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Clinical & Laboratory Profile of Typhoid Fever in Children with Special Emphasis on Drug Resistance.

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Abstract:
Background: *Enteric fever (typhoid and paratyphoid fever)is a major public health concern in developing countries including India. Wide variation in clinical presentations makes its diagnosis on clinical ground a challenging task. Emergence of strain with polymicrobial resistance is a matter of serious concern. This study was conducted in a tertiary care settingto study the myriad clinical manifestations, complications &antibiotic sensitivity pattern of typhoid fever in children.*
Methodology: *This prospective observational study was done at N.M.C.H, Patna from November 2017- April 2019 (18 months).Children between 1-16 years of age with fever for >3 days and suspicion of enteric fever wereenrolled and investigated. 60 blood culture positive cases were finally analyzed.*
Results:*Mean duration of fever was 6.9±2.1 days and the mean duration of hospital stay was 5.5±1.4 days. Most of the cases were >5 years age (80%) with only 20% children being <5 years of age. There was no sex difference with girls and boys ratio being 1.14:1. Fever was the most consistent symptom (100%) followed by malaise(78.33%),anorexia(75%), vomiting(60%), chills(58%), diarrhoea(53.33%) etc; constipation and joint painwere rare. Among the signs, coated tongue was seen in 70%, splenomegaly in 63.33%, hepatomegaly in 53.33% and hepatosplenomegaly in 36.66% cases. Rose spots, icterus as well as complications were not seen. CBC changes were non-specific. Widal test was positive in only 71.7% of culture positive cases. Incidence of MDTRF was high(21.7%). 3rd generation cephalosporins were sensitive in 80-90% cases. Reserve drugs Azithromycin and Meropenemwere sensitive in >90% cases. Some strains were resistant to most of the drugs including 3rd generation cephalosporins, which isworrisome. Re-emergence of sensitivity to 1st line drugs chloramphenicoland TMP-SMZis a good news.*
Conclusion: *Typhoid fever is a multisystem disease with variable clinical presentations. No sign or symptom is specific for its diagnosis which needs correlation with lab investigations which again are not always helpful. Polymicrobial resistance mandates heightened focus on preventive measures.*
Keywords: *Blood culture, clinical profile, drug resistance, multi drug resistant typhoid fever, Salmonella typhi, typhoid fever*
Abbreviations: *MDRTF: multi drug resistant typhoid; NARST: Nalidixic acid resistant salmonella typhi; S. typhi: Salmonella typhii; TMP-SMZ: Trimethoprin-sulfamethoxazole combination drug;*

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I. Introduction

Assessment of a child presenting with fever without an obvious focus is a challenge to most of us. To determine the etiology and plan the management in the first few days is always difficult and yet imperative. In view of the anxiety of the parents, most pediatricians have the tendency to start some antibiotics before any real clue about the etiology irrespective of the act that most of these fevers might just be of viral etiology. In enteric fever this initial antibiotic might modify the course of the disease and pose significant difficulty in interpretation of lab investigations.

Typhoid fever also known as "Enteric fever", is a collective term that refers to both typhoid and paratyphoid fever. It is one of the most common causesof fever in children with variable presentations and significant difference in the signs and symptoms compared to adults.[1]It is a common infectious disease presenting as acute multisystem febrile illness caused by gram negative organism several serovar-S. enterica serotype typhi (formerly S. typhi).Other Salmonella serotypes, particularly S. enterica serotype paratyphi A, B, or C and occasionally typhimurium.[2] In contrast to the western world where its incidence has decreased considerably with the improvements in food handling and water/sewage treatment, it continues to be a major

public health problem in the Indian subcontinent[3,4]. The diagnosis of enteric fever on clinical ground alone is difficult as the presenting features are diverse and similar to those observed with other common febrile illnesses. Definite diagnosis requires the isolation of S.typhi/paratyphi from culture of blood, stool, urine, rose spot, bone marrow and gastrointestinal secretions. Bacteria can be isolated from blood in 80-97% of cases before use of antibiotics.[5] Prompt recognition with timely &appropriate antibiotics and other supportive measure can considerably reduce both morbidity and mortality and is important for favorable outcome.

A major epidemic of drug resistant typhoid fever was first reported in 1972 and subsequently resistance to all the first line drugs (chloramphenicol, co-trimoxazole & ampicillin) was reported. These were called as as Multi Drug Resistant typhoid fever (MDRTF).[6]An increasing frequency of resistance has been reported from all parts of the world, but more so from developing countries.[7] Some strains have shown resistance to fluoroquinolones&3rd generation cephalosporins, which is a matter of great concern.[8]

In endemic areas such as India, classical signs and symptoms in enteric fever are not often seen[9]. This may be owing to the widespread and indiscriminate use of antimicrobials and antipyretics. Unusual manifestations lead to diagnostic dilemma and delay in diagnosis. With this background, we decided to study the clinical presentations, laboratory parameters and drug sensitivity of typhoid fever in a tertiary care setting, which most often caters to cases unsuccessfully treated elsewhere, so that appropriate antibiotic as indicated can be started and incidence of antibiotic resistance decreases.

II. Aims and objectives

Aim: To study the presentations & antibiotic resistance of typhoid fever in children.

Objectives:

1. To study the clinical& laboratory profile of typhoid fever.
2. To evaluate the sensitivity pattern of S.typhi to the commonly used antibiotics.

III. Methodology

Study setting: Pediatrics OPD and IPD at NMCH, Patna

Study duration: 1.5 years from November 2017 to April 2019.

Type of study: Prospective observational study.

Sample size consideration: As average cases of blood culture positive *S.typhi* was 38 per year in our hospital. So, the expected population size was 57 in 1.5 years. Considering confidence level of 95% and Confidence interval of 5% the minimum sample size derived was 50.

Study participants:

Inclusion criteria: Children between 1-16 years of age presenting to OPD or IPD of our hospital with fever for more than 3 days with suspicion of enteric fever on the basis of history, clinical exam & relevant laboratory reports were investigated for the possibility of enteric fever. Other focus of infection like respiratory, nervous, cardiac and genitourinary were ruled out. Children who were blood culture positive for S.typhi were finally analyzed.

Exclusion criteria: Children with negative blood culture or growth of an organism other than S. typhi, and cases diagnosed as enteric fever on clinical ground or Widal tests were excluded.

Afterobtaining informed consent participants were enrolled in this study. Detailed history, thorough clinical examination and laboratory investigations at the time of admission and during the course of hospital stay were performed in all and the findings recorded in the study proforma.In this study, suspected cases of enteric fever were started on intravenous Ceftriaxone @75mg/kg/day in two divided doses. If fever didn't subside and the organism was found to be resistant to ceftriaxone in culture report, treatment was changed to another suitable sensitive drug.

Data analysis: Pertaining data was entered in Microsoft excel sheet and analyzed using SPSS Software version 18. Chi-square test for discrete variables and Student t–test for continuous variables was used. Confidence limit was set at 95% &P value <5% was considered significant.

IV. Observations And Results

In our study period, we analysed 60 culture positive cases of S. typhi and following observations were made:

Table 1: Basic variables of patients:

Symptoms	Number	Percentage
Age <5 years	12	20%
Age 5.-16 years	48	80%
Males	28	46.67%
Females	32	53.33%

Past history of typhoid	3	5%
History of street food in <2 weeks	34	56.66%
Water supply source: Municipality Borewell Others	 38 18 4	 63.33% 30% 6.66%

Table 2: Peak Temperature profile

Temperature in °F	**No. of cases & (%)**
99-101°F	8(13.33%)
101.1-103°F	43(71.66%)
103.1-105°F	9(15%)

Table 3: Total duration of fever:

Fever duration (days)	**No. of cases & (%)**
4-7	24(40%)
8-14	36(60%)
>14	0 (0)

Table 4: Analysis of symptomatology

Symptoms	**Number**	**Percentage**
Fever	60	100
Chills	35	58.4
Headache	31	51.66
Malaise	47	78.33
Vomiting	36	60
Pain abdomen	27	45
Cough	21	35
Diarrhoea	32	53.33
Constipation	11	18.33
Anorexia	45	75
Joint pain	5	8.33
Altered behaviour	0	0

Table 5: Analysis of signs

Clinical Sign	**Number**	**Percentage**
Pyrexia	60	100
Delirium	0	0
Bradycardia	14	23.3
Dehydration	28	46.7
Coated tongue	42	70
Rash	0	0
Anaemia	22	36.66
Abdominal tenderness	0	0
Hepatomegaly	32	53.33
Splenomegaly	38	63.33
Hepatosplenomegaly	22	36.66
Signs of LRTI	4	6.66
Signs of meningitis	0	0
Complications	0	0

Table6: Comparison of symptoms

Symptoms	< 5 YEARS (n=12)		5- 15 YEARS (n=48)		P value
	Present	Absent	Present	Absent	
Fever	12	0	48	0	-------
Chills	1	11	34	14	0.0001
Headache	3	9	28	20	0.0404
Malaise	7	5	40	8	0.0623
Vomiting	8	4	28	20	0.6014
Pain abdomen	5	7	22	26	0.7968
Cough	3	9	18	30	0.4207
Diarrhoea	9	3	23	25	0.0952
Constipation	1	11	10	38	0.3209
Anorexia	9	3	36	12	1.0000
Joint pain	1	11	4	44	1.0000
Altered behaviour	0	12	0	48	--------

Table 7: Comparison of signs

Signs	< 5 YEARS (n=12)		5- 15 YEARS (n=48)		p value
	Present	Absent	Present	Absent	
Pyrexia	12	0	48	0	-------
Delirium	0	12	0	48	-------
Bradycardia	2	10	12	36	0.545
Dehydration	8	4	20	28	0.123
Coated tongue	4	8	38	10	0.002
Rash	0	12	0	48	-------
Anaemia	3	9	19	29	0.352
Abdominal tenderness	0	12	0	48	-------
Hepatomegaly	6	6	26	22	0.797
Splenomegaly	5	7	33	15	0.084
Hepato-splenomegaly	3	9	19	29	0.352
Signs of LRTI	1	11	3	45	0.797
Meningeal signs	0	12	0	48	-------
Complication	0	12	0	48	-------

Table 8: Laboratory parameters:

Lab Parameter	**Levels**	**Number(%)**
HB	Anaemia (<11g %)	39(65)
	Hb (>11g%)	21(35)
TLC	Leucocytosis(>11000/cum3)	9(15%)
	Count (4000-11000/cum3)	38(63.3)
	Leucopenia(<4000/cum3)	13(21.7)
Polymorphs	Neutrophil count (>65%)	11(18.33)
	Neutrophil count (50-65%)	32(53.33)
	Neutrophil count (<50%)	17(28.33)
Eosinophils	Eosinophil count (0-1%)	12 (20)
	Eosinophil count (2-5%)	35(58.33)
	Eosinophil count (>5%)	13(21.66)
Lymphocytes	Lymphocyte count (<20%)	6(10)
	Lymphocyte count (20-50%)	49(81.66)
	Lymphocyte count (>50%)	5(8.33)
Widal test	TO ≥1:120 Significant	43(71.7)
BBlood Culture	Positive for S. typhi---------	-----60 (100) 60(100) 60(100)-----

Table 9: Antibiotic sensitivity pattern:

Antibiotics tested	**Sensitivity No. (%)**	**Resistance No. (%)**
Ampicillin	24 (40%)	36 (60%)
Chloramphenicol	48 (80%)	12 (20%)
Co-trimoxazole	44 (73.33%)	16 (26.67%)
Ciprofloxacin	31 (51.66)	29(48.33%)
Ofloxacin	34(56.66%)	26(43.33%)
Levofloxacin	44 (73.33%)	16(26.67%)
Azithromycin	55 (91.7%)	5 (8.3%)
Cefixime	50 (83.33%)	10 (16.66%)
Cefotaxime	51 (85%)	9 (15%)
Ceftriaxone	54 (90%)	6 (10%)
Cefuroxime	43 (71.7%)	17 (28.3%)
Amikacin	53(88.3%)	7(11.7%)
Meropenem	56(93.3%)	4 (6.7%)

Table 10: Clinical response to treatment

Onset of defervescence	**Frequency**	**Percentage** (%)
3 Days	29	48.33
4-7 Days	26	43.33
>7 Days	5	8.33

V. Discussion

Typhoid fever is a common infectious disease presenting as acute multisystem febrile illness. Our study has presented detailed study of 60cases of blood culture positive Typhoid fever about symptoms, clinical signs, investigations and in vitro antibiotics sensitivity/resistance pattern and treatment response.

In our study 48(80%) children were above 5 years and 12(20%) children were below 5 years. Mean age was 7.4 years (SD 2.84). Our findings are similar to most of the studieswho have reported typhoid fever being more common beyond 5 years[10] of age. The higher incidence in school going children can be explained from the fact thatschool children are at high risk of consuming contaminateddrinking water. They are also exposed to various food items from street vendors. These factors make them more vulnerable to exposure to typhoid bacilli. Hoverer the study of Sinha A et al found almost equal incidence in the two age groups. This however can be attributed to the fact that they carried out their study in a low-income urban area of Delhi, with active surveillance for case detection.[11]Variability in diagnosis among younger children could be related to the high incidence of other illnesses in this age group, difficulty in obtaining adequate volumes of blood for culture, lower rates of exposure, and protective effect of breastfeeding. Also, we didn't find any sex predilection in this study, Different researchers[12,13,14] have also reported variable sex incidences. In this study, fever was the presenting symptom in all the patients which was more of remittent or intermittent type, classical stepladder rise of temperature was not seen.The shortest duration of fever observed was 5 days in one patient who was admitted on day 3 of fever, and longest duration was 13 days. 60% cases had fever for 8-14days and 40% had fever for 4-7days. Mean duration of fever was 6.9±2.1 days. Similar finding has been reported byRanganatha*et al*[15] and others.Defervescence of fever shows the clinical response to treatment. In 48.3% cases, onset of defervescence was by 3 days, in 43.3% cases it was 4-7 days and only in 8.3% cases the onset of defervescence was >7days. Mean duration for onset of defervescence was 3.8 days and the mean duration of hospital stay was 5.5±1.4 days.Other common symptoms after fever (in order) were malaise(78.33%),anorexia(75%),vomiting(60%), chills(58%),diarrhoea(53.33%),headache(51.66%), pain abdomen (45%), cough(35%)and in few cases constipation & joint pain. Our findings are in agreement (with few variations which is quite obvious given the variable presentations of the disease)with the studies of Modi[16], Kakaria*et al*[17], &Gupta*et al*[18].

Among signs, presence of coated tongue was seen in 70% cases. However, other studies have reported the presence of a coated tongue in the range of 35-65%.[19,20]Higher incidence in our study may be due to poor oral hygiene seen among the high number of poor and underprivileged children visiting our hospital.In our study splenomegaly was found in 63.3% case which is comparable to the findings of Joshi*et al*[21] and Laishram*et al*[22]. Bradycardia was found in only 23.3% cases which is not a consistent finding among chidren with typhoid. Other signs observed were dehydration due to diarrhoea and in few cases anemia. In our study, other signs like rose spots and icterus were not noted. Complications like GI bleeding, ulceration, altered sensorium, meningitis were also not noted. This was probably because these children presented to us early in the course of disease before complications could ensue.

We also compared symptomatology as well as signs between the age groups of <5 years and 5-16 years in this study to find out if any specific difference exists in the presentation between pre-school children and school going children. Though chills and headache was significantly more common in 5-16 years age group, this can be simply due to the under-reporting of chills and headache in case of small children. However, there was also a statistically significant difference in the presence of coated tongue between the two age groups, with the sign commoner in school going children. The exact reason for this difference is not known but it is suggested that it might be related to the food habits and oral hygiene. In a recent meta-analysis, Britto C et al[23] couldn't find any specific relationship between age groups and typhoid presentation in Indian children. However there was some relationship in African children in their analysis.

In the present study 65% cases had anaemia with haemoglobin less than 11gm%. The lowest haemoglobin level found was 6.7gm% in 1.5 year old male child. The lowest TLC noted was 2100/cu mm and highest TLC noted was 16400/cu mm. 15% cases had leucocytosis, 21.7% had leukopenia and 63.3% had TLC within normal range. Neutrophilia was seen in 18.33%, Neutropenia in 28.33% and normal counts in 53.33%. Eosinophilia was seen in 21.66%. Eosinopenia in 20% and the rest had normal eosinophil counts.Lymphocytosiswas seen in 8.33% cases and lymphpenia in10% cases. From this, it is clear that there is no specific pattern in blood counts which is hallmark of typhoid fever. This is in agreement with the findings of IAP task force report.[24]We did Widal test in all cases and it was considered positive if there was atleast 2 fold or more rising titre or a titre of 'H'1:120 or more or 'O'1:120 or more. Among the 60 culture positive cases, only 43 (71.7%) cases showed a positive reaction which is lesser as compared to 89% as reported by Sudharshan[25]. This can be attributed to inadequate blood sampling or prior intake of antibiotics.

In the present study, antibiotic sensitivity testing was donein all culture positive cases with the drugs commonly used in typhoid fever. Ampicillin, chloramphenicol, co-trimoxazole were considered the first line drugs in past and resistant to all these three drugs is known as multidrug resistant typhoid fever (MDRTF). In our study, first line drug Ampicillin was sensitive in only 40% cases, Chloramphenicol in 80% cases and Co-trimoxazole in 73% cases which indicate re-emergence of sensitivity of these 2 first line drugs. However, 21.7% (13) cases were MDRTF which is comparable to the studies ofGeetika D *et al*[26] *and* Gopal*et al*[27]and it corroborates with the trend of increasing sensitivity to chloramphenicol and cotrimoxazole. However, the incidence of MDRTF is high in studies by Kumar et al,[28] this high incidence may reflect the indiscriminate use of antibiotics in their region. In Quinolone group, ciprofloxacin was sensitive in only 51.66% and ofloxacin in

56.66%, meaning almost half of patients were resistant to them. However, sensitivity of levofloxacin was surprising high (73.33%). The lessersensitivity of ciprofloxacin and ofloxacin may be attributed to their frequent, unjustified as well as underdose usage in diarrhea and other common childhood ailments, thereby resulting in resistance. Levofloxacin is less commonly misused in children, so it might have retained its sensitivity to a greater extent. Among 3rd generation cephalosporins, oral drug Cefixime was sensitive in 81.7% cases. I.V antibiotics cefotaxime and cetriaxone were sensitive in 85% and 90% cases respectively. We also found Azithromycin to be sensitive in 93.3% cases, and to our great relief it was sensitive in all cases which were resistant to all first line drugs as well as quinolones plus cephalosporins. However, this is a matter of great concern that there was sizable number of such cases which were resistant to this extent (6.6%). Amikacin was sensitive in 88.3% cases which is worrisome given its near 100% sensitivity reported in most of the earlier studies. Surprisingly there were 5% cases resistant to even Meropenem which is considered to be the most effective drug against S. typhi. To add to our worry was 1 patient who was sensitive to only Azithromycin, cotrimoxazole & chloramphenicol and resistant to all other drugs including Meropenem. This means than the alarm bell is ringing loud[29] and there needs to be a heightened focus on robust preventive measures, especially conjugate vaccines before we come across more cases with such high degree drug resistance.

VI. Conclusion

Fever, malaise, anorexia, vomiting, chills, headache, coated tongue, diarrhea and organomegaly are the common clinical manifestations of enteric fever. Normal to raised leukocyte count is more common,however, neutropenia and eosinopenia may be a prominent finding. We found re-emergence of strains with high sensitivity to previously used first line antibiotics like chloramphenicol (80%) and co-trimoxazole (73.33%) but less with ampicillin (40%). The emergence of MDRTFstrains remains an area of much concern. Most importantly, there were even cases with resistance to all antibiotics except for 2-3 drugs. This poses a serious public health concern and demands heightened interest in robust preventive measures including effective vaccines. Though we found increased emergence of sensitivity tochloramphenicol & co-trimoxazole, further research is needed for recommendation regarding a trial for theses oral antibiotics before starting injectable drugs.

Limitation:

There were few limitations to our study. First (and perhaps the most important), it's a single centre study with a low sample size. Second, Nalidixic acid sensitivity test was not done, which is considered as surrogate marker of quinolones sensitivity/resistance. Third, Bacteriophage typing facility is not available in to differentiate between S.typhi and S. paratyphi A,B,C. Fourth, facility to determine the minimum inhibitory concentration (MIC) of different antibiotic is not available to assess the increasing or decreasing susceptibility of isolates. Fifth, most of the patients didn't turn up for follow up, so, we couldn't study the relapse rates of treatment.

Conflict of interest: None

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