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Trends of Socio-Demographic Determinants, Clinical Features and Drug Resistance Pattern among Cases of Enteric Fever in Western Uttar Pradesh, India

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Abstract

Introduction: Typhoid fever is a prolonged illness caused by *Salmonella enterica* subspecies *enterica* serotype Typhi, causing an estimated 16.6 million new infections and 600,000 deaths each year. Clinical manifestation of typhoid fever varies from uncomplicated high-grade fever to serious complications involving encephalopathy, peritonitis, perforation and hemorrhage. With development of resistance against commonly used antibiotics, quinolones and third generation cephalosporins are being used against multi drug resistant infections.

Aims and objective: We studied the changing trends of socio-demographic determinants, clinical features and drug resistance pattern among cases of Enteric fever in western Uttar Pradesh in India. so that it may prove helpful to the clinicians for the early diagnosis, management and finally reducing mortality in our region.

Materials and methods: The study was performed on all patients attending Pediatric and Medicine OPD or admitted in wards of Jawaharlal Nehru Medical College and Hospital (J.N.M.C.H), AMU, Aligarh, with clinical presentation suggestive of typhoid fever.

Results: Out of 104 clinically suspected patients 44 (42.30%) belonged to age-group 21-40 years and 55 (52.88%) were males. maximum number of patients belonged to socio-economic class V with 42 (40.38%) patients, majority of the cases were seen during April-June 46 (44.23%), most of the patients were educated up to pre-school level consisting of 42 (40.38%). Fever was the most constant symptom in our series representing 104 (100%) patients, Headache was present in 92 (88.46%), abdominal pain in 83 (79.80%) patients, vomiting in 17 (16.34%), coated tongue 24 (23.07%), diarrhoea in 6 (5.77%), and constipation was seen in 8 (7.69%) patients in our study. All the cases 12 (100%) sensitive for the azithromycin, ceftriaxone and Cefoperazone-Salbactum, while 8 (66.67%) cases showed resistance to ampicillin, chloramphenicol, and co-trimoxazole. While cefexime, cefepime and ciprofloxacin were 10 (83.33%), 11 (91.66%), and 10 (83.33%) sensitive. While 2 (16.67%) cases were resistant to nalidixic acid i.e., NARST.

Conclusion: enteric fever is endemic in our country and a significant number of patients are dying each year and frequency of complications is also on rise so knowing the socio-demographic determinants , clinical features and drug resistance pattern among cases may prove useful for the early diagnosis, management and finally reducing mortality.

Keywords: Drug resistance; Enteric fever

Introduction

Typhoid fever is a prolonged illness characterized by bacteremia with *Salmonella enterica* subspecies *enterica* serotype Typhi, a highly evolved gram-negative bacteria that infects humans. Typhoid is one of the major cause of morbidity and mortality worldwide, causing an estimated 16.6 million new infections and 600,000 deaths each year [1]. Clinical manifestation of typhoid fever varies from uncomplicated high-grade fever to serious complications involving encephalopathy, peritonitis, perforation and haemorrhage. The diagnosis of typhoid fever on clinical grounds is difficult, as the presenting symptoms are diverse and overlapping [2].

The incidence of salmonellosis is on the rise in the most of the developing countries, emergence of antibiotic resistance is also alarming. Therefore, the effectiveness of antimicrobial chemotherapy is limited, and also multidrug resistance strains were disseminated worldwide; in 2004, *Salmonellae* resistant to extended spectrum cephalosporins (ESCs) were reported in 43 countries [3]. β- Lactams constitute the most important antibiotic family in therapeutic use, because of their efficiency and relative low toxicity. ESCs are currently the agents of choice for such chemotherapy especially for infants and neonates, for whom the use of fluoroquinolones is not yet approved [4,5].

Materials and Methods

The present study was carried out in the Department of Microbiology, J.N Medical College A.M.U, Aligarh during the period from September 2011 to February 2014. This study was approved by the institutional ethical committee JNMC, AMU, Aligarh.

Study group and design

The study was conducted on all patients attending Pediatric and Medicine OPD or admitted in wards of Jawaharlal Nehru Medical College and Hospital (J.N.M.C.H), AMU, Aligarh, with clinical

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presentation suggestive of typhoid fever. The inclusion criteria was clinical presentation of the patients with history of fever, associated symptoms/signs and complications (if any), history of antibiotic intake, previous history of enteric fever and results of investigations. After obtaining informed consent, patients was enrolled in the study.

Inclusion criteria for cases

Fever with sign/symptoms associated with enteric fever for 3 days or more, prior to the start of antibiotic treatment. Any other additional presentation suggestive of typhoid fever like headache, anorexia, nausea, vomiting, abdominal discomfort with diarrhoea, soft enlarged spleen, coated tongue, toxic look and relative bradycardia. Individuals of both sex representing all ages.

Exclusion criteria of the cases

1. Fever with any obvious focus for other infection such as urinary tract infection, otitis media, malaria.
2. History of antibiotic treatment prior to taking of blood sample.

Controls: 10 persons with no clinical evidence suggestive of enteric fever were selected as control for our study.

Consent taking

Informed written consent was obtained from each patient or from guardian of the minor patients before his/her entry into the study and ethical clearance was obtained from the concerned authority.

Socioeconomic condition

Socio-economic conditions of the study population were ascertained on the basis of their occupation or monthly income of the patients/their guardians from all possible sources. The cases and controls were classified into five groups [6].

Processing of blood culture

Blood was withdrawn by venipuncture. A total 10 ml of peripheral blood from adults and 6 ml from paediatric patients was collected by a 10 ml dispovan syringe. The vein from which the blood was withdrawn was chosen before the skin was disinfected. If a patient had an existing IV line; blood was withdrawn below the existing IV line. A 5ml of peripheral blood from adults and 3 ml from paediatric patients was transferred in 50 ml (for adults) and 30 ml (for childrens) brain heart infusion broth (BHIB) medium (i.e., 1:10 dilution) with 0.025% sodium polyethanol sulphate (SPS) for culture.

Samples collected in brain heart infusion broth (BHIB) prepared in department of Microbiology were incubated overnight at 37°C and subculture was done on blood agar and MacConkey's agar after 24, 48 hrs and 1 week. If there was no growth after 7 days. The culture was taken as negative for no *S. Typhi*. Preliminary identification of *S. Typhi* was based on the colony morphology, gram staining, motility by hanging drop preparation and biochemical characteristics of the organism. Serotyping of the isolates was done using poly-O, O-9 and H-d antisera for the species identification done according to the standard guidelines [7].

Antimicrobial sensitivity testing: Antimicrobial susceptibility testing was performed on all the *S. Typhi* isolates by Kirby-Bauer disc diffusion method on Mueller Hinton Agar commercially prepared discs of Himedia (India) and results were interpreted as Resistant (R), Intermediate (I) or Susceptible (S) as per Clinical and Laboratory Standards Institute (CLSI 2010) guidelines [8].

Antibiotic discs: Commercially available antibiotic discs (Himedia) were used for antibiotic susceptibility testing. Following antibiotics were selected for the susceptibility testing of *Salmonella* Typhi, Cefepime (30 *μg*), ceftriaxone (30 *μg*), cefotaxime (30 μg), cefexime (30 *μg*), cefoperazone-sulbactam (30/15 *μg*), levofloxacin (5 *μg*), amikacin (30 *μg*), azithromycin (15 *μg*), ciprofloxacin (1 *μg*), chloramphenicol (30 μg), Ampicillin (30 μg), Nalidixic acid (30 *μg*). The discs were stored in sealed cartridges along with the desiccant at -20°C. A small working supply of discs was kept at 4°C for maximum of one week. Before using, the discs were left at room temperature for one hour. Before use each lot of antibiotic discs was tested with standard strains of *Escherichia coli* ATCC 25922.

Results

Maximum number of patients 44 (42.30%) belonged to age-group 21-40 years followed by less than 20 years age-group with 42 (40.38%) patients. majority of patients 26 (25.00%) were males belonged to age-group 21-40 years while majority of female patients 25 (24.03%) belonged to age-group 0-20 years with male: female ratio of 1.2:1 . Males dominated females in all age-groups except in 0-20 age-group where females were more than males. Maximum number of patients belonged to socio-economic class V with 42 (40.38%) patients, followed by class IV with 34 (32.70%) patients (Table 1).

In our study majority of the cases were seen during April-June 46 (44.23%), next in the frequency were during July-September 34 (32.70%).

Most of the patients in our study group were educated up to pre-school level consisting of 42 (40.38%), followed by illiterate patients which comprised 34 (32.70%) patients. 74 (71.15%) patients in our study group resided in rural areas while 30 (28.85%) patients resided in urban area. Farmer and labourer were 44 (42.30%) in number and formed the largest group in our study, followed by students with 18 (17.31%) patients.

Open field defaecation were practiced by 42 (40.38%) most patients in our study group, followed by Insanitary latrine with 34 (33.70%) patients.

In our study group hand pump was the most frequent source of drinking water noted in 46 (44.23%) patients. In our study out of the 104 case 12 (11.53%) patients were positive by Blood culture method and 90 cases 87 (86.53%) were negative. 2 (1.94%) samples were grossly contaminated during collection.

Fever was the most constant symptom in our series representing 12 (100%), Headache was present in 8 (66.67%), abdominal pain in 9 (75.00%), coated tongue in 2 (16.67%), vomiting in 6 (50.00%), diarrhoea in 4 (33.33%). Constipation was seen in 3 (25.00%) cases in our study among the blood culture positive patients. In our study maximum number of the blood culture 8 (66.67%) were positive during the first week, followed by 3 (25.00%) case which were positive during 1-2 week and 1 (8.33%) case was found positive after the 2nd week of presentation (Table 2).

All the 12 isolates of *S.* Typhi were tested for antimicrobial susceptibility, and all isolates were sensitive for the azithromycin, ceftriaxone and Cefoperazone-Salbactum, while 8 (66.67%) cases showed resistance to ampicillin, chloramphenicol, and co-trimoxazole. While for cefexime, cefepime and ciprofloxacin were 10 (83.33%), 11 (91.66%), and 10 (83.33%) were sensitive. While 2 (16.67%) isolates were resistant to nalidixic acid i.e., NARST (Table 3 and Figures 1 and 2).

Income group	No. of patients (%)	Controls (n=10)
Upper high-income group (I)	2 (1.92%)	0 (0%)
High income group (II)	4 (3.85%)	1 (10%)
Upper middle-income group (III)	22 (21.15%)	3 (30%)
Lower middle-income group (IV)	34 (33.70%)	2 (20%)
Poor income group (V)	42 (40.38%)	4 (40%)
Total	104 (100%)	10 (100%)
*Figure in parenthesis shows percentage.		

Table 1: Socioeconomic status of the patient's (n=104).

Presenting complaints	Distribution of all clinically suspected patients (n=104)	Distribution of all blood culture confirmed patients (n=12)
Fever	104 (100%)	12 (100%)
Headache	92 (88.46%)	8 (66.67%)
Abdominal pain	83 (79.80%)	9 (75.00%)
Vomiting	17 (16.34%)	6 (50.00%)
Coated tongue	24 (23.07%)	2 (16.67%)
Constipation	8 (7.69%)	3 (25.00%)
Diarrhoea	6 (5.77%)	4 (33.33%)
Total no. of patients	104 (100%)	12 (100%)
*Figure in parenthesis shows percentage.		

Table 2: Distribution of patients according to presenting complaints.

In our study among total 12 isolates 4 (33.33%) isolates were found to be multi drug resistance (MDR), while other 4 (33.33%) isolates showed variable sensitivity pattern.

Discussion

In the present study, 104 clinically suspected cases of typhoid fever were selected. Maximum number of patients 44 (42.30%) belonged to age-group 21-40 years followed by less than 20 years age-group with 42 (40.38%) patients. In control group 7 (70%) were male and 3 (30%) were females. In various study the highest incidence of enteric fever was seen in the 5–19 years age group. After age 20, the incidence drops, probably due to acquisition of immunity from clinical or subclinical infection [9]. Mohanty et al. reported more than 50% of cases in the age group of >5 and <19 yrs of age which is in accordance to our study group [10].

Mean age of male patients in our study was 28.12 yrs, while mean age of female patients was 27.9 age of yrs, while the overall mean age was is 28.1 yrs. Minimum and maximum range of ages in our study is between 1 yrs to 72 yrs of age, standard deviation of 15.7 was found.

Among 104 clinically suspected typhoid cases in our study 55 (52.88%) were male and 49 (47.12%) were Female, and most of the patients were residents of rural areas 74 (71.15%). Another study done by Butler et al. and others also reported similar result that infection rate was slightly higher in male [11]. Butler expressed his opinion that greater exposure of male to contaminated food and water outside the home might be the reason of higher rate of infection among this population.

The socio-demographic characteristics of suspected cases of typhoid fever in present study showed that the majority of the cases were educated upto pre-school level 42 (40.38%) and 34 (32.70%) were illiterate, belonged to poor income group 42 (40.38%), used open toilets 42 (40.38%) and drinking water from hand pump 46 (44.23%), and mostly 44 (42.30%) were farmers and labourer by occupation. Similar findings also have been reported by Sur et al. and others showing that the illiteracy rates were highest in the cases of typhoid fever. In the same study unhygienic toilets were the main sources of spreading typhoid diseases and the sanitation condition of low income areas was remarkably poor [12]. Lack of safe drinking water and unhygienic sanitation are believed to contribute the transmission of typhoid fever [13]. It has been observed that the water and sewage pipelines lie close together in the slum areas of India and they are prone to leakage and cross-contamination. In addition most of the people cannot afford the sanitary latrines in most of the villages due to poverty which further carries the risk of exposure to *Salmonella* Typhi.

Enteric fever is known to occur throughout the year with some seasonal variation. There was a peak during the months of April, May, and June 46 (44.23%) followed by 34 (32.70%) cases during July and August probably due to the monsoon and pre monsoon showers that is known to occur in these months in the western part of India accounting for contamination of drinking water. Mohanty et al. found in a study in Delhi that for typhoid fever, the peak incidence was between April–June, followed by the monsoon season from July to September [10]. Similar study by Surinder et al., it was observed that a large number, 120 (69.0%), of the cases of enteric fever clustered in the hot months of April, May and June, and in the monsoon season, with a larger peak in the summer and a smaller peak in the monsoon season . The number of cases decreased during autumn and winter. During the summer and monsoon months the water supply and sanitation systems are under a great strain in Delhi, which could account for the higher incidence in these months [14].

Clinical presentations of enteric fever is non specific classical step ladder pattern of fever is not commonly found in all patient group. In our study the different clinical manifestations among the patients who were positive in the Blood culture was seen. Fever was the most constant symptom representing 12 (100%), Headache was present in 8 (66.67%), abdominal pain in 9 (75.00%), coated tongue in 2 (16.67%), vomiting in 6 (50.00%), diarrhoea in 4 (33.33%). Constipation was seen in 3 (25.00%) cases. Our findings were similar according to Bienvenido et al. in which Fever was the most constant symptom in their study, Headaches and chills were present in 53%, abdominal pain 48%, anorexia in 44%, malaise in 33%, vomiting in 31%, diarrhoea in 29%. Jaundice was seen in 15.5% of the patients, Constipation and nausea

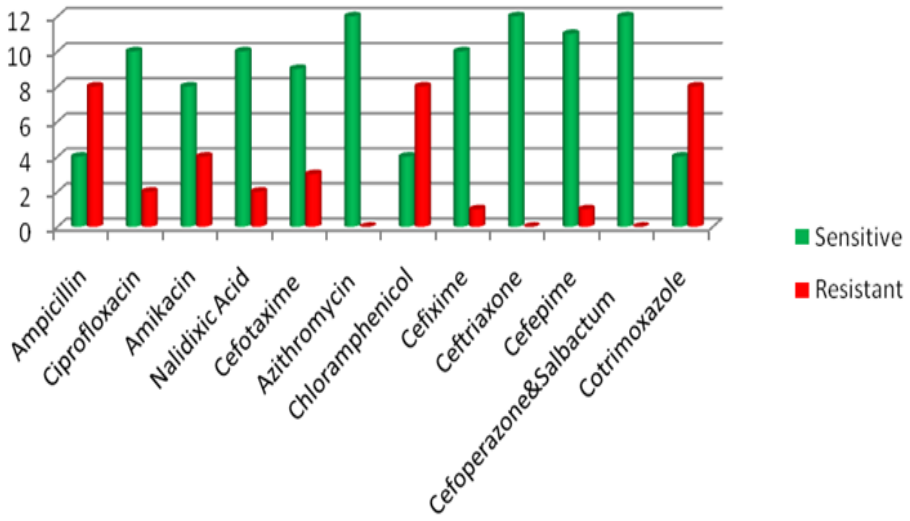
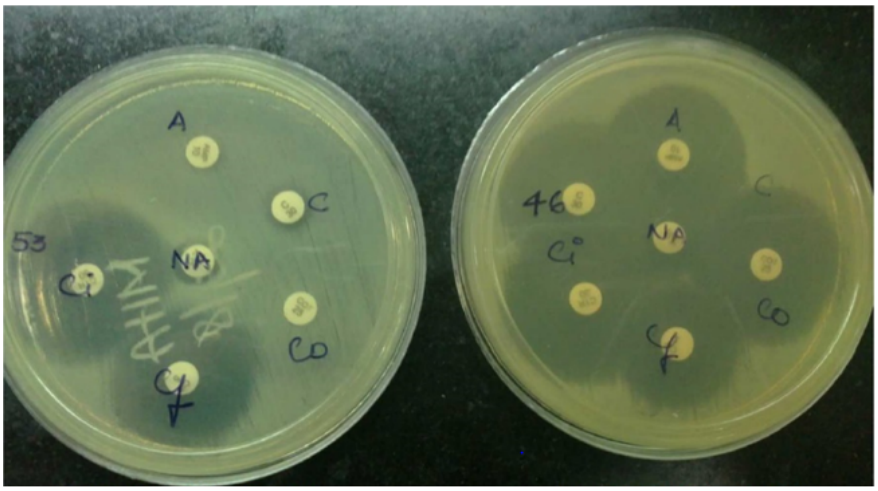


Figure 1: Antimicrobial resistance pattern of isolates.



NARST & MDR STRAIN **SUSCEPTIBLE STRAIN**

Figure 2: NARST and MDR strain, Susceptible Strain. A=Ampicillin, C= Chloramphenicol, Co= Cotrimoxazole, CF=Cefixime, Ci= Ciprofloxacin, NA= Nalidixic Acid.

Drugs	Sensitive	Resistant
Ampicillin	4 (33.33%)	8 (66.67%)
Ciprofloxacin	10 (83.33%)	2 (16.67%)
Amikacin	8 (66.67%)	4 (33.33%)
Nalidixic Acid	10 (83.33%)	2 (16.67%)
Cefotaxime	9 (75.00%)	3 (25.00%)
Azithromycin	12 (100%)	0 (0.00%)
Chloramphenicol	4 (33.33%)	8 (66.67%)
Cefixime	10 (83.33%)	1 (8.33%)
Ceftriaxone	12 (100%)	0 (0.00%)
Cefepime	11 (91.66%)	1 (8.33%)
Cefoperazone-Salbactum	12 (100%)	0 (0.00%)
Cotrimoxazole	4 (33%)	8 (66.67%)

Table 3: Antimicrobial resistance pattern of *Salmonella* Typhi isolated from patients (n=12).

were seen in 12% and disorientation in 3% of patients [15].

In our study all the cases 12 (100%) sensitive for the azithromycin, ceftriaxone and Cefoperazone-Salbactum, while 8 (66.67%) cases showed variable resistance among ampicillin, chloramphenicol, and co-trimoxazole, among this 4 (33.33%) isolates were resistant to all the three first line drugs i.e., they were multi drug resistance isolated (MDR). While cefexime, cefepime and ciprofloxacin were 10 (83.33%), 11 (91.66%), and 10 (83.33%) sensitive. While 2 (16.67%) cases showed resistant to nalidixic acid (NARST) i.e., low level résistance in Ciprofloxacin.

In a study done by Surinder et al. Multidrug resistance (resistance to chloramphenicol, ampicillin and co-trimoxazole) sequentially increased from 34% in 1999 to 66% in 2005. Increasing resistance was also noticed to the other antibiotics, especially to the cephalosporins.

Moreover 8% of the *S.* Typhi isolates were found to be presumptive extended spectrum b-lactamase producers. There was a gradual development of resistance to fluoroquinolones over the 7 years [14].

No resistance was observed to fluoroquinolones in 1999, while in 2005 4.4% resistance was observed to sparfloxacin, 8.8% resistance to ofloxacin and a high resistance, 13%, to ciprofloxacin. This is an alarming development and it is of paramount importance to limit unnecessary use of fluoroquinolones and third generation cephalosporins so that their efficacy against salmonella is not jeopardized further [14]. In another study in 1995, 28% of all isolates of *S.* Typhi from humans in the USA were resistant to a wide range of drugs including ampicillin, chloramphenicol, streptomycin, sulphonamides, and tetracyclines [16]. There are also reports from the Indian subcontinent of isolates that are fully resistant to fluoroquinolones and the extended spectrum cephalosporins [17-19]. These reports further support the need for alternative antibiotics such as azithromycin for treating drug-resistant enteric fever.

Conclusion

Enteric fever is endemic in our country and a significant number of patients are dying each year and frequency of complications is also on rise so knowing the socio-demographic determinants, clinical features and drug resistance pattern among cases may prove useful for the early diagnosis, management and finally reducing morbidity mortality.

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