Original Research Article

A study on clinico-epidemiological profile of typhoid fever in a rural based medical college & hospital; West Bengal; India

Bandyopadhyay S.[1], Pal A. C.[2], Dey S.[3], Samanta S.[4], Chakraborti S.[5], Mandal R.[6]

[1]Dr. Sudipta Bandyopadhyay, Post Graduate Trainee, [2]Dr. Abhay Charan Pal, Associate Professor, [3]Dr. Subhendu Dey, Assistant Professor; [4]Dr. Subhendu Samanta, Post Graduate Trainee; [5]Dr. Snehansu Chakraborti, Professor and HOD, above all authors affiliated with Department of Pediatric Medicine, B.S Medical College, Bankura, West Bengal, India, [6]Dr Ramkrishna Mandal, Professor, Department of Surgery, B.S Medical College, Bankura, West Bengal, India.

Corresponding Author: Dr. Abhay Charan Pal, Associate Professor, Department of Pediatric Medicine, B.S Medical College, Bankura, West Bengal, India, E-mail: abhaypal80@gmail.com

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Abstract

Introduction: Typhoid fever is estimated to have caused 26.9 million cases and 5.74 lakhs deaths worldwide in 2010. It remains a major public health problem in India and other part of developing world. **Background:** Non-provision of safe drinking water and sanitation measures, non-implementation of adequate vaccination strategies and emergence of multidrug resistant salmonella strains is responsible for why typhoid fever is till now remaining an important health problem in some parts of world and the disease is even becoming more complex. **Objective:** This study was conducted in a tertiary care centre to find out the clinico-epidemiological profile of patients admitted with typhoid fever. **Design:** Cross sectional observational study. **Subjects:** 460 Widal positive typhoid fever pediatric cases admitted from 1st June 2016 to 30th November 2016. **Methods:** Both clinical and laboratory data of all the patients were retrieved, compiled and analyzed. **Results:** Out of 460 patients 238(51.74%) were males and 222 (48.26%) were females. Fever (100%), vomiting (49.13%), diarrhea (30.21%), cough (30.0%) and hepatomegaly (73.26%) were commonly observed.Response to injection Ceftriaxone was excellent.355(77.17%) patients responded to Ceftriaxone alone and 99 (21.52%) patients needed addition of oral Azithromycin.Average hospital stays in our study ranged from 3-9 days. **Conclusion:** In the present series typhoid fever accounted for 10.94% of pediatric admissions. Though mortality has significantly reduced typhoid fever continues to be an important cause of hospitalization in pediatric population.High incidence among lower age group indicates high endemicity and emphasizes the need of widespread use of vaccination.

Keywords: Cross-sectional, Observational study; India; Rural based Medical College Hospital; Typhoid fever.

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Introduction

Typhoid fever is a systemic infection caused by Salmonella enterica serovar Typhi (S Typhi)[1]. S typhi, a highly adapted human–specific pathogen that evolved around 5000 years ago, has remarkable mechanisms for persistence in its host [1,2,3].

Though provision of clean water and good sewage system has led to great decline in the incidence of typhoid fever in Europe and the USA since the early 20th century; the disease has remained a serious public health problem in developing countries [4,5].

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Advent of Chloramphenicol treatment has changed typhoid fever from a serious, often fatal disease to a readily manageable infection [5,6]. Even after the development of Chloramphenicol resistant strains in 1972, the isolates were still sensitive to Cotrimoxazole, Ampicillin and Amoxycillin[1]. Out breaks of typhoid caused by strains resistant to Chloramphenicol, Co-trimoxazole, Ampicillin and Amoxycillin were reported in late 1980s and 1990s [6].

Currently Fluoroquinolones and third generation cephalosporins are the drugs of choice in typhoid fever but decreased susceptibility to these

antimicrobials has been reported [7,10]. Possible emergence of an untreatable strain may be prevented by prudent use of existing drugs and resisting the temptation to use yet more antimicrobials[1].

Typhoid fever imposes a serious global burden amounting to 26.9 million cases (symptomatic infection with Salmonella typhi) of typhoid fever reported in 2010 and apparently 5.74 lakh deaths worldwide [11]. Inspite of provision of safe water and sanitation, better treatment and vaccination, burden of the disease in certain areas of the Globe is however remaining quite high and moreover the disease is becoming more complex in certain areas of World like some parts of African Subcontinent [1,12].

There has been intense study regarding the genomics of S. typhi and the genetic mechanism behind its unique human-adaptiveness. There has been exciting new genetic technological innovation to demonstrate that the same genes in S. typhi and S.typhimurium may have different regulatory pathways and different function [12]. This under standing may help for developing newer target for vaccine development and new antibacterial drug for S.typhi in endemic areas.

The different genes responsible for development of drug resistance in S.typhi are haplotype 58(H58), a group of plasmids, incH11, gyrA and gyrB genes etc accounting for resistance against Fluoroquinolones and other agents[1,13,14].

Two types of vaccine are in current use namely purified Vi polysaccharide vaccine and a new conjugate vaccine (less widely available). Though programmatic use of vaccine in high-risk population has been advocated by WHO, only a few countries have taken such actions; namely Pondichery(India) in 2004 after Tsunami, Fiji in 2010 after cyclone Tomas and Sri Lanka in 2009 after the civil war and some other countries like Pakistan, Nepal and china[12,15,16]. Clinical presentation of typhoid fever is highly variable ranging from only fever with little other morbidity to marked toxemia and multisystem involvement.

Complications include gastrointestinal bleeding (10-20%); intestinal perforation (1-3%); neuro-psychiatric symptoms like coma vigil (around 2%) and severe complications like DIC and death [1].

With modern treatment; if initiated early, the average case fatality ratio for typhoid fever is less than 1%; however mortality as high as 30-50% has been reported from Papua New Guinea and Indonesia for severe typhoid fever[17,18].

Treatment may range from oral medications like Fluoroquinolones (Ofloxacin, Ciprofolxacin); combination of Ciprofloxacin and Amoxycillin; combination of Ciprofloxacin and Gentamycin; oral Cefixime and Azithromycin (Quinolone-resistant cases) and injectable Ceftriaxone or Cefotaxime for severe typhoid fever [19,20].

An increase in incidence of typhoid fever has been reported from countries like India, Pakistan and Indonesia; younger populations are more likely to be involved in areas with high incidence rates (>100/100000 population/year)[1,21].

Considering the global disease burden, rapidly evolving multidrug resistant typhoid strains, changing clinical profile and variable case fatality rate this observational study was conducted in a tertiary care Medical College Hospital. The intention of this study was to find out the disease burden, clinical profile and efficacy of the commonly used treatment regimens in admitted typhoid patients. The study results may help to contemplate treatment and prevention strategies like implementation of effective vaccination programs as advocated by the WHO apart from elevation of water supply and sanitation measures.

Materials and Methods

Study Design: Cross-sectional observational study

Place: The Department of Pediatrics; BS Medical College; Bankura; West Bengal; India.

Duration: Study period extended from 1st June2016 to 30th November 2016.

Sample size: 460 cases of Widal positive typhoid fever cases admitted in the Pediatric ward BS Medical College Hospital.

Studypopulation: Patients fulfilling the inclusion criteria and none satisfying the exclusion criteria.

Inclusioncriteria

1. Fever (temp>37.5ºc) for at least 5 days and serum Widal test positive (O titre>1:160 or H titre>1:160)[22.23].

The above case definition is very close to the WHO case definition[24].

2. Parents of patients who gave informed and written consent.

Exclusioncriteria

1. Patients having fever less than 5 days.

2. Patients with Widal test negative

3. All the fever patients having serum Widaltitre less than 1:160 for O and/or H antigen

4.All the patients who left the study or took discharge against medical advice or not willing to give consent.

Methods: Detailed clinical examination of all the patients were carried out and laboratory work up was done. Complete blood count and Widal test was performed in all children and Chest X ray, USGabdomen, CT or MRI brain, CSF examination and other investigations were done as and when necessary.

All the cases were treated with injectable Ceftriaxone and Oral Azithromycin was added if the patients remained febrile after 5 days of injectable Ceftriaxone. Patients were closely monitored for development of any complications and were treated accordingly.

As most patients came after 1 week of fever and because of technical constraints culture could not be done.

Rather we performed tube agglutination test (Widal) against O and H antigens for the diagnosis of typhoid fever considering sufficient sensitivity and specificity and cost-effectiveness.

Widal test is easier to perform and also less time consuming. Blood culture, though is taken as gold standard lacks sensitivity and our institute does not have good set up for the same [25].

Statistical Methods: Data analysis was done using SPSS20 software. Standard statistical tests were applied. Rate and proportions were calculated with 95% confidence intervals and level of significance was set up at P<.05.

Permission from IEC/IRB: Necessary permission for conducting the study and to publish the results observed were obtained from the Institutional Ethics Committee/ Institutional Review Board of this College.

Results

Table-1: Shows the age and sex distribution of typhoid fever.

Age(years)	Total patients(n=460)	Male (n=238(51.74%))	Female (n=222(48.26%))
<1	10(2.17%)	6(2.52%)	4(1.8%)
1-<2	58(12.61%)	30(12.6%)	28(12.61%)
2-<5	150(32.61%)	76(31.93%)	74(33.34%)
5-<10	162(35.22%)	85(35.72%)	77(34.68%)
≥10	80(17.39%)	41(17.23%)	39(17.57%)

Out of total 460 patients, 238 were males and 222 females giving a male: female ratio of 1.07.

Age wise incidence shows highest incidence in 5-<10years age group (162 patients, 35.21%) and lowest incidence in <1 year age group (10 patients, 2.17%).

Remarkable finding was rising incidence in <2year age group (14.77%) which indicates changing trend of the disease.

Age- wise distribution of signs-symptoms shows that fever was present in all 460(100%) patients. Almost all infants (<1year) presented with diarrhea, hepatomegaly and vomiting.

Hepatomegaly was observed with remarkably high frequency in all age groups.

Table-2: Demonstrate age-related clinical features of typhoid fever.

Age (year)	Fever (n=460)	Vomiting (n=226)	Diarrhea (n=139)	Coated tongue (n=76)	Hepatomegaly (n=337)	Splenomegaly (n=190)
<1(n=10)	10 (100%)	7(70%)	10 (100%)	1 (10%)	10 (100%)	7 (70%)
1-<2 (n=58)	58 (100%)	30 (51.72%)	22 (37.93%)	5(8.62%)	42(72.41%)	7(12.06%)
2-<5 (n=150)	150 (100%)	56 (37.34%)	44 (29.34%)	18(12%)	118(78.67%)	60(40%)
5-<10 (n=162)	162 (100%)	92 (56.79%)	42 (25.92%)	36(22.23%)	108(66.67%)	62(38.27%)
≥10 (n=80)	80 (100%)	41 (51.25%)	21 (26.25%)	16(20%)	59(73.75%)	54(67.5%)

Table-3: Illustrates overall distribution of clinical features of typhoid fever taking into account all age groups.

Clinical features	No of Patients (n=460)	%
Fever	460	100
Vomiting	226	49.13
Diarrhea	139	30.21
Anorexia	306	66.52
Malaise, bodyache, headache	318	69.13
Cough	138	30.0
Altered sensorium	18	3.91
Convulsion	16	3.48
Intestinal perforation	5	1.08
Intestinal hemorrhage	6	1.30
Hepatomegaly	337	73.26
Splenomegaly	190	41.30
Hepatosplenomegaly	94	20.43

Apart from fever which was present in all cases; hepatomegaly (73.26%), malaise, bodyacheand headache (69.13%), anorexia (66.52%), splenomegaly (41.30%), vomiting (49.13%) and diarrhea (30.21%) were the main presenting features.

Table-4: Elaborates hematologicalprofile observed in typhoid fever cases.

Age (years) n=460	Hemoglobin level (Anemia n= 106 (23.04) (gm/dl)			Leucocytosis (>10000/mm^3) n=81(17.6%)	Leucopenia (<4000/mm^3) n=184(40%)	Eosinopenia (no eosiniphil in PBS) n=66 (14.34%)	Thrombo cytopenia (<1.5lak/ mm^3)n=50 (10.87%)
	< 7	7-≤11 n=106 (23.04%)	>11				
<1 (n=10)	0	0	10(100%)	6(60%)	0	0	0
1-<2 (n=58)	0	14(24.13%)	44 (75.87)	19(32.75%)	21(36.2%)	5(8.62%)	0
2-<5 (n=150)	0	37(24.67%)	113 (75.33%)	23(15.34%)	52(34.67%)	28(18.67%)	14(9.34%)
5-<10 (n=162)	0	37(22.84%)	125 (77.16%)	23(14.2%)	70(43.2%)	23(14.2%)	24(14.81 %)
≥10 (n=80)	0	18(22.5%)	62 (77.5%)	10(12.5%)	41(51.25%)	10(12.5%)	12(15%)

Anemia was observed in 23.04% of cases while 17.6% of cases had leucocytosis. 40% of typhoid fever cases showed leucopenia and eosinopenia was seen in 14.34% of cases. Thrombo cytopenia was noted in 10.87% of cases. Remarkably leucocytosis was found in younger populations; 60% in less than 1-year age group and 32.75% in 1-<2 year age group.

Table-5: Elaborates the antibiotics used in our study and the response obtained.

Antibiotics	No of patients (n=460)	%
Inj Ceftriaxone alone	355	77.17
Inj Ceftriaxone+ Oral Azithromycin	99	21.52
Other drugs	6	1.31

All patients (460) were started treatment with inj. Ceftriaxone after inclusion in the study. Out of them 355(77.17%) responded. In 99(21.52%) patients oral Azithromycin had to be added on 5th or 6th day of Ceftriaxone therapy. Inj. Cefoperazone and inj. Amoxyclav were needed in 6 patients (3 each).

Table-6: Shows the duration of hospitalization in the study population with typhoid fever.

Duration of Hospitalization (days)	No of Patients (n=460)	%
<3	70	15.21
3-6	106	23.04
6-9	239	51.95
>9	45	9.80

51.95% of patients required hospital stay of 6to 9 days; while 9.8% patients had to be kept in Hospital for more than 9 days. Those patients requiring longer hospital stay, had complications like intestinal perforation, hemorrhage, convulsion and altered sensorium. Only 15.21% patients could be discharged within 3 days.

Discussion

Typhoid fever continues to be a significant cause of morbidity in children in developing countries. In the present series typhoid fever accounted for 10.94% of pediatric admissions (460 out of 4200). The majority of cases were seen between 5-10 years of age similar to earlier observation[26]. Highest clustering of cases was observed in the months of August to October. This findingalso corroborated with earlier finding by other researchers [27].

There is an increasing trend of incidence of typhoid fever in children younger than two years. In our series 14.77% cases occurred below 2 years, among them 2.17% (out of 460) cases occurred below 1 year ($p<.05$). Similar findings were noted by other observers also who found high incidence of typhoid fever below 2 years of age [28,29]. In our series high incidence of typhoid fever was noted in children below 5 years (47.37%), which is also due to the fact that our institute is located in a highly typhoid endemic area. This finding is consistent with observations of earlier researchers which showed high incidence of typhoid fever in younger children in highly endemic areas [30]. The high disease burden in preschool children in our study emphasizes the need of vaccination program and improvement in potable water supply and sanitation [31]. In our series 51.74% of cases were male and 48.26% children were females making male: female ratio 1.07, like earlier observation [21,32].

In this study common presenting complaints were fever (100%); hepatomegaly (73.26%); splenomegaly (41.30%); anorexia (66.52%); malaise, bodyache and headache (69.13%); vomiting (49.13%) and diarrhea (30.21%).

Rare but important complications in our series were altered sensorium and 'coma vigil' i.e. muttering delirium (3.91%); convulsion (3.48%); intestinal perforation (1.08%) and intestinal hemorrhage (1.30%). Similar observations were also made by earlier workers in this field though rates of complications were somewhat lower in our series

[32,33]. The zero mortality in our study was mostly due to less complications and early intervention whenever complications were detected and a quite good PICU set-up. Only one child out of 5 cases of intestinal perforation required surgical intervention.

The mortality profile (0%) in our series is consistent with observation by other workers [32,33].

Hematological profile in our study revealed anemia in 23.04% of cases; leucocytosis and leucopenia in 17.6% and 40% cases respectively; eosinopenia in 14.34% children and thrombocytopenia in 10.87% of cases. These hematological alterations were consistent with findings by earlier researchers excepting incidence of leucopenia [33].

Leucopenia was observed in 40% of cases with highest incidence (51.25%) in children in the age group above 10 years ($p<.05$).

Logistic regression analysis comparing patients with and without complications revealed that presence of prolonged fever(>1 week), eosinopenia, elevation of AST, splenomegaly and lack of typhoid vaccination were associated with high risk of complications; similar to observations by other researchers [32,33].

In our series 77.17% patients became afebrile within 6-7 days of IV Ceftriaxone therapy. In only 21.52% of cases Azithromycin had to be added to Ceftriaxone. Treatment with other drugs namely inj. Cefoperazone and inj. Amoxyclav was required in 1.13% of cases. Similar trends were observed in other series also [32,33].

Only 28% of patients in our series received Vi capsular polysaccharide vaccine and vaccine efficacy in our series was only 42% (calculated by the formula: (incidence among unimmunized-incidence among immunized)/ incidence among unimmunized).

The mean duration of hospital stay in our series was 6.7 days which is in conformity with observations by other researchers [33]. In our study Widal test was used as the diagnostic test for typhoid fever because of its cost-effectiveness, availability and rapid performance. Blood culture though considered the gold- standard is not feasible in all settings, lacks specificity and may be false-negative in cases with prior antibiotic treatment [34,35].

Conclusions

Typhoid fever continues to be a major public health problem in children worldwide. In our series typhoid fever hadaccounted for 10.94% of all pediatric admissions. Global emergence of multidrug resistant strains with reduced susceptibility to Fluoro-quinolones is of great concern. Control of typhoid fever relies on clinical information, diagnosis and on understanding of epidemiology of the disease. Different Salmonella sppserovars causing enteric fever have very different ancestries and vaccines are not cross-protective. Public health interventions to minimize human carrier contact, improved personal hygienic measures, incorporation of typhoid vaccination in immunization schedule and inhibition to use of antibiotics in an irrational manner will definitely go a long way to reduce the disease burden both on a short-term and a long-term basis.

Our study shows the pattern of typhoid fever in this part of the country and changing trend affecting younger population; emphasizing the need for implementation of typhoid vaccination (including newly innovated conjugate typhoid vaccine) in a wider scale in highly endemic areas.

Larger studies in this field specially in regions with high incidence of typhoid fever is needed for better understanding of the epidemiology of the disease and hence better disease- control.

Author's Contributions

- Dr Bandyopadhyay performed the entire work. He collected datas from all the cases and compiled them. He performed the statistical analysis.
- Dr Pal conceived the idea and contemplated the study plan. He actually drafted the final manuscript and revised the same by adding many intellectual contents.
- Dr Deyprovided all sorts of technical guidance and assistance for the work.
- Dr Samanta assisted Dr Bandyopadhyay in the study at all points and maintained all coordination with the departments ofPathology, Radiology, Biochemistry and Microbiology as and whenever needed.
- Dr Chakraborti gave necessary guidance during the study. He also added some intellectual contents.

- Dr Mandal provided technical assistance in the study and managed the surgical emergencies in the present series. He also contributed some intellectual contents.

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