Profile of Culture Positive Enteric Fever from Bangalore

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Abstract

Background: Enteric fever is endemic in India. The aim of this study was to analyse the clinical, laboratory, antibiotic sensitivity profile and response to antibiotics of culture positive enteric fever patients from Bangalore.

Methods: In this retrospective study only culture positive enteric fever patients were taken and their clinical, laboratory, antibiotic sensitivity profile and the clinical response to antibiotics studied.

Result: Eighty one culture positive enteric fever patients were taken into the study. Presenting symptoms included fever, pain abdomen (18.5%), loose stools (25%), vomiting (33%) and headache (30%). Absolute bradycardia at admission was not found in any of our patients. Normal or low total leucocyte count was seen in 97.5%. Typhoid hepatitis was seen in 8.5%. *Salmonella enterica* subspecies *enterica* serovar typhi (*S typhi*) were isolated in 80% of cases; 83% of all cases showed nalidixic acid resistance. All isolates were sensitive to chloramphenicol and third generation cephalosporins. Ciprofloxacin resistance was found in 19% cases. The time to defervescence in patients treated with ceftriaxone was 4.3 days. There was no statistical difference in time to defervescence in nalidixic acid resistant and sensitive strains. Complications included gastro intestinal bleed and encephalopathy.

Conclusion: Prevalence of nalidixic acid resistance is high, while clinical resistance to quinolones may be higher than that found in the laboratory which requires detailed study. Chloramphenicol sensitivity has returned and nalidixic acid resistant and sensitive isolates are uniformly sensitive to third generation cephalosporins with no difference in time to defervescence.

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Key Words : Enteric fever; Nalidixic acid resistance; Ciprofloxacin resistance; Time to defervescence

Introduction

Enteric fever is a systemic infection caused by *Salmonella enterica* subspecies *enterica* serovars typhi (*S typhi*) and paratyphi (*S paratyphi*). The disease is endemic in India with an incidence ranging from 102 to 2219 per 100,000 population [1].

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.

Nalidixic acid resistance predicts fluoroquinolone resistance. Prevalence of Nalidixic Acid Resistant *Salmonella* (NARS) in India has increased [2,3]. Therapy of enteric fever has evolved due to the changing resistance pattern of the organism and toxicity profile of the earlier used drugs.

The aim of this study was to evaluate the antibiotic sensitivity profile and clinical response to antibiotics of *S typhi* and *S paratyphi* organisms isolated from

patients with enteric fever from Bangalore. We also studied the clinical and laboratory profile of these patients.

Material and Methods

This was a retrospective study of cases of patients admitted with enteric fever at Command Hospital Air Force Bangalore. The case sheets were retrieved from the medical records section of the hospital. Only blood or bone marrow culture positive cases were included. An excel sheet was used to analyse data extracted from the case sheets. Clinically diagnosed cases with a positive Widal test but with sterile blood or bone marrow cultures were excluded.

Results

The total of 81 culture positive patients were included. The clinical features are as shown in Table 1. The average age of patients were 18.2 (range 2 - 45) years. Half of our patients were less than 18 years of age. Majority (76/81) did not give history of travel out of Bangalore one month prior to presentation. All patients presented with fever with a mean duration of 8.8 (range 2 to 30) days. None had bradycardia (defined as a pulse of < 60 at admission), on the contrary 37% patients had tachycardia (pulse > 100) at admission.

The mean white blood cell (WBC) count was 5928/cmm

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Table 1**Clinical features at admission**

Clinical Features	Number of cases (n=81)	Percent
Males	52	62.2
Pain abdomen	15	18.5
Vomiting	27	33.3
Diarrhoea	20	24.7
Headache	25	30.9
Cough	20	24.7
Hepatomegaly only	19	23.5
Splenomegaly only	6	7.1
Hepato-splenomegaly	42	51.9
No organomegaly	14	17.3
Melena	6	7.5

(range 800/cmm to 12600/cmm), 17/81 (21%) had leucopenia (defined as a TLC of < 4000/cmm) while 62/81 (76.5%) had WBC counts within normal range defined as 4000-11000/cmm, both inclusive. Leucocytosis defined as WBC count of > 11000/cmm was seen in only two cases. Anaemia (defined as haemoglobin < 10 gm/dl) was present in 8/81 (10%), and 12/81 (14.8%) had thrombocytopenia (defined as platelet count of < 1.5 lacs/cmm). Four patients had pancytopenia (defined as depletion of two or more cell lines as per above definition). Hyperbilirubinemia (> 1.5 mg/dl) was present in 7/81 (8.6%) patients. More than half (42/81) of the cases had elevation of aspartate aminotransferase or alanine aminotransferase or both of > 60 IU/L, of which 25/81 (31%) had alanine aminotransferase levels > 60 IU/L. Other causes for fever, hyperbilirubinemia and transaminitis (e.g malaria, viral hepatitis, leptospirosis etc) were excluded.

Widal Test results (single titres) were positive (defined as *S typhi* O antigens $\geq$ 160 and *S typhi* H antigen or *S paratyphi* H antigen $\geq$ 160) in 35/81 (43.2%) of patients. Widal was positive in 21/54 (38.8%) patients presenting in the first week of fever, while those presenting in second week or after had positive test in 14/27 (51%) cases.

All culture isolates were from blood culture. *Salmonella enterica* subspecies *enterica* serovar *typhi* (*S typhi*) was isolated from 65 (80%) patients while *Salmonella enterica* subspecies *enterica* serovar *paratyphi* (*S paratyphi A*) was isolated from the remaining. All blood cultures were sent at admission, a mean of 8.8 days after the onset of fever. The antibiotic sensitivity profile of the organisms is shown in Table 2. Out of the 65 patients with *S typhi* infection, 56 (86%) showed nalidixic acid resistant *Salmonella typhi* (NARST strain) while 11/16 (68.75%) of *S paratyphi A* isolates showed nalidixic acid resistance. Ciprofloxacin resistance was found in 10/65 (15.4%) patients with *S typhi* infection while 5/16 (31.25%) of *S paratyphi A* isolates were resistant. Ampicillin resistance was found in 7/65 *S typhi* strain while all isolates of *S paratyphi A* were sensitive. All isolates of *S typhi* and *S paratyphi A* were sensitive to ceftriaxone, cefotaxime and chloramphenicol.

Based on clinical suspicion, antibiotics were initiated in 74/81 (91.4%) of the patients before the availability of blood

Table 2**Antibiotic sensitivity profile of isolated salmonella organisms (*S typhi* & *paratyphi A*)**

Antibiotic	Number resistant (Total: 81)	Percent
Nalidixic Acid	67	82.7
Ciprofloxacin	15	18.5
Cefotaxime	0	0
Ceftriaxone	0	0
Chloramphenicol	0	0
Ampicillin	7	8.6

culture. Ceftriaxone was the initial antibiotic of choice in 70/81 (86.5%) of the patients. In 67 patients the antibiotic was initiated before availability of blood culture. Fluoroquinolones were used as the initial antibiotic in 11 patients (ciprofloxacin 10, ofloxacin 1), which included seven cases of empirical use, before the availability of blood culture. Isolates from all the 11 patients were sensitive to ciprofloxacin. The antibiotic was changed to ceftriaxone after mean 3.2 days (range 3-5 days) in eight of these patients due to perceived lack of response by treating clinician. The other three responded to ciprofloxacin (2) and ofloxacin (1) and completed the course of antibiotic.

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 deg C for at least 48 hours. Time to defervescence for patients treated with ceftriaxone was 4.3 days (range of 1-9 days). The time to defervescence for patients with *S typhi* infection was 4.7 days (range 2-9 days) while that for patients with *S paratyphi A* infection was 2.8 days (range 1-5 days). The difference between the two was found to be highly significant ($p < 0.001$) using the t test. Days to defervescence in patients infected with nalidixic acid resistance strains was 4.2 days (range 1-9 days) while in those infected with nalidixic acid sensitive strains was 4.4 days (range 1-8 days). The difference was not statistically significant ($p = 0.5$). The mean duration of antibiotics usage was 11.5 days (range 7-18 days).

Complications in the form of gastrointestinal bleed occurred in 6/81 (7.5%) of our patients. None of them were significant enough to require blood transfusions or intervention. Two patients (*S typhi* infection) developed abnormal behaviour progressing to delirium with irrelevant talk, picking movements of bed clothes, tremulousness of both hands and bilateral extensor plantar. Contrast enhanced computed tomography (CECT) brain and cerebrospinal fluid (CSF) examination were normal. They were managed as typhoid encephalopathy and given high dose dexamethasone 56 mg IV 6 hourly for 48 hours. They showed a good recovery with reversal of the encephalopathy. There was no mortality in our patients.

Discussion

This is a large single centre study from Bangalore. The age profile in our study was that of a dominantly young population. All the symptoms reported by our

patients were similar to those reported in other studies in almost the same proportions [1,3]. Absolute bradycardia was not seen in our patients and this has been reported by other studies in India earlier [1, 3] and other countries especially in children [5]. However nearly two thirds of our patients had pulse rate within normal range (60-100) at admission despite having fever. Hence a patient with discordant finding of relatively normal pulse rate in the presence of fever even if no bradycardia is present must arouse the suspicion of enteric fever.

Leucopenia and relatively normal leucocyte count is common in enteric fever, which was also seen in our study. Bone marrow depression in the form of pancytopenia is less common and was seen in 4/81 (5%) of our patients. This is in agreement with the findings of Dutta et al [6]. In an etiological study of pancytopenia in children, around 30% of patients with infections as a cause for pancytopenia had enteric fever [7]. The bone marrow suppression is believed to be due to a maturity arrest of the myeloid series, erythroblasts and megakaryocytes and excessive phagocytic activity of the histiocytes in the marrow [8].

Typhoid hepatitis was present in 8.6% of our patients. This is similar to the finding of Shetty et al [9]. Our findings suggests that typhoid fever should be included in the differential diagnosis of patients presenting with fever and jaundice.

Widal test continues to be used in India for diagnosis of enteric fever despite its poor sensitivity and specificity. In our study only half of all culture positive patients who presented with fever of more than a week's duration had positive widal titres, which shows that absence of raised widal titres 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.

In our study one fifth of the isolates were *S paratyphi A*, which is in agreement with other studies [10]. We found a high prevalence of nalidixic acid resistance in our isolates with a return of sensitivity of chloramphenicol as seen in other Indian studies [1,11]. We did not find any third generation cephalosporin resistance. We found ciprofloxacin resistance of 18.4% in laboratory studies. Although fluoroquinolones were the initial choice of antibiotic in 11 patients, they were changed to ceftriaxone in eight cases due to perceived lack of response by the treating clinician. We feel the change of antibiotic was premature and arbitrary for us to derive a conclusion in this retrospective study about clinical fluoroquinolones resistance. Recently reports of in vitro

and in vivo resistance to ciprofloxacin have raised this concern [12,13].

In our study the time to defervescence in patients treated with ceftriaxone was similar to other Indian studies [3]. Studies outside India [14] have reported longer time to defervescence. We found that patients with *S paratyphi A* infection became afebrile significantly faster.

NARST portends fluoroquinolones resistance. It is known that two patients, both growing *S typhi* with similar antibiotic sensitivity profile in the laboratory can behave differently due to several host and organism factors. One of them could be NARST. We have tried to analyse if NARST strains behave differently from NAS strains in a clinical scenario even when they are treated by a different class of antibiotics like ceftriaxone by showing a delayed response to not only fluoroquinolones but also to ceftriaxone. The fact that we found no statistical difference in response to ceftriaxone between the two groups suggests that NAR is only class specific. This is at variance from a study by Walia et al [4] who found a significant difference in the time to defervescence in nalidixic acid resistant salmonella and those which were sensitive possibly due to the fact that their groups were treated with fluoroquinolones. Due to the small group of patients who were treated only with fluoroquinolones a sub group analysis of response to that antibiotic in NAR and NAS group could not be done.

We encountered two cases of typhoid encephalopathy that were given high dose dexamethasone with good response. The decision to give high dose steroids was based on a previous study by Hoffman et al [15] where they found significant mortality reduction in patients with suspected typhoid fever who were delirious, obtunded, stuporous, comatose, or in shock. Both our patients recovered well. High dose dexamethasone may be an option to treat patients with typhoid encephalopathy.

The chief limitation our study is that it is a retrospective analysis of data with no laid down protocol.

Despite these limitations some important conclusions can be drawn from our study. The antibiotic sensitivity profile and response to antibiotics of patients with enteric fever in Bangalore appears similar to other areas in India. The prevalence of nalidixic acid resistance is high; fluoroquinolones resistance is emerging and may be higher than that found in the laboratory. Prospective studies to ascertain the antibiotic resistance pattern in India is required. In India chloramphenicol sensitivity has returned, while nalidixic acid resistance appears to be class specific and does not serve as a marker for resistance to ceftriaxone.

Conflicts of Interest

None identified

Intellectual Contribution of Authors

Study Concept : Wg Cdr S Gupta, Wg Cdr A Handa

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