ISSN Print: 2664-7591
ISSN Online: 2664-7605
Impact Factor: RJIF 5.2
IJAN 2023; 5(2): 41-45
www.pharmaceuticaljournal.in
Received: 25-07-2023
Accepted: 01-09-2023

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Clinical profile of enteric fever with special reference to blood culture and serum Widal in a tertiary care center in India

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DOI: https://doi.org/10.33545/26647591.2023.v5.i2a.61

Abstract
Objective: To study clinical profile of enteric fever and to analyze clinical features, laboratory results, Serum Widal test, blood culture and antibiotic sensitivity, the response to treatment and outcome.
Materials and Methods: Prospective, observational study at BJ Medical College, Civil Hospital, Ahmedabad from 1st August, 2018 to 31st July, 2020.
Inclusion Criteria:
- Age between 6 months and 12 years diagnosed as having Enteric fever with
- Serum Widal titer O/H/both O and H >= 1:160 and/or blood culture showing Salmonella typhi

Methodology: After written informed consent from the guardian of the patient and approval by the Institutional Ethics Committee, detailed history was taken according to predefined proforma along with complete physical examination. Necessary laboratory investigations were done and blood culture was taken by proper method. Appropriate treatment was instituted as per hospital protocol. All cases were observed for progress in the ward and observations were noted in the proforma.
Statistical Methods: Quantitative data was expressed in mean, median and mode. Qualitative data was expressed in percentage. All analysis was carried out using Microsoft Excel and social statistics calculator.
Results: Clinical profiles of 135 patients were studied, constituting 1.3% of total admissions during the period of study. Widal test was positive in 92.5% while blood culture in 17%. Most patients showed sensitivity to third generation cephalosporins. All the patients were discharged.
Conclusion: Blood culture is the gold standard for diagnosis and helps plan treatment as per antibiotic sensitivity while Serum Widal lacks sensitivity and specificity. Early diagnosis and prompt treatment with health education and encouragement for Typhoid vaccine is necessary.

Keywords: Enteric fever, blood culture, serum Widal

Introduction
Enteric fever is caused by Salmonella typhi, S Para typhi A and S Para typhi B and humans are the only hosts. Disease results by the ingestion of contamination of food and water by chronic carriers and is more common in developing countries like India. Around 5 million cases occur annually in India with 10% of cases in the infant age group where diagnosis may be difficult and mortality is higher. A major problem has been the emergence of plasmid encoded multi drug resistance ranging 17-90% as reported by various studies, especially to the quinolones. Children constitute 40-50% of MDR typhoid fever with higher case fatality rates [1]. Data for typhoid fever in India reported in 2013 shows 1.53 million cases and 361 deaths, maximum cases reported from Bihar followed by Andhra Pradesh. Other states with large number of cases include, Uttar Pradesh, Madhya Pradesh, West Bengal, Maharashtra and Odisha [2].
In present study, the clinical profile of paediatric patients presenting with Enteric Fever has been studied and its association with blood culture and Widal positivity is determined.

Materials and Methods
- Study Design: Prospective, observational
- Study Area: Paediatric patients admitted in Civil Hospital, Ahmedabad

- Study Duration: 1st August, 2018 to 31st July, 2020.

All patients clinically suspected of having enteric fever as defined by IDSP [3]
Any patient with fever for more than one week and with any two of the following:

- Toxic look
- Coated tongue
- Relative bradycardia
- Splenomegaly
- Exposure to confirmed case
- Clinical presentation with complications e.g. GI bleeding, perforation etc.

Fulfilling any one of the following inclusion criteria were included in the present study.

- Age between 6 months and 12 years diagnosed as having Enteric fever with
- Laboratory result: Serum Widal titer more than 1:80 and/or blood culture result showing Salmonella typhi.

Approval was taken from Institutional Ethics Committee. Written and Informed consent was taken from the patient's guardians. Detailed history was taken according to predefined proforma along with complete physical examination and anthropometry, useful laboratory investigations were sent and appropriate treatment was instituted.
All cases were observed for progress in the ward and observations were noted in the proforma.

The investigations were carried out as below

- CBC
- RFT and LFT
- S Widal (Repeat S Widal after 48 hours of first test to look for rising titer. A repeat Widal was also carried out within 5 days of 1st negative test in case of a strong clinical suspicion)
- Blood culture and sensitivity
- ECG (as and when required)
- USG Abdomen and CXR and AXR as and when required
- Other investigations as and when required

Widal test for somatic O antigen and flagellar H antigen was done using slide agglutination method.
Sample for Blood Culture was collected before starting antibiotics by proper aseptic measures with a blood: broth ratio of 1:5 to 1:10. Blood Culture was performed using BACTEC or BacT Alert 3D automatized blood culture systems. The culture tubes in which some colonies were observed were centrifuged at 3000 rpm for 3-5 minutes and then subculture was performed into blood and EMB agar. Positive colonies were identified by Vitex 32 Biomeriux autmoized system.

Therapeutic Regimen

In Ceftriaxone was used as a first line drug and was given in a dose of 100 mg/kg/day in two divided doses. Second line antibiotics were added to those who did not respond by day 5.
2nd line drugs were one of the below:

- Azithromycin
- Cefotaxime
- Meropenem
- Ampicillin/Cotrimoxazole, only if blood culture showed sensitivity

Response to treatment was noted as below:
No Response: no change in pyrexia or appearance of complication
Good response: gradual defervescence in pyrexia and return of appetite.
Treatment was given for a total duration of 14 days.
A proper health education regarding the disease and its preventive measures like proper sanitation, hygiene and vaccination was provided to all patients and they were motivated for the same.
Patients were called for regular follow up and were monitored on follow up. Typhoid vaccine (VI polysaccharide) was given on follow up after 4 weeks.

Results

There were total 10376 admissions in Paediatrics between 1st August, 2018 and 31st July, 2020. Out of them, there were 135 cases of Enteric fever identified by the inclusion criteria. Thus, proportion of patients presented to Civil Hospital, Ahmedabad with Enteric Fever was 1.3%. In the present study, 49.6% of cases of Enteric Fever were found in the age group of 5-10 years, followed by 35.2% cases seen in less than 5 years age group and 12% cases seen in more than 12 years age group. This indicates less restrictive nurturing and increase in unhygienic food practices with increasing age. 59.26% of the patients belonged to Lower socio-economic class according to Modified Kuppuswamy Classification of 2019, 24% of patient's belonged to upper lower socio-economic class and 16% of patients belonged to upper middle socio-economic class of Modified Kuppuswamy classification of 2019. None of the patients in present study belonged to upper socio-economic class. This indicates increased association with poor sanitation and unhygienic living environment as observed among the lower socio-economic classes. Also since the institute is a Tertiary care centre located in urban slum area, major chunk of patients here are from lower socio-economic class. There were no patients in the study who had a history of Enteric fever in close family contacts.

Table 1: Symptoms of Enteric fever at time of Admission

Symptoms	No. of Patients = 135	%
Fever	135	100%
Anorexia	103	76%
Abdominal pain	86	64%
Vomiting	74	55%
Headache	66	49%
Diarrhoea	40	30%
Abdominal Distention	18	13%
Constipation	16	12%
Seizures	6	4%

All the patients presented with Fever at the time of admission. 55% of the patients had complaint of fever for 5-10 days at the time of admission.20% had fever for 10-15 days, 15% had fever for more than 15 days while 10% had fever for less than 5 days. This indicates increased use of medical assistance and in-patient admissions when patients are not able to control symptoms without patient treatments or over the counter medications after 5 days of illness. The classical fever pattern of step ladder variety was seen among 17% of patients.30% patients had a mixed type of fever pattern.25% had

intermittent fever and 21% had continuous fever. Remittent fever was seen only in 7% of patients. The use of anti-pyretic medications during hospitalization modifies the fever pattern observed in the course of treatment. 76% patients presented with anorexia and 64% presented with abdominal pain, 55% had vomiting and 49% presented with headache.30% patients presented with diarrhea. Abdominal distension (13%), constipation (12%) and seizures (4%) were the least common symptoms observed in the present study.

Table 2: Clinical Signs at the time of Admission

Signs	No. of Patients (n= 135)	%
Toxic Look	96	71%
Pallor	60	44%
Coated Tongue	50	37%
Hepatomegaly	23	17%
Murmur	16	12%
Splenomegaly	14	10%
Hepatosplenomegaly	14	10%
Relative Bradycardia	13	10%
Icterus	11	8.14%
Tachypnoea	5	4%
Altered Sensorium	4	3%
Oedema	3	2%

71% of patients had toxic look at the time of admission and pallor was present in 44% of patients. 37% of patients had coated tongue and 17% had hepatomegaly. Relative bradycardia was seen in 10% of patients. 10% of patients each had hepatosplenomegaly and splenomegaly. Icterus was seen in 8% of patients.

Table 3: Complications in patients with Enteric Fever

Complication	Number n= 135	%
Hepatitis	11	8%
Myocarditis	4	0.7%3%
Bronchitis	3	2%
Intestinal Obstruction	2	1.5%
Intestinal Perforation	1	0.7%
Right Knee Salmonella Arthritis	1	0.7%
Enteric encephalopathy	1	0.7%

In the present study, the most common complication seen in patients with Enteric Fever was Hepatitis, followed by myocarditis. Features of bronchitis were present in 3 patients and intestinal complications were also seen in 3 patients with one of them having intestinal perforation. Enteric encephalopathy was seen in only 1 patient and arthritis was seen in 1 patient as well.

Most common co-morbid condition observed in patients with Enteric Fever was UTI with 11.85% patients and its most common causative organism was E. coli, followed by Klebsiella pneumonia. 2.2% patients had concomitant lower respiratory tract infection in form of lobar pneumonia.2 patients had COVID-19 along with Enteric fever. Concomitant viral hepatitis of feco-oral origin was seen in a total of 3 patients and 1 patient had Dengue and Enteric co-infection. There was one patient with Sickle cell Anemia who presented with Salmonella bacteremia. Out of total 135 patients, 60 had normal nutritional status. Out of the 45 patients belonging to less than 5 years age group, there were 4% patients with PEM grade I, 7% had PEM grade II, 2% had PEM grade III and 1% had PEM grade IV. Remaining 90 patients of age equal or more than 5 years had 22% with under nutrition and 19% with severe under nutrition. Severe anemia of nutritional origin was seen among 11 patients out of which 3 had congestive cardiac failure. Out of 135 patients in the present study, 60 (44%) patients had pallor at the time of admission. Laboratory evidence of anemia was seen in 91 (67.4%) patients. Grading of anemia was done according to WHO classification of anemia. Leucopenia – TLC <=4000 was seen in 17.8% while Leucocytosis – TLC >=7000, was observed in 17.8%. Thrombocytopenia- PLT <=150000 was seen in 34% patients and Thrombocytosis- PLT >=400000, was seen in 17% patients. 33.3% patients had eosinopenia.

Table 4a: Serum Widal Analysis done 48 hours apart

Widal Titre		
Antigen O	**At time of Admission**	**48 Hours after first titre**
1:80	0	0
1:160	27	11
1:320	96	114
Widal Titre		
Antigen H	**At time of Admission**	**48 Hours after first titre**
1:80	0	0
1:160	28	11
1:320	94	114

Serum Widal test was positive in 125(92.5%) of patients against blood culture positivity seen among 23 (17%).

Table 4b: Blood Culture Analysis

Blood Culture	No of patients	Percentage
Positive	29	21%
Negative	106	79%
Organism isolated	No of Patients	Percentage
S. Typhi	23	79.31%
Others	6	20.69%

Out of total 135 patients of Enteric Fever, Blood Culture was positive among 29 patients and Salmonella typhi was isolated from 23 out of the 29. Other organisms included CONS, Staph aureus, *E coli* and *Bacillus subtilis*.

Defervescence was considered when patients' core temperature dropped below 99.7 degree F after initiation of therapy and remained so for at least three days without use of antipyretics. 44% of patients had fever defervescence within 3-5 days of admission, 38% had fever defervescence within 5-10 days of admission. 15% patients showed defervescence within 3 days after admission indicating erratic use of over the counter and outpatient based medications before admission. 3% patients needed 10-14 days to develop defervescence. Mean duration of achieving defervescence was 4.5 days.

In the present study, 68.88% patients responded to use of third generation cephalosporins only. 13.33% patients responded to combination of third generation cephalosporins and ofloxacin while 8.89% required combination with azithromycin.5.9% required usage of both, ofloxacin and azithromycin, along with third generation cephalosporins.2.9% patients responded to antibiotics other than cephalosporins, azithromycin and Ofloxacin.

51% patients had less than 7 days of admission while 41.5% had been admitted for 7-14 days. Only 7.41% patients had been hospitalized for more than 14 days. Average days of hospitalization were 7.No mortality was seen among the 135 patients of enteric fever.80% patients had uncomplicated Enteric Fever. 20% had complicated Enteric fever, including co-infections and relapse. None of the child was vaccinated

before the disease. All the patients interviewed were educated regarding proper hygiene and sanitation and explained regarding the importance of the same.

Table 5: Antibiotic Sensitivity in blood culture of Salmonella typhi

Antibiotic	Sensitive	Intermediate	Resistant
Ceftriaxone	17	4	2
Cefotaxime	15	5	3
Cef Sulbactam	16	5	2
Cefepime	21	1	1
Ofloxacin	19	3	1
Norfloxacin	16	2	5
Ciprofloxacin	17	2	4
Imipenem	21	2	0
Meropenem	21	2	0
Gentamycin	14	4	5
Amikacin	16	6	3
Azithromycin	19	4	0
Cotrimoxazole	4	4	15
Amoxicillin	9	5	9
Nalidixic Acid	3	5	15
Chloramphenicol	3	2	18

Limitation of Present Study

- Limited period of study and small sample size hamper the extrapolation of results of this study to general population.
- Several of children had received IV or oral antibiotics before admission which affected the yield of blood culture.
- The antibiotic susceptibility was based on clinical response rather than blood culture report.
- 27.4% of children were too lost to follow-up.

Discussion

Enteric fever is caused by Salmonella typhi, S Para typhi A and S Para typhi B. around 5 million cases occur annually in India. 10% of cases occur in the infant age group when diagnosis may be difficult and mortality is higher. A major problem in the last two decades of the twentieth century has been the emergence of plasmid encoded multi drug resistance ranging 17-90% as reported by various studies, especially to the quinolones. Children constitute 40-50% of MDR typhoid fever with higher case fatality rates [1].

Salmonellae are Gram negative, flagellate, non-spore forming, non-encapsulated, aerobic and facultative anaerobic bacilli belonging to Enterobacteriaceae family [7].

S. typhi is highly adapted to infection of humans to the point that it has lost the ability to cause transmissible disease to other animals. Man is the only known reservoir of infection *viz*. cases and carriers [5]. Typhoid fever is mainly transmitted via feco-oral route or urine-oral route. This may take place directly or indirectly.

Incubation period of the disease is usually 7 – 14 days, but it may be as short as 3 days to as long as 30 days [5].

The clinical features fever may vary depending on the age of the patient [6]. The clinical spectrum ranges from a mild febrile illness with low grade fever, malaise, and dry cough to a lethal disease due to multiple complications. The severity and outcome of the infection depends on the duration of the fever before starting treatment, antimicrobial agent used, age of the patient, previous exposure, immunization status, virulence of the strain, and size of the inoculum ingested, immune status, HLA type and history of concomitant drug intake like H2 receptor blockers. People living with HIV and AIDS are at increased risk for typhoid fever.

Enteric fever presents as high-grade fever with different features like myalgia, abdominal pain, hepatomegaly, splenomegaly and loss of appetite. Children can have the loose stools in early stage and may be followed by constipation. It is difficult to differentiate the typhoid fever from other endemic infections like malaria, dengue fever, leptospirosis and acute viral hepatitis in the early stages of typhoid fever. Following recovery, up to 5% of patients become chronic carriers [7].The mortality rate is less than 1% if correct treatment is given. It is around 20-30%, if not treated. The most important reason for poor outcome is almost certainly a delay in starting antibiotic treatment. Relapse rate in typhoid fever is usually around 2 to 4% [1].

Since typhoid fever is a multisystem disease, complications have been reported in every system of the body. Complications occur in 10 to 15% of patients. Most of them develop during second or third week of fever [8, 9, 10].

Blood cultures are the gold standard diagnostic method for diagnosis of enteric fever. The sensitivity of blood culture is highest in the first week of illness and reduces with advancing illness, almost 90% in first week, 75% in second week, 60% in third week and 25% in fourth week. Overall sensitivity is around 50% but drops considerably with prior antibiotic therapy [11].

The Widal test as a diagnostic modality has suboptimal sensitivity and specificity. It can be negative in up to 30% of culture proven cases of typhoid fever. Sub optimal sensitivity results from negativity in early infection, prior antibiotic therapy and failure to mount an immune response by certain individuals. Risk of anamnestic reaction with Widal test further decrease its specificity. Notwithstanding these problems, the Widal test may be the only test available in certain resource poor settings for diagnosis of typhoid fever. So proper history and strong suspicion is necessary before prescribing this test [11].

Prevention is based on ensuring access to safe water and by promoting safe food handling practices. Health education is paramount to raise public awareness and induce behavior change.

Conclusion

Enteric Fever is a common illness among pediatric population in endemic country like India, more prevalent among lower socio-economic class. Blood culture is the gold standard method for diagnosis of Enteric Fever. Serum Widal test lacks sensitivity as well as specificity for diagnosis of Enteric Fever. Third generation Cephalosporins, fluoroquinolones and macrolide antibiotics are effective against S. typhi. Early diagnosis and prompt treatment with health education regarding hygiene and sanitation and encouragement for Typhoid vaccine can significantly reduce its incidence and complications

References

1. Ghosh A, Mitra M. Typhoid Fever. In: Gupta P, Menon P, Ramji S, Lodha R, editors. PG Textbook of Pediatrics. 2nd ed. Delhi. Jaypee Brothers. Medical Publishers Pvt. Ltd.; c2014. p. 1276-80.
2. Govt. of India National Health Profile 2013, DGHS, Ministry of health and Family Welfare, New Delhi; c2014.

3. Balasubramaniam P, Hira S, Reddy K. Operational pathways for integrating national disease control programmes for universal health coverage. Available at SSRN 2821364; c2014.
4. Bhutta ZA. Salmonella. In: Kliegman RM, Stanton BF, St Geme III JW, Schor NF, editors. Nelson Textbook of Pediatrics. 20th ed. Elsevier; p. 1382-8.
5. Park K. Epidemiology of Communicable Diseases. In: Park's Textbook of Preventive and Social Medicine. 23rd ed. Jabalpur: Bhanot Publishers; c2015. p. 234-8.
6. Feigin RD, Cherry JD, Kaplan SL, Harrison GJ, Feigin. Cherry's text book of pediatric infectious diseases. Saunders and Elsevier. 6th edition; c2017. p. 1572-1577.
7. Textbook of Pediatric Infectious diseases. IAP; c2013. p. 217-223.
8. Ramaswamy G, Janakiraman L, Thiruvengadam V, Malathy S. Profile of typhoid fever in children from a tertiary care hospital in Chennai- South India. Indian J Pediatrics. 2010;77:1089-1092.
9. Jagadish K, Patwari AK, Sarin SK, Prakash C. Hepatic manifestations in typhoid fever, Indian Pediatrics. 1994, 31.
10. Osuntokun BO. Neuropsychiatric Manifestations of Typhoid Fever in 959 Patients. JAMA Neurology. 1972;27:1.
11. Shah AK. Common Bacterial Infections. In: Parthasarathy A, Kundu R, Yewale VN, editors. Textbook of pediatric infectious diseases. 2nd ed. Jaypee Brothers Medical Publishers (P) Limited; c2019. p. 241-6.
12. WHO. Treatment of Typhoid Fever. Background document: The diagnosis, prevention and treatment of typhoid fever. In: Communicable disease surveillance and response: Vaccines and biologicals, Geneva, World Health Organization; c2003. p. 19-23.
13. Oguntoke O, Aboderin OJ, Bankole AM. Association of water-borne diseases morbidity pattern and water quality in parts of Ibadan City, Nigeria. Tanzania Journal of health research; c2009. p. 11(4).