

A Study on Clinical, Laboratory Profile and Drug Sensitivity Pattern in *Salmonella* Positive Patients

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Abstract

Introduction: Enteric fever is endemic and is a major public health burden in India. This study is conducted to assess the change in clinical presentation, morbidity and the sensitivity pattern to the drugs used in enteric fever.

Aim: (1) To study the clinical presentation, laboratory features and sensitivity pattern of *Salmonella* positive patients in blood culture, (2) to analyze the treatment, complications, morbidity, and mortality related to the disease.

Materials and Methods: It is a prospective observational study conducted in a Tertiary Care Medical College Hospital at Chennai between May 2014 and May 2016 in patients above 18 years of age who tested positive for *Salmonella* in blood culture. From the patient, details of history, clinical examination, investigations, and treatment were collected. Their antibiotic sensitivity pattern was recorded. Patients were followed up throughout the course of hospital stay and complications were also recorded. Defervescence of fever after antibiotics was also recorded.

Results: A total of 76 patients were studied who were blood culture positive. Fever with vomiting, loose stools, headache, and cough were the common clinical manifestations of enteric fever. Absolute eosinopenia, mildly elevated liver enzymes with normal leukocyte count or leukopenia with neutrophilia can be a pointer for enteric fever. Nalidixic acid resistance (97.4%), return of susceptibility to chloramphenicol (98.7%), co-trimoxazole (98.7%), and ampicillin (88.2%) are other important findings in this study.

Conclusion: There is a trend toward emerging resistance to 3rd generation cephalosporins due to increased defervescence time is seen in patients treated with cephalosporins. Common complications two decades ago causing high mortality and morbidity has reduced. However, other atypical presentations and complications involving other system sparing gastrointestinal system should be kept in mind due to antibiotic exposure prior hospitalization.

Key words: Antibiotic susceptibility, Fever defervescence, Nalidixic acid resistance, *Salmonella*

INTRODUCTION

Enteric fever is a major public health burden in India, and estimated cases range from 11.9 to 26.9 million and 129,000-217,000 deaths worldwide each year. The hallmark feature of enteric fever includes fever and gastrointestinal (GI) symptoms such as abdominal pain, vomiting, and loose stools which occur in varying frequency. High

prevalence of drug resistance, inadequate and inappropriate antibiotic exposure leads to various atypical manifestations of the disease and high index of suspicion is required for the diagnosis. *Salmonella paratyphi* A is thought to cause milder disease than *Salmonella typhi* which is also becoming atypical and severe. Resistance to nalidixic acid which is an early generation quinolone can serve as a marker for decreased susceptibility to fluoroquinolones. This study is conducted to assess the change in clinical presentation, morbidity and the sensitivity pattern to the drugs used in enteric fever.

Aim of the Study

- To study the clinical presentation, laboratory features and sensitivity pattern of *Salmonella* positive patients in blood culture.

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- To analyze the treatment, complications, morbidity and mortality related to the disease.

MATERIALS AND METHODS

Inclusion Criteria

1. Patients aged ≥ 18 years.
2. Both males and females.
3. All cases of *Salmonella* positive in blood culture. Includes all species of *Salmonella* such as *typhi*, *paratyphi*, and *typhimurium*.
4. Patients associated with other causes of fever such as malaria, dengue with *Salmonella* positive in blood culture.
5. Stool, urine, and bone marrow positive for *Salmonella* species.

Exclusion Criteria

1. Patients aged < 18 years.
2. Only widal or other serological tests for enteric fever positive cases with sterile blood culture.
3. Outside culture positive cases are not included.

It is a prospective observational study conducted in a Tertiary Care Medical College Hospital at Chennai between May 2014 and May 2016. After appropriate informed consent from the patient, details of history, clinical examination, investigations, and treatment were collected. Their antibiotic sensitivity pattern especially for ampicillin, chloramphenicol, co-trimoxazole, tetracycline group of antibiotics, sensitivity to nalidixic acid, quinolones including ciprofloxacin, norfloxacin, cephalosporins, and azithromycin was recorded. Patients were followed up throughout the course of hospital stay and complications were also recorded. Defervescence of fever after antibiotics was also recorded.

RESULTS

Demographics

In our study, a total of 76 patients were studied of which males predominated with 78.9% of the total study population, i.e., 60 patients, and females comprised 21.1% which was 16 patients. Most patients were from 19 to 40 age group (86.9%) and the 41-60 years' age group (10.5%).

In our study, most patients compromised 1-7 days of fever group (68.5%), fever of 8-14 days comprising 19.7%. Most patients took an antibiotic before admission comprising 67.1%. Most common clinical sign seen in our study was relative bradycardia comprising 44.7%. Unusual manifestations such as polyarthritits, crepitations, oral candidiasis, and parotid swelling were seen.

Laboratory Profile

Mean hemoglobin was 12.599, mean total count was 5488.158 cells per cubic mm, and average platelet count was 1,65,140. On analyzing the complete blood cell count, anemia was seen in 17.1% of the patient. Leukocyte count was normal in most of the patients (80.3%). Neutrophilia and eosinopenia were seen in a significantly higher number of patients in about 98.7% and 89.5%, respectively. Thrombocytopenia was seen in 27.6% of patients which became normal on treatment. Acute kidney injury (AKI) was seen in 8 patients out of whom 6 patients had an increase in blood urea nitrogen too, who also had symptoms of GI loss and clinical signs of dehydration consistent with prerenal AKI. On comparing the baseline liver function test, it was noted that the average aspartate aminotransferase test and ALT were 3 times the baseline values.

Ultrasound Findings

The most common ultrasound abdomen findings were normal in 56.6%, mild splenomegaly in 22.4% of patients, mild hepatomegaly in 6.6% of patients, and mild hepatosplenomegaly in 6.6% of patients.

Widal Test and Culture

Widal test was done only in 40 patients out of 76 who presented with fever duration of more than 7-10 days. In that positive results were seen in only 35% of patients. Majority of culture positive patients were *S. typhi* positive accounting for 81.6%.

Antibiotic Sensitivity Pattern and Time to Fever Defervescence

There is a high prevalence of nalidixic acid resistance in our study which was 97.4% and the return of sensitivity to ampicillin (88.2%), chloramphenicol (98.7%), co-trimoxazole (98.7%), and tetracycline (98.7%). Empirical treatment was started in 27 patients. Fluoroquinolones though started empirically in 16 patients, it was changed to cephalosporins after the culture report due to nalidixic acid resistance.

Time to defervescence or clinical response was defined as the time taken from the initiation of antibiotic to the time in days when temperature remained below 37.5°C for at least 24-48 h. Time to defervescence for patients treated with ceftriaxone was 3.86 days (range of 2-7 days). Azithromycin was added as a second line agent if the patient takes longer time for defervescence mostly more than 3-4 days. Hence, mean defervescence time is higher in combination therapy accounting 4.96 days.

Complications

Most common complication seen in our study was AKI accounting to 8% of patients.

DISCUSSION

A total of 76 culture positive enteric fever were collected during the study period. Fever was present in all patients. Most patients presented with fever duration of 1-7 days (68.5%). Only 10% had fever more than 2 weeks duration. Mean duration of fever was 8.66 days (range 2-60 days). This is similar to that seen in Gupta *et al.*¹ (8.8 days) and Jog *et al.*² (7 days). Very prolonged fever lasting for 60 days was seen in one patient which was unusual for enteric fever. Almost most of the patients showed the intermittent type of fever which was due to the use of antipyretics and antibiotics. No case in this study had step ladder type of fever, and this finding is same as reported by Pandey *et al.*³ and Kapoor *et al.*⁴

GI symptoms such as vomiting and loose stools were present only in 34.2% and 31.6 %, respectively. This was similar to the study conducted by Gupta *et al.*¹ (vomiting 33.3% and loose stools 24.7%) and Jog *et al.*² (vomiting 42% and loose stools 31%). None of the cases had pea soup diarrhea which is typical of enteric fever. Burning micturition is an atypical presentation which was seen in 10.5% of a patient similar to that seen in a study by Dutta *et al.*⁵ (15.6%). Cough was seen in 15 patients (19.7 %) out of which 7 had mucoid expectoration. 67.1% of patients took an antibiotic before admission. The usual perception by the clinicians that culture positivity falls with prior use of antibiotics proves wrong in our study and recommends to send blood culture in suspected enteric fever even if the patient is on antimicrobials.

Relative bradycardia was observed at admission in 44.7% of patients. Clinically nontender, mild splenomegaly was present in around 7.9% of patients, with mild hepatomegaly being present in 3.9% of patients and mild hepatosplenomegaly in the only one patient. Unusual presentations include hypotension (1.3%), oral candidiasis (1.3%), parotitis (1.3%), pneumonia (1.3%), and reactive arthritis (2.6%). No other cause of these manifestations could be found.

One patient had hypotension which was secondary to GI loss. Hypotension in an enteric fever should raise the suspicion of ileal perforation or rarely cardiac manifestations like carditis or rhythm abnormalities. Hypotension without perforation is uncommon in enteric fever as evidenced by Chandrasekar *et al.*⁶ and Gupta *et al.*¹

Oral candidiasis was reported in one patient who was HIV negative and did not have any immunocompromised state. This is similar to a case reported by Claudia Colomba *et al.* Typhoid fever causes a transient immunodepression state evidenced by transient fall in CD4 cell count.

One patient had painful parotid enlargement with no evidence of abscess formation. Parotitis with abscess has been reported in HIV patient in a case report from Moser *et al.* Unlike this case report our patient was HIV negative and did not have any immunocompromised state and patient also responded well to treatment. Two patients had features of polyarthritis. Investigations for other causes of polyarthritis were negative and synovial aspiration was also reactive fluid.

Anemia was present in 17.1% with normal hemoglobin in 82.9%. Total leukocyte count was in normal range in around 80.3%. Leukopenia was seen in 19.7%. None of the patients had leukocytosis on admission. Mean leukocyte count was 5488.15. Neutrophilia was present in 98.7%, and eosinopenia was present in 89.5% of patients. Absolute eosinopenia can be used a pointer for enteric fever if complete blood count is available similar to Deshmukh *et al.* (71.4%) and Jog *et al.*² (77%). Thrombocytopenia was seen in 27.6% of patients which became normal on treatment. Mean platelet count was 1, 65, 140. Thrombocytopenia was comparatively more common compared to the previous studies like Chandrasekar *et al.*⁶ which had 13.4%.

Pancytopenia which occurs due to bone marrow suppression in enteric fever is less common and was seen in 2 of our 76 patients (2.6%). This is similar to the finding reported by Gupta *et al.*¹ (5%) and Dutta *et al.*⁵ (6%). The bone marrow suppression is believed to be due to maturity arrest of the myeloid series, erythroblasts and megakaryocytes and excessive phagocytic activity of the histiocytes in the marrow.

AKI was seen in 8 patients out of whom 6 patients had an increase in blood urea nitrogen too, who also had symptoms of GI loss and clinical signs of dehydration consistent with prerenal AKI.

Anicteric hepatitis was seen in 46 patients whereas icteric hepatitis was seen in 13 patients. This is similar to the finding of Shetty *et al.*, Chandrasekar *et al.*,⁶ and Gupta *et al.*¹ Our findings suggest that typhoid fever should be included in the differential diagnosis of patients presenting with fever and jaundice.

The most common ultrasound abdomen findings were normal in 56.6%, mild splenomegaly in 22.4% of patients, mild hepatomegaly in 6.6% of patients, and mild hepatosplenomegaly in 6.6% of patients.

Widal test was done only in 40 patients out of 76 who presented with fever duration of more than 7-10 days. In that positive results were seen in only 35% of patients. Test was done after the 2nd week in 56% of patients

among those who had negative test reports. This finding although not new, emphasizes the fact that the universal use of blood culture to diagnose enteric fever should be encouraged before starting antibiotic to a patient suspected with enteric fever.

Majority of culture positive patients were *S. typhi* positive accounting for 81.6. In contrary, our study had only 13.2% of *S. paratyphi* A positive species. *S. typhimurium* was seen in one patient, and three patients had undifferentiated *Salmonella* species. Antibiotic sensitivity pattern was done by disc diffusion method. There is a high prevalence of nalidixic acid resistance in our study which was 97.4% and the return of sensitivity to ampicillin (88.2%), Chloramphenicol (98.7%), Co-trimoxazole (98.7%), and tetracycline (98.7%) as seen in other Indian studies such as Chandrasekar *et al.*,⁶ Gupta *et al.*,¹ Jog *et al.*,² and Gautam *et al.* Only one isolate was medical device reporting which belonged to *S. typhi* group. Although fluoroquinolones were the initial choice of antibiotic in enteric fever the high prevalence of NARST raises concern over their efficacy. Azithromycin resistance was not reported in any of the isolate as in previous studies.

Out of *S. paratyphi* a growth, only 1 had ampicillin resistant, and all the species were nalidixic acid resistant. Other drugs were sensitive. *S. typhimurium* and undifferentiated *Salmonella* species showed resistance only to nalidixic acid and sensitive to all other drugs.

Ceftriaxone was the initial antibiotic of choice in 90.78% of patients and cefotaxime for 7.8% of patients in our study. Although fluoroquinolones were started in 16 out of 27 patients empirically, they were changed to ceftriaxone after culture report in view of resistance to nalidixic acid. Change of antibiotic from fluoroquinolone to cephalosporin was premature. Hence, the efficacy of the drug could not be found in our study. 69.73% of cases in our study required second-line antibiotic therapy with azithromycin for poor response to cephalosporins as first-line antibiotic. Addition of second line agent was observed in higher numbers compared to the previous studies like Chandrasekar *et al.*⁶ (13.46%), nil in Gupta *et al.*¹ Jog *et al.*²

Time to defervescence for patients treated with ceftriaxone was 3.86 days (range of 2-7 days). This was similar to other studies such as Jog *et al.*² (4.2 days) and Gupta *et al.*¹ (4.3 days). The time to defervescence for patients with *S. typhi* infection was 4.66 days (range 2-9 days) while that for patients with *S. paratyphi* A infection was 3.8 days (range 3-7 days). Combination therapy with cephalosporins and azithromycin did not show significant change to defervescence since it took 4.96 days for defervescence (range 2-9 days) compared to ceftriaxone

alone had 3.86 days for defervescence (range 2-7 days). Azithromycin was added in the most patient only when fever was persistent for more than 3-4 days in most of the patients. 18% of our patients underwent investigation for pyrexia of unknown origin though blood culture was positive since defervescence of fever took longer time. This should be avoided and defervescence time should be given unless there is suspicion for other causes of fever.

All the complications seen in our study were reported from *S. typhi* infection only. Myositis was seen in one patient in our study. Proposed mechanisms for *Salmonella*-induced rhabdomyolysis and myositis include tissue hypoxia caused by sepsis, toxin release, direct bacterial invasion of muscle, and altered muscle metabolic capacity. Secondary hemophagocytic lymphohistiocytosis or macrophage activation syndrome was seen in one patient in our study.

Only one patient who presented with fever for 7 days had rectal bleeding after admission during the third day of ceftriaxone. The patient was diagnosed to have a terminal ileal perforation, and laparotomy was done. The patient also developed pseudomembranous colitis following ceftriaxone and vancomycin was also given, and the patient improved. One patient who presented with fever for 60 days had constipation and abdominal pain after the start of treatment. Colonoscopy was done which showed terminal ileal ulcer. Antibiotic course was completed and symptoms resolved. In Gupta *et al.*¹ study, among 105 adults with enteric fever, intestinal perforation was observed in 10% of patients.

Typhoid intestinal perforation usually occurs in the ileum during the 3rd week of febrile illness and is due to necrosis of the Peyer's patches in the antimesenteric bowel wall. Affected patients present with increasing abdominal pain, distension, peritonitis, and sometimes secondary bacteremia with enteric aerobic and anaerobic microorganisms.

CONCLUSION

Fever with vomiting, loose stools, headache, and cough were the common clinical manifestations of enteric fever. Cardinal signs of enteric fever such as splenomegaly and hepatomegaly were less commonly seen in our study probably due to early presentation and prior antibiotic intake. Other important conclusions which can be drawn from the study include importance of absolute eosinopenia as a diagnostic marker of typhoid, mildly elevated liver enzymes with normal leukocyte count or leukopenia with neutrophilia can be a pointer for enteric fever, high culture positivity despite receipt of prior antibiotics, high prevalence of nalidixic acid resistance (97.4%), return of

susceptibility to chloramphenicol (98.7%), co-trimoxazole (98.7%), and ampicillin (88.2%). 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 a trend toward emerging resistance to 3rd generation cephalosporins due to increased defervescence time seen in patients treated with cephalosporins. Ileal perforation and GI bleeding which was a common complication two decades ago causing high mortality and morbidity has reduced. However, other atypical presentations and complications involving other system sparing GI system should be kept in mind due to antibiotic exposure prior hospitalization. Mortality rate was nil in our study.

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