in typhoid. Fluoroquinolones are widely regarded as the most effective drug for the treatment of typhoid fever (Parry *et al.,* 2002). But unfortunately, some strains of S. Typhi have shown reduced susceptibility to fluoroquinolones (Gupta *et al.,* 2001). On routine disc testing with the recommended break points, organisms showing susceptibility to fluoroquinolones show poor clinical response to actual treatment. These organisms when tested by disc testing with nalidixic acid show resistance. So in other words resistance to nalidixic acid is a surrogate marker which predicts fluoroquinolones failure and can be used to guide antibiotic therapy. The resistance to fluoroquinolones may be total or partial. The nalidixic acid resistant *S. typhi* (NARST) is a marker of reduced susceptibility to fluoroquinolones.With the development of fluoroquinolones resistance third generation cephalosporins were used in treatment but sporadic reports of resistance to these antibiotics also followed (Saha *et al.,* 1999). Recently, azithromycin is being used as an alternative agent for treatment of uncomplicated typhoid fever (World Health Organization, 2003; Parry *et al.,* 2002). The fluoroquinolones, other second-line antibiotics, such as third-generation cephalosporins (eg, ceftriaxone and cefixime), and azithromycin are currently regarded as the antibiotics of choice for treating MDR strains. However, an issue of great concern is the emergence of strains of *S. typhi* and *S. paratyphi* with reduced susceptibility to fluoroquinolones. We undertook this study to analyze the varied clinical presentations, culture positivity and correlation with lab investigations, with special reference to antibiotic sensitivity in a tertiary hospital in Bangalore.

## RESULTS AND DISCUSSION

### *Results and Analysis*

A total of 727 children less than 15 years of age with fever ≥ 5 days with or without hepatosplenomegaly were screened for enteric fever (Figure1). 104 children (14.3%) were found to be widal positive and/or culture positive. 52(50%) children out of 104 children were found to be culture positive and these subjects formed the study group.

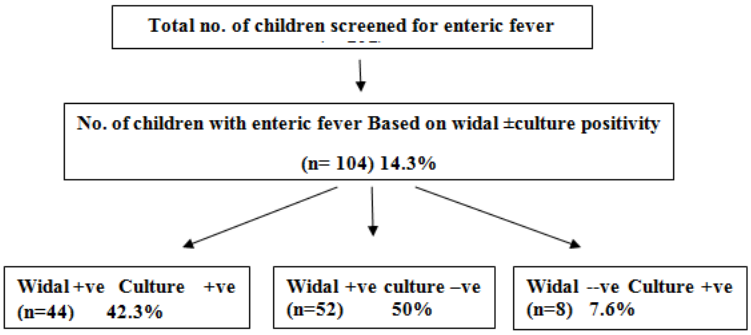


**Figure 1: Study Flow Chart**

**Table 1: Base line characteristics**

| Variable | Description | Number (%) |
|---|---|---|
| Age | ≤5yrs | 21 (40) |
| | >5yrs | 31 (59.65) |
| Sex | males | 29 (55.7) |
| Socio economic status Kuppuswamy's scale | upper (i) (26-29) | 3 (5.7) |
| | upper middle (ii) (16-25) | 39 (75) |
| | middle lower middle (iii) (11-15) | 3 (5.7) |
| | lower upper lower (iv) (5-10) | 5 (9) |
| | lower (v) (<5 ) | 0 (0) |
| Water source | corporation water (kaveri) | 38 (73.1) |
| | ground water | 14 (26.9) |
| Other details | vaccination status | 6 (11.53) |
| | cases who received antibiotics before admission | 11 (21.15) |

Base line characteristics of study subjects are as in shown Table 1. Majority of children 39 (75%) were from upper middle class and had access to the corporation water supply that is from Kaveri River. 11% of the children were immunized within 3 yrs before the illness and 21% had received antibiotics before presenting to us.Majority of culture positive cases were distributed in two age groups, 3-5 yrs and 9-15 yrs with approximately equal proportions. Only 2 children were less than 2 yrs old.

***Clinical Features***

Proportion of subjects with different clinical findings is depicted in Table 2. Age related difference in clinical features is depicted in Table 3. Anorexia, nausea, vomiting, pain abdomen and cough were the predominant symptoms in children with enteric fever at presentation. 84% of the children had organomegaly with half of the children having both liver and splenic enlargement. Jaundice was found to be an uncommon finding manifesting in only 5 % of cases.

**Table 2: Clinical Features at Admission**

| Clinical Features | No of Cases | Percent |
|---|---|---|
| **Symptoms** | | |
| Anorexia | 25 | 47.1 |
| Nausea/vomiting | 25 | 47.1 |
| Pain abdomen | 23 | 43.33 |
| Cough | 21 | 39.6 |
| Diarrhoea | 14 | 26.4 |
| Headache/myalgia | 13 | 24.5 |
| Arthralgia | 11 | 20.7 |
| Constipation | 4 | 7.6 |
| Malena | 0 | 0 |
| Abnormal behaviour | 0 | 0 |
| **Signs** | | |
| Hepatosplenomegaly | 24 | 46.1 |
| Hepatomegaly | 11 | 21.1 |
| Splenomegaly | 9 | 17.30 |
| Coated tongue | 7 | 13.46 |
| Jaundice | 3 | 5.7 |

**Table 3: Difference in clinical features related to age**

| Clinical Features | < *5* Years (n %) | > 5 Years (n %) |
|---|---|---|
| Anorexia | 12 (57.14) | 11 (34.3) |
| Vomiting | 9 (42.85) | 17 (53.1) |
| Abdominal pain | 8 (38.09) | 13 (40.6) |
| Diarrhoea | 8 (38.09) | 6 (18.75) |
| Cough | 6 (28.57) | 11(34.37) |
| Coated tongue | 6 (28.57) | 8 (25) |
| Myalgia | 5 (23.80) | 6 (18.75) |
| Headache | 2 (9.5) | 11 (34.37) |
| Constipation | 3 (14.28) | 1 (3.1) |
| Jaundice | 2 (9.5) | 1 (3.1) |

Anorexia and diarrhoea were more common symptoms in children < 5yrs, while vomiting, head ache and cough was more common in children > 5yrs.

***Laboratory Findings***

Laboratory findings are depicted in table 4. Using cut off Hb of 11gm%, 34% of the children were found to be anemic and up to 40% of the children had leucopenia and eosinopenia and 13.4% had thrombocytopenia. Liver enzymes were found to be elevated 2-3 times of normal in 38% cases.

**Table 4: Laboratory profile**

| Lab Parameter | Mean ± SD | Abnormal Levels | No. of Patients (%) |
|---|---|---|---|
| HB | 11.27±1.33 | Anemia (<11g %) | 18 (34.6) |
| TLC | 6547.1±2879 | Leucocytosis(>13500/cumm$^3$) | 4 (7.68) |
| | | Leucopenia(<5000/cumm$^3$) | 20 (38.4) |
| EOSINOPHILS | 1±1.2 | Eosinopenia(<1%) | 20 (38.4) |
| | | Eosinophilia(>3%) | 3 (5.76) |
| POLYMORPHS | 54.3±11.6 | Neutrophilia (>62%) | 17 (32.6) |
| | | Neutropenia (<54%) | 10 (19.2) |
| PLT COUNT( LACS) | 2.26±0.80 | Thrombocytopenia | 7 (13.4) |
| SGOT | 107.5±85 | Elevated SGOT (>55IU/L) | 38 (73) |
| SGPT | 108.5±92.4 | Elevated SGPT (>45IU/L) | 36 (69.2) |
| WIDAL TITRES | | TO ≥1:120 | 96 (92.3) |
| | | TH ≤1:120 | 93 (89.4) |
| BLOD CULTURE+VE | - | - | 52 (50) |

**Table 5: Difference in lab parameters related to age**

| Lab parameter | ≤ *5 years* | > *5 years* |
|---|---|---|
| Hemoglobin (gm%) | 10.49 | 11.7 |
| Total leukocyte count | 8054 | 7085 |
| Polymorphs (%) | 52.86 | 43.26 |
| Lymphocytes (%) | 42.33 | 41.2 |
| Eosinophils (%) | 0.68 | 1.2 |
| Platelet count(Lacs) | 2.27 | 2.25 |
| SG O T (IU /L) | 107.5 | 112.3 |
| SG P T (IU /L ) | 108.2 | 121.7 |

No difference in laboratory parameters was noticed between the two age groups of culture positive cases of enteric fever cases (Table 5).

***Organisms Isolated and their Sensitivity Pattern***

Out of the 52 cases of culture positive enteric fever 43 were caused by *S. typhi* and 9 were caused by *S. paratyphi* A (table 6). Resistance pattern of isolated S.typhi is depicted in table 7 and also in figure 2 and 3. Not all organisms were tested against all antibiotics shown in the Table 7.

Approximately 77% of the strains of *S. typhi* isolated were resistant to nalidixic acid and 3 were resistant to all first line antibiotics ampicillin, chloramphenicol and co-trimoxazole (MDR). Resistance to chloramphenicol, ampicillin and trimethoprim-sulphmethoxazole was 7.7%, 13% and 9.7% respectively. 3 isolates were found to be resistant to ceftriaxone.

**Table 6: Culture and Sensitivity Pattern**

| **Organism** | | **N (%) of Cases** |
|---|---|---|
| | Total | 43 (82.69) |
| *S. typhi* | NARST | 30 (76.9) |
| | MDR | 3 (6.8) |
| | Total | 9 (17.3) |
| *S. paratyphi A* | NAR *S. paratyphi A* | 7 (77.78) |
| | MDR | 0 |

Diagnostic value of Widal test was assessed taking titers (TO & TH $\geq$ 1:120) as positive and culture positivity as Gold standard for diagnosis of enteric fever. Sensitivity and specificity was found to be 84.16% and 54.4% respectively. The Positive predictive value and Negative predictive value was found to be 45.83% and 98.73% respectively.

**Table 7: Sensitivity /resistance pattern of *S. typhi* (N=43) and *S. paratyphi* (n=9)**

| **Antibiotics** | ***S. typhi* (N=43)** | | ***S. paratyphi* (n=9)** | |
|---|---|---|---|---|
| | **Total tested** | **Resistance n(%)** | **Total tested** | **Resistance n(%)** |
| 1. Amoxicillin | 23 | 3 (13) | 7 | 1 (11.11) |
| 2. Nalidixic acid | 39 | 30 (76.9) | 9 | 6 (66.67) |
| 3. Trimethoprim/Sulphmethoxazole | 31 | 3 (9.7) | 9 | 1 (11.11) |
| 4. Chloromycetin | 39 | 3 (7.7) | 9 | 0 (0) |
| 5. Gentamicin | 9 | 0 (0) | 3 | 0 (0) |
| 6. Ciprofloxacin | 36 | 6 (16.7) | 6 | 0 (0) |
| 7. Cephotaxime | 22 | 3 (13.6) | 9 | 0 (0) |
| 8. Ceftriaxone | 24 | 3 (12.5) | 9 | 0 (0) |
| 9. Imipenem | 24 | 0 (0) | 7 | 0 (0) |
| 10. Ofloxacin | 32 | 1 (3.1) | 7 | 0 (0) |
| 11. Azithromycin | 25 | 4 (16) | 6 | 1 (11.1) |
| 12. Cefipime | 17 | 0 (0) | 3 | 0 (0 |
| 13. Cefixime | 12 | 1 (8.3) | 4 | 0 (0) |

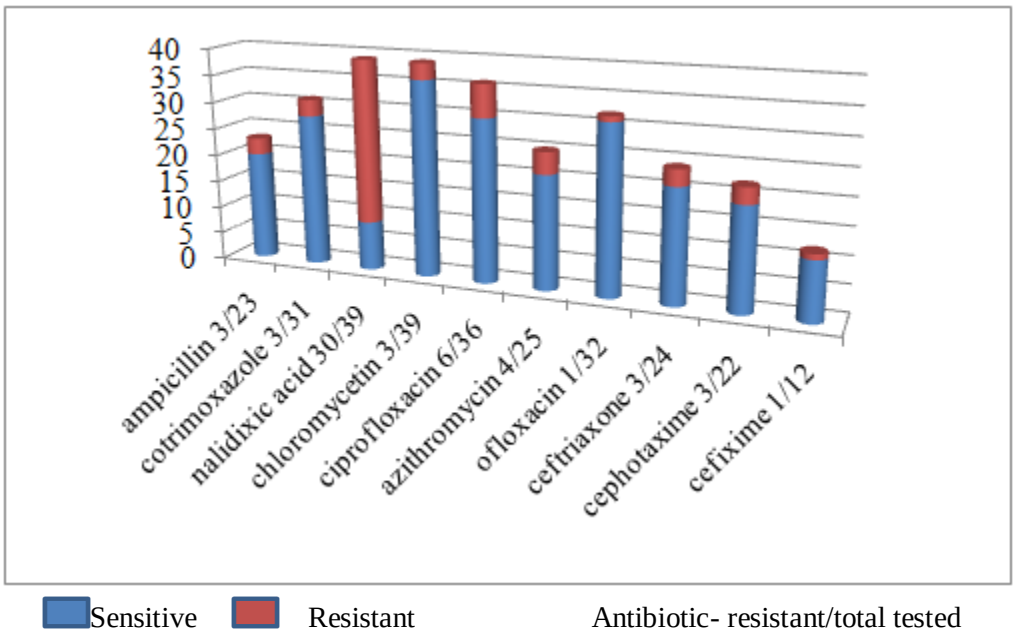


**Figure 2: *S. typhi*: Sensitivity pattern**

Resistance pattern of isolated *S. paratyphi* A strains is depicted in table 7 and figure 3. Approximately 30% of the strains of *S. paratyphi* A isolated were resistant to nalidixic acid and none were resistant to all first line antibiotics ampicillin, chloramphenicol and co-trimoxazole (MDR). Resistance to chloramphenicol, ampicillin and trimethoprim-sulphmethoxazole was 0%, 14.28% and 11.1% respectively. None of the isolates were found to be resistant to ceftriaxone.

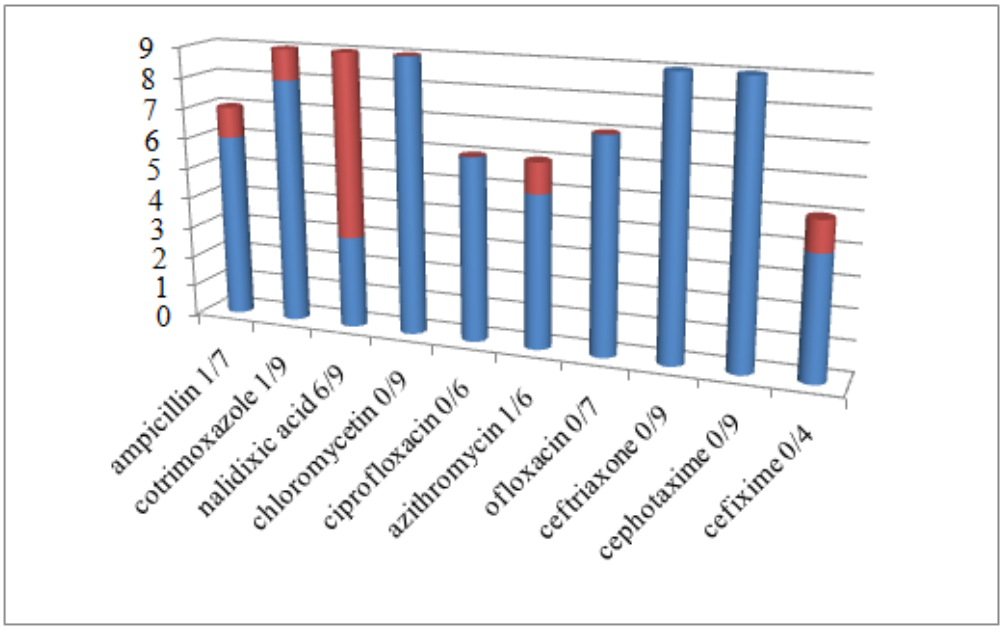


**Figure 3: *S. paratyphi*: Sensitivity pattern**

***Discussion***

This is a single centre study of culture positive enteric fever cases highlighting the clinical features, laboratory profile and sensitivity pattern of salmonella strains isolated from these cases. Enteric fever is found to be a common cause of fever persisting for greater than 5 days. Anorexia, vomiting, abdominal pain, diarrhoea, cough and hepato-splenomegaly were found to be the common clinical manifestations. Out of this anorexia and diarrhoea were the predominant symptoms in children less than 5 yrs while cough was found to be more common in children greater than 5 years. Leukopenia, eosinopenia and mildly elevated liver enzymes are the common laboratory findings.

There are few studies on clinical manifestations of enteric fever in the paediatric age group. In previous studies most common age group affected was more than 5yrs, while in our study 40% of culture positive cases were less than 5 yrs (Walia *et al.,* 2006). Relative bradycardia, rose spots considered to be salient features of enteric fever were not seen in our study. Step ladder pattern of fever could not be demonstrated in any of the cases in our study probably because most of them were receiving antipyretics. Constipation was found to be common finding in adults but in our study, similar to previous studies in children (Walia *et al.,* 2006), diarrhoea was more common. None of the cases had pea soup diarrhoea which is typical of enteric fever. 86% of children in our study had organomegaly out of which 46% had both hepatic and splenic enlargement. A recent study from Nepal also found that hepato-splenomegaly was present in 43 % of cases (Patankar and Shah, 2009).

Four patients in our study had leucocytosis and 3 cases had eosinophilia, a laboratory finding that is uncommon in enteric fever. In our study 40% cases had leukopenia and eosinopenia similar to that reported by Lefebvre *et al.,* (2005) mildly elevated liver enzymes were seen in 70% of our patients similar to that reported by Malik *et al.,* (2001). There was no case of complicated enteric fever in our study the reason being easy access to medical facilities and early initiation of antibiotic therapy.

Widal test continues to be used in India for diagnosis of enteric fever despite its poor sensitivity and specificity. Culture positivity rate in Widal positive cases was found to be 50%. Taking titres $\geq$ 1: 120 as positive sensitivity and specificity of Widal test for predicting culture positive enteric fever cases was found to be 84.16% and 54.4% respectively. The positive predictive value and negative predictive value of Widal test was found to be 45.83% and 98.73% respectively, suggesting it to be a good screening test for diagnosis of culture positive enteric fever in children. In a study, by Choo *et al.,* (1993), assessing the usefulness of widal test in diagnosing enteric fever using widal titers TO &/or TH $\geq$40 as cut off, found both sensitivity and specificity of 89 %. In our study 10% of all culture positive patients who presented with fever of more than a week's duration had negative widal titers, which shows that absence of raised widal titers does not exclude enteric fever. This finding although not new, reiterates the fact that the universal use of blood culture to diagnose enteric fever should be encouraged and the practice of sending at least one blood culture before exhibiting antibiotic to a patient with fever and suspected enteric fever should be adopted by all physicians. Majority of culture positive enteric fever cases were caused by *S.Typhi* and only 20% were caused by *S. paratyphi A.* No case was caused by *Paratyphi B.* This is in agreement with literature (Crump *et al.,* 2004). 6(11.5%) cases developed enteric fever in spite of receiving typhoid vaccination in the last 3 years suggesting that vaccination does not provide 100% immunity against typhoid fever. 11(21.1%) cases in our study were culture positive in spite of receiving antibiotics 5-7 days before taking samples for blood cultures. This is similar to finding reported by Gavhane *et al.,* (2010). We found a high prevalence of nalidixic acid resistance in our isolates with a return of sensitivity to chloramphenicol, co-trimoxazole and amoxicillin as seen in other Indian studies (Gavhane *et al.,* 2010). In spite of high nalidixic acid resistance we found ciprofloxacin resistance in only 16%. Recent reports of in vitro and in vivo resistance to ciprofloxacin have raised this concern as reported by Raveendran *et al.,* (2008). Although fluoroquinolones were the initial choice of antibiotic in enteric fever the high prevalence of NARST raises concern over their efficacy. The sensitivity to chloramphenicol, ampicillin and co-trimoxazole in all the isolates was very high which are in agreement with the recent studies (Gavhane *et al.,* 2010). Only three multi drug resistant strains were observed and

they belonged to *S.Typhi* group. We found 3rd generation cephalosporin resistance in 3 isolates as against other studies (Raveendram *et al.*, 2008; Chowta and Chowta, 2005) where none of the isolates were resistant to 3rd generation cephalosporins. Seven cases in our study required second line antibiotic therapy with azithromycin for poor response to cephalosporins as first line antibiotic. Thus it is likely that drug resistance to these drugs may be seen in the future and there may be emergence of multi-drug resistant strains in typhoid as has been reported by Gavhane *et al.*, (2010).

***Conclusion***

Enteric fever is an important cause of febrile illness in children. Fever with anorexia, cough, diarrhoea, headache, hepatosplenomegaly were the common clinical manifestations of enteric fever. Leucopenia, eosinopenia and mildly elevated liver enzymes are common laboratory findings. Widal is though a good screening test but has poor specificity for diagnosing culture positive enteric fever cases. There is re-emergence of strains with high sensitivity to first line antibiotics chloramphenicol and co-trimoxazole except nalidixic acid to which there is persistence of high resistance. An adequate trial of first line antibiotics like oral co-trimoxazole, ampicillin or chloramphenicol can be tried before starting injectable antibiotics due to increased emergence of sensitivity to these drugs. In view of increased resistance to nalidixic acid, indiscriminate use of quinolones to be avoided and initial antibiotic has to be started based on the sensitivity pattern in the area. There is trend towards emerging resistance to 3rd generation cephalosporins.

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