

Assessment of the Clinico-Epidemiological Profile and Trends of Antibiotic Susceptibility of Enteric Fever

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Abstract

Aim: This study was conducted to evaluation of clinico epidemiological profile and patterns of antibiotic sensitivity of enteric fever in Bihar region. **Methods:** A prospective observational study was conducted in the Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India for for 1 year. Total 170 Children aged below 18 years with history of fever of more than 4-14 days duration were included in this study. In each case, age, sex, presenting complaint, laboratory investigations and antibiotic sensitivity pattern are collected and analysed. **Results:** Out of 170 cases, 110 cases (64.71%) were males and 60 cases (35.29%) were females. The most common symptom was fever (100%), followed by anorexia (61.76%), vomiting (44.12%), pain abdomen (20.59%), diarrhea (8.24%), headache (7.06%), and cough (5.89%). The most common sign we observed was toxic look in 72.94% of the cases followed by coated tongue in 48.82%, hepatomegaly 43.53%, splenomegaly 23.53%, hepatosplenomegaly in 17.65% of cases and pallor in 5.88% of cases. Anemia found in 40 (23.53%) cases, leucopenia and leucocytosis was observed in 55(32.35%) cases and 36(21.18%) cases respectively. Neutropenia found in 66(38.82%) cases and neutrophilia was found in 57(33.53%) cases. Eosinopenia was seen in 80(47.06%) cases, eosinophilia in 10(5.88%) cases and thrombocytopenia in 26(15.29%) cases. SGOT levels was elevated (>200IU/ml) in 23(13.53%) cases and SGPT (>200IU/ml) in 24(14.12%) cases. The elevated levels of liver enzymes lasted only few days. There were no complications observed during our study period. *Salmonella typhi* O titres >1:100 was seen in 158(92.94%) cases and TH titres >1:200 in 127(74.71%) cases. Blood culture positive for *Salmonella typhi* noted in 40(23.53%) cases. **Conclusion:** Fever, malaise, anorexia, vomiting, chills, headache, coated tongue, diarrhea and organomegaly are the common clinical manifestations of enteric fever. Normal to raised leukocyte count is more common, however, neutropenia and eosinopenia may be a prominent finding.

Keywords: Children, Clinical profile, Coated tongue, Typhoid fever

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Introduction

The word typhoid is derived from Greek word 'TYPHOS' meaning smokes or stupor.[1] Typhoid is a multi systemic bacterial illness caused by *Salmonella* species, subspecies enterica and serovar typhi. A milder form of the disease is caused by serovars paratyphi A, B and C. About 26.9 million typhoid cases and more than 2 lakh deaths occur each year, with majority of the cases reported in Asia.[2] The incidence of typhoid varies substantially within Asia, with a very high incidence noted in India and Pakistan.[3] Low standards of living and poor hygiene practices have contributed to the disease burden and made India endemic to typhoid fever. For developing countries like India, it is a big public health problem as the sanitation and public health standards are poor. Back in the 19th century, Typhoid fever was an important cause of hospital admission and death in the overcrowded and unsanitary urban conditions of the Europe and United states.[4] The introduction of clean water and good sewage systems contributed to a dramatic decrease in the incidence of typhoid. Today most of the disease burden is seen in developing countries, where sanitary conditions are poor. The diagnosis of enteric fever on clinical ground alone is difficult as the presenting features are diverse and similar to those observed with other common febrile illnesses. Definite diagnosis requires the isolation of *S.typhi*/paratyphi from culture of blood, stool, urine, rose spot, bone marrow and gastrointestinal secretions. Bacteria can be isolated from blood in 80-97% of cases before use of antibiotics.[5] Prompt recognition with timely & appropriate antibiotics and other supportive measure can considerably reduce both morbidity and mortality and is important for favorable outcome. A major epidemic of

drug resistant typhoid fever was first reported in 1972 and subsequently resistance to all the first line drugs (chloramphenicol, cotrimoxazole & ampicillin) was reported. These were called as Multi Drug Resistant typhoid fever (MDRTF).[6] An increasing frequency of resistance has been reported from all parts of the world, but more so from developing countries.[7] Some strains have shown resistance to fluoroquinolones & 3rd generation cephalosporins, which is a matter of great concern.[8] In endemic areas such as India, classical signs and symptoms in enteric fever are not often seen.[9] This may be owing to the widespread and indiscriminate use of antimicrobials and antipyretics. Unusual manifestations lead to diagnostic dilemma and delay in diagnosis. With this background, we decided to study the clinical presentations, laboratory parameters and drug sensitivity of typhoid fever in a tertiary care setting, which most often caters to cases unsuccessfully treated elsewhere, so that appropriate antibiotic as indicated can be started and incidence of antibiotic resistance decreases. The first major epidemic of multidrug resistant *S. typhi* was reported in 1972.[10] in Mexico. Since then, an increasing frequency of antibiotic resistance has been reported from all parts of the world, but more so from the developing countries.[9] The uses of chloramphenicol, ampicillin and cotrimoxazole have become infrequent and quinolones have become the first line of treatment of typhoid fever. It is one of the common causes of fever in children with varied presentation and significant difference in the signs and symptoms compared to adults. The classic Widal agglutination test is one of the most utilized diagnostic tests for typhoid fever,

especially in developing countries. This study was conducted to evaluation of clinical and laboratory profile of typhoid fever in bihar region children.

Material and Methods

This prospective observational study was carried out in the Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India for 1 year. after taking the approval of the protocol review committee and institutional ethics committee.

Methodology

Total 170 Children aged below 18 years who presented to the Paediatric department with history of fever of more than 4-14 days duration were included in this study. Previously antibiotic treated patients and patients with proven localised infection were excluded. These cases were either Widal positive (Widal test TO Titer >1:100 or TH titre >1:200) or blood culture positive for Salmonella species. The cases which were discharged against medical advice and cases for which consent was not obtained were excluded from the study. Antibiotics were started in

each case after blood was drawn for Widal test and blood culture for Salmonella species. Each case was followed up clinically for improvement. For those cases which did not show improvement after 5 days of antibiotics, changes made according to the culture reports. Antibiotic sensitivity pattern was noted for culture positive cases. Cases were followed till discharge. The data collected was analyzed with respect to age, sex and presenting complaints.

Results

In this study, all the cases presented to OPD with a median of 4-14 days duration of fever. 105 cases (61.76%) had received antibiotics for a minimum period of 3-5 days prior to admission. Table 1 shows Out of 170 cases, 110 cases (64.71%) were males and 60 cases (35.29%) were females. Table 2 shows, most of the cases were aged between 6 and 12 years. 37 cases were below 6 years, representing 21.76%. 43 cases were aged above 12 years, representing 25.29%. 90 cases were aged between 6 and 12 years (52.94%). In all the above age groups male predominance was seen.

Table 1: Sex Distribution of patients

Sex	N=170	%
Male	110	64.71
Female	60	35.29

Table 2: Age wise distribution

Age(years)	N=170	%
0-6 years	37	21.76
6-12 years	90	52.94
12-18 years	43	25.29

Duration of hospital stay varied from up to two Week. As shown in Table-5, most of the cases (74.71%) stayed in hospital up to two Week after admission. 25.29% cases stayed up to one Week day in hospital. In these cases, fever persisted beyond one

Week. No mortality was observed during our study period. Although mild elevated liver enzymes were observed in some cases, no complications were seen in any case.

Table 3: Peak Temperature profile

Temperature in °F	No. of cases & (%)
99-101°F	24(14.12%)
101.1-103°F	130(76.47%)
103.1-105°F	16(9.41%)

Table 4: Total duration of fever

Fever duration (days)	No. of cases & (%)
4-7	73(42.94%)
8-14	97(57.06%)
>14	0 (0)

Table 5: Duration of hospital stay

Duration of hospital stay	No. Of cases	P-value
One Week	43 (25.29%)	0.17
More than one Week	127 (74.71%)	0.00

Typhoid fever presents with a wide range of symptoms. Due to the use of antibiotics prior to diagnosis, children may not present with typical symptoms. However, in our study, the most common symptom was fever (100%), followed by anorexia (61.76%), vomiting (44.12%), pain abdomen (20.59%), diarrhea (8.24%), headache (7.06%), and cough (5.89%).

Table 6: Common presenting symptoms

Presenting symptom	No. of Cases	P-value
Fever	170 (100%)	0.001
Anorexia	105(61.76%)	0.000
Vomiting	75 (44.12%)	0.001
Pain abdomen	35 (20.59%)	0.015
Diarrhea	14 (8.24%)	0.067
Headache	12 (7.06%)	0.88
Cough	10 (5.89%)	0.153

Table 7: Various physical findings

Signs	No. of Cases	P-value
Toxic look	124(72.94%)	0.001
Coated tongue	83(48.82%)	0.001
Hepatomegaly	74 (43.53%)	0.002
Splenomegaly	40 (23.53%)	0.050
Hepatosplenomegaly	30(17.65%)	0.081
Pallor	10(5.88%)	0.212

Coming to physical findings, the most common sign we observed was toxic look in 72.94% of the cases followed by coated tongue in 48.82%, hepatomegaly 43.53%, splenomegaly 23.53%, hepatosplenomegaly in 17.65% of cases and pallor in 5.88% of cases.

Table 8: Laboratory parameters

Laboratory parameters	Abnormal values	No. of cases	P-value
Hemoglobin	Anemia (Hb <11g%)	40 (23.53%)	0.032
Total leukocyte count	Leucocytosis (>11000cells/mm ³)	36 (21.18%)	0.027
	Leucopenia (<4000cells/mm ³)	55 (32.35%)	0.00
Polymorphs	Neutropenia	66 (38.82%)	0.00
	Neutrophilia	57 (33.53%)	0.00
Eosinophils	Eosinophilia	10 (5.88%)	0.18
	Eosinopenia	80 (47.06%)	0.00
Platelets	Thrombocytopenia	26 (15.29%)	0.01
SGOT	Elevated SGOT	23 (13.53%)	0.22
SGPT	Elevated SGPT	24 (14.12%)	0.24
Widal titres	TO >1:100	158 (92.94%)	0.00
	TH >1: 200	127 (74.71%)	0.00
Blood culture positive	Salmonella	40 (23.53%)	0.01

Table 8 depicts the laboratory parameters. Anemia found in 40 (23.53%) cases, leucopenia and leucocytosis was observed in 55(32.35%) cases and 36(21.18%) cases respectively. Neutropenia found in 66(38.82%) cases and neutrophilia was found in 57(33.53%) cases. Eosinopenia was seen in 80(47.06%) cases, eosinophilia in 10(5.88%) cases and thrombocytopenia in 26(15.29%) cases. SGOT levels was elevated (>200IU/ml) in 23(13.53%) cases and SGPT (>200IU/ml)

in 24(14.12%) cases. The elevated levels of liver enzymes lasted only few days. There were no complications observed during our study period. *Salmonella typhi* O titres >1:100 was seen in 158(92.94%) cases and TH titres >1:200 in 127(74.71%) cases. Blood culture positive for *Salmonella typhi* noted in 40(23.53%) cases. Out of 170 cases only 71 cases had been immunized with typhoid vaccine. All of them had taken typhoid polysaccharide vaccine more than 3 years prior to illness.

Table 9: Antibiotic sensitivity pattern

Drug	Sensitivity	P-value
Ceftriaxone	93%	0.000
Cefixime	91%	0.000
Ofloxacin	89%	0.000
Chloramphenicol	75%	0.000
Cefotaxime	72%	0.004
Azithromycin	47%	0.106
Ciprofloxacin	76%	0.001
Amoxicillin	59%	0.043

Significant p<0.01

Table 9 depicts antibiotic sensitivity patterns among culture positive cases. the most common sensitivity was seen in all

the cases ceftriaxone (93%) and followed by cefixime(91%) , ofloxacin (89%), ciprofloxacin (76%), chloramphenicol (75%), cefotaxime (72%), amoxicillin (59%) and azithromycin in (47%). *S. typhi*

was more sensitive to ceftriaxone, cefixime followed by ofloxacin. Least sensitivity was seen with azithromycin.

Discussion

Assessment of a child presenting with fever without an obvious focus is a challenge to most of us. To determine the etiology and plan the management in the first few days is always difficult and yet imperative. In view of the anxiety of the parents, most pediatricians have the tendency to start some antibiotics before any real clue about the etiology irrespective of the fact that most of these fevers might just be of viral etiology. In enteric fever this initial antibiotic might modify the course of the disease and pose significant difficulty in interpretation of lab investigations. The definitive diagnosis of typhoid fever requires a confirmed diagnosis based on the blood or bone marrow culture. However, blood culture has several limitations including amount of blood required due to low levels of bacteremia and prior antibiotic use.[11] All the cases presented to OPD with a median of 7-10 days duration of fever.

105 cases (61.76%) had received antibiotics for a minimum period of 3-5 days prior to admission. Out of 170 cases, 110 cases (64.71%) were males and 60 cases (35.29%) were females. Similar results were reported in other studies.[12] most of the cases were aged between 6 and 12 years. 37 cases were below 6 years, representing 21.76%. 43 cases were aged above 12 years, representing 25.29%. 90 cases were aged between 6 and 12 years (52.94%). In all the above age groups male predominance was seen.

A study done by R Modi et al also reported maximum incidence of typhoid in the age group 6 to 10 year.[13] Another study also reported maximum number of cases in the age group above 5 years.[14] The duration of hospital stay varies, with maximum number of cases staying in hospital between 7-14 day. Cases were discharged after 3 consecutive days of

afebrile period without antipyretics. These results were in accordance with study done by Hyder et al.[15] We observed high incidence of typhoid fever in lower class, lesser in middle class society and least in higher class. This can be explained by differences in drinking water sources and hygienic practices like hand washing and sanitary latrine facilities. Similar results were reported in other study.16 in our study; the most common symptom was fever (100%), followed by anorexia (61.76%), vomiting (44.12%), pain abdomen (20.59%), diarrhea (8.24%), headache (7.06%), and cough (5.89%). A study done by Sinha A et al.[17] Kapoor JP et al also reported similar results.[18] Other studies also showed similar clinical picture.[19-21] Contradictory to this, a study done by Joshi et al reported headache as the most common symptom next to fever.[22] In our study the most common sign we observed was toxic look in 72.94% of the cases followed by coated tongue in 48.82%, hepatomegaly 43.53%, splenomegaly 23.53%, hepatosplenomegaly in 17.65% of cases and pallor in 5.88% of cases. Study done by Laishram et al reported coated tongue (80%) as the most common sign followed by Hepatomegaly (76%) and splenomegaly (38%).[23] In other study they had reported relative bradycardia and hepatomegaly as the most common sign.[24]

During our study, all cases were positive for Widal. Blood culture was positive in 23.53% of cases. Other study also reported 16% culture positive cases.[15] A study done by Banu et al also reported 28% culture positive cases.[24] Due to prior use of antibiotics, the culture positive cases are decreasing. Thus, need for relay on other serological tests for diagnosis of typhoid exists. Study done by Modi et al reported 97% Widal positive cases.[13] Anemia was seen in 23.53% of cases. The other studies reported little higher percentage of anemias. A study done by Raj C et al reported anemia in 41.8% of patients and

Lefebvre et al reported anemia in 78% of cases.[25,26] in our study Leucocytopenia and Eosinopenia found in 55 (32.35%) and 80(47.06%) respectively. Similar results reported in Lefebvre et al.[26] Although leucocytosis and eosinophilia are rare in typhoid, our study reported leucocytosis in 36 (21.18%) of cases and eosinophilia in 10 (5.88%) cases respectively. Thrombocytopenia was found in 26(15.29%) of cases. SGOT levels was elevated (>200IU/ml) in 23(13.53%) cases and SGPT (>200IU/ml) in 24(14.12%) cases. The other study reported elevated liver enzymes in 70% of cases.[27]

Antibiotic sensitivity was similar to other studies. Most of the culture positive cases showed sensitivity to ceftriaxone, cefixime, ofloxacin, ciprofloxacin. Similar sensitivity pattern reported in other study.[22] However sensitivity pattern varies from place to place. Other studies showed return of sensitivity pattern with chloramphenicol, cotrimoxazole, amoxicillin.[20,28,29] A study done by Mishra et al reported 100% sensitivity to azithromycin.[30] In our study the sensitivity to azithromycin was 47%. A Study done by Hyder et al reported 100% sensitivity to ceftriaxone and ciprofloxacin.[15]

Conclusion

Fever, malaise, anorexia, vomiting, chills, headache, coated tongue, diarrhea and organomegaly are the common clinical manifestations of enteric fever. Normal to raised leukocyte count is more common, however, neutropenia and eosinopenia may be a prominent finding.

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