ORIGINAL RESEARCH

To study the antibiotic sensitivity pattern among typhoid fever cases in a tertiary care

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ABSTRACT
Background: Typhoid fever occurs in all parts of the world but over the past four decades with the advent of improvements in food handling and water /sewage treatment, enteric fever has become a rare occurrence in the western part of the world. But in contrast it continues to be a major public health problem where there is substandard water supply, sanitation and poor hygiene mainly in low socio-economic strata and it is endemic in most developing countries including India where patients report throughout the year with monsoon clustering patterns. Low standards of living, rapid population growth, increased urbanization, inadequate human waste treatment, limited water supply and overburdened health care system are the main reasons behind the higher endemicity in India. **Aim:** Therefore, this study is aimed to study the antibiotic sensitivity pattern among typhoid fever cases in a tertiary care setting, which most often caters to referred cases unsuccessfully treated elsewhere. **Methods:** The present study was conducted at Dept. of PEDIATRICS, NALANDA MEDICAL COLLEGE AND HOSPITAL, PATNA, after obtaining clearance from institutional ethical committee, Informed consent was taken from the parents before including into the study. **Results:** In the present study, minimum age was 1year and maximum age was 15 years. Number of cases below 2 years constituted 12.66%, 2-10 years constituted 54% and 10-15 years constituted 33.33%. Overall cases of males were 58.67% and of female were 41.33%. In each age group male cases were more than female cases. **Conclusions:** In cephalosporin group, ceftriaxone sensitivity is high and it is in use since last two decades with good results.An adequate trial for antibiotics like chloramphenicol or oral co-trimoxazole can be tried before starting injectable antibiotics due to increased emergence of sensitivity to these drugs.
Keywords: antibiotic sensitivity pattern, typhoid fever

INTRODUCTION

Assessment of a child presenting with fever is always a challenge to most of the Pediatricians. To determine the etiology and plan the management in the first few days is always difficult. In view of the anxiety of the parents most pediatricians have the tendency to start some antibiotics before any real clue about the etiology. Most of these fevers might just be of viral etiology unnecessarily managed with antibiotics. 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 and it is one of the common causes of fever in children with varied presentation 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-*Salmonella enterica*serotype *typhi* (formerly *S. typhi*) and other Salmonella serotypes, particularly *Salmonella enterica*serotypes, *paratyphi A, B, or C* and occasionally *typhimurium*[2]. In contrast to other salmonella serotypes, the etiologic agents of enteric fever have no known hosts other than humans. It is usually transmitted by the faeco-oral route in many countries with poor sanitation and contaminated water and food. It is also transmitted through close contact with acutely infected individuals or chronic carriers[3]. The incubation period is 7 -14 days but can range up to 30days.

Typhoid fever occurs in all parts of the world but over the past four decades with the advent of improvements in food handling and water /sewage treatment, enteric fever has become a rare occurrence in the western part

of the world. But in contrast it continues to be a major public health problem where there is substandard water supply, sanitation and poor hygiene mainly in low socio-economic strata and it is endemic in most developing countries including India where patients report throughout the year with monsoon clustering patterns. Low standards of living, rapid population growth, increased urbanization, inadequate human waste treatment, limited water supply and overburdened health care system are the main reasons behind the higher endemicity in India.

Disease is clinically characterizedby prolonged fever with chills and rigor (in>75%), headache, anorexia, nausea, vomiting, cough, weakness, sore throat, abdominal discomfort with either diarrhea or constipation. Physical findings include coated tongue, rose spot, hepatomegaly, splenomegaly, epistaxis, and relative bradycardia. In general, typhoid patients are less severely ill and severity in typhoid usually reflects localization of the infection to the Payer's patches and consequent intestinal ulceration rather than fulminant septicemia[4].Sometime the disease presents with complications like gastrointestinal perforation, hemorrhage, hepatitis, cholecystitis, neuropsychiatric symptoms, pneumonia, anemia, disseminated intravascular coagulation, relapse and chronic carrier state[4].The diagnosis of enteric fever on clinical ground is difficult as the presenting features are diverse and similar to those observed with common febrile illness. So the definitive diagnosis of enteric fever requires the isolation of*S.typhi/ paratyphi* from culture of blood, stool, urine, rose spot, bone marrow and gastrointestinal secretion (can be useful for diagnosis). Bacteria can be isolated from blood in 80-97% of cases before use of antibiotics[5]. The prompt recognition and timely appropriate management with appropriate antibiotics and supportive measure of typhoid fever can considerably reduce both morbidity and mortality and are important for favorableoutcome. The introduction of Chloramphenicol in 1948 by Woodward and his associates, initiated an era in the treatment of typhoid[6]. Apart from Chloramphenicol many other drugs were tried in the treatment ofenteric fever like Ampicillin, Cotrimoxazole with good result and all these drugs were in first line of treatment.

The firstmajor epidemic of multi drug resistance to *Salmonella typhi* was reported in 1972[7]. And resistancedeveloped simultaneously to all the drugs used in first line treatment (chloramphenicol, co-trimoxazole and ampicillin) and are known as Multi Drug Resistant typhoid fever (MDRTF).[8]

Since then an increasing frequency of antibiotic resistance has been reported from all parts of the world, but more so from developing countries[9]. And after the outbreak of MDRTF, the fluoroquinolones and cephalosporins were in use. Then later onazithromycin was introduced in treatment of typhoid fever with good results. Thethird-generation cephalosporins (ceftriaxone, cefotaxime, cefoperazone and cefixime) and azithromycin are currently regarded as the antibiotics of choice for treating MDR strains. However, an issue of great concern is that currently some strains of S.typhi have shown reduced susceptibility to fluoroquinolones and third-generation cephalosporin.[10,11,12,13]

With this background in mind, it becomes imperative to assess the extent of drug sensitivity before treatment is administered and appropriate antibiotic as indicated by sensitivity tests should be employed to prevent the development of resistant strains of*S. typhi*.and indiscriminate use of drugs in typhoid fever should be discouraged. Therefore, this study is aimed to study the antibiotic sensitivity pattern among typhoid fever cases in a tertiary care setting, which most often caters to referred cases unsuccessfully treated elsewhere.

METHODOLOGY

The present study was conducted at Dept. of PEDIATRICS, NALANDA MEDICAL COLLEGE AND HOSPITAL, PATNA, after obtaining clearance from institutional ethical committee, Informed consent was taken from the parents before including into the study.Children of 1 to 15 years who are admitted in NMCH ,Patna with fever of more than 5 days and are clinically suspected to have typhoid fever.Prospective Observational Study.A total sample size was taken into study group is 60.

STUDY DURATION

December 2017 to December 2019.

INCLUSION CRITERIA

1. Children of 1 to 15 years who are getting admitted in NMCH, Patna
2. Children having fever of more than 5 days.
3. Only those subjects will be selected who aew suspected to have typhoid by history, physical examinations and routine laboratory investigations.
4. Febrile children with suspected typhoid fever will be included in the study irrespective of receiving antibiotics before admission in NMCH.

EXCLUSION CRITERIA

1. Declined consent.
2. Known or suspected impairment of immunological function in patients.
3. Cases with developmental delay or neurological impairment.
4. Patients on medication like antiepileptics, antitubercular drugs or chemotherapy.
5. Patients who received any immunosuppressive drug or immunoglobulin within last 12 weeks of before admission.
6. Patients with severe malnutrition.

STUDY PROTOCOL

A detailed clinical history, a thorough clinical examination and laboratory investigations at the time of admission and during the course of hospital stay

were performed in all cases and the findings were recorded in a pre-made proforma. Informed consent was obtained from the parents.

Clinical history: On admission, a detailed clinical history was taken in each case which included the duration of fever, presence of symptoms like loss of appetite, nausea and vomiting, diarrhea/constipation and pain abdomen. History of headache, cough, burning micturition, high colored urine and skin rashes were also taken.

Clinical examination: A detailed general and systemic examination was done in all cases. In general examination, note of general condition, level of consciousness, temperature, pulse rate, pulse character, respiratory rate, blood pressure, pallor, icterus, rash, petechiae and lymphadenopathy was noted. In systemic examination, children were thoroughly examinedforaltered sensorium, meningismus, abdominal distension, abdominal tenderness, respiratory added sounds, hepatomegaly and splenomegaly. All associated findings and complications, if any, were noted in all children.

Laboratory investigations: A blood sample for complete hemogram (Normal Hb>11gm%, TLC 4000-11000 Poly 50-65%, Lympho-20-45% Eosinophil 1-4%).[70]Widal test,Typhi dot ,blood culture and sensitivity were obtained in all children on admission and thereafter if the child condition warranted it. The chest and abdominal X-rays, ultrasound abdomen was done in children when indicated.

Culture & Isolation: 5ml venous blood samples will be inoculated into Mac- Conkey Broth by streaking method after which the plates will be incubated at 37°C for 24hours. Isolates from the primary cultures will be sub-cultured into fresh Mac Conkey Broth medium to obtain pure isolates. Pure isolates will be inoculated in nutrient agar slant and stored at 5°C for further characterization and identification.[14]

Antibiotic Sensitivity Test: Test will be done using Kirby-Bauer method on Mueller Hinton Agar. 3.8 g of this agar will be dispensed into a sterile conical flask.100 mL of distilled water will be poured into the flask and stirred to dissolve the agar. The mixture will be autoclaved and then poured into petri dishes. On gelling, the negative antibiotic sensitivity disk will be introduced using sterile forceps and then incubated for 24 hours at 37°C.[14]

List of Antibiotics for which Sensitivity test were carried out and recorded for studied: – Amoxicillin, Amikacin, Ciprofloxacin, Cefuroxime, cotrimoxazole, Ofloxacin, Azithromycin, Levofloxacin, Meropenem, Cefotaxime, Ceftriaxone, Cefixime, Chloramphenicol.

Treatment : The patients with a presumptive clinical diagnosis of typhoid fever were initially treated with ceftriaxone-100mg/Kg/day in two divided doses by intravenous route for 2 weeks. In some patients who didn't want to stay after defervescence period were discharged with oral Cefixime 20mg/kg/day in two divided doses. The midcourse modification of therapy was done after the availability of blood culture and sensitivity report. The clinical course was closely monitored and both the period of defervescence and regression of hepatosplenomegaly were recorded The clinical response to therapy was considered inadequate if there was deterioration or no clinical improvement within 7 days of starting specific therapy. The drug efficacy was judged primarily by the patient's clinical response with particular attention being given to the number of days of treatment required to make the patient afebrile. On discharge, the children were put on a course of cefixime 20mg/kg/day or oral ciprofloxacin 20mg/kg/day to complete a total duration of 14days.

ASSESSMENT

- Daily examination of the cases was done and progress was recorded. Time taken for temperature to touch normal was recorded. Pulse rate at the height of temperature was also noted.
- Regression of hepatosplenomegaly was also noted.
- Patients were monitored for any complications or side effects of the drugs given.
- Duration of stay of patients inhospital.
- Follow up of patients for evidence ofrelapse.

RESULTS

The statistical analysis of data was performed using the computer program, statistical package for social sciences (SPSS for windows, version 20.0 Chicago, SPSS Inc.) And Microsoft Excel 2010.

In the present study, minimum age was 1year and maximum age was 15 years.Number of cases below 2 years constituted 12.66%, 2-10 years constituted 54%and 10-15 years constituted 33.33%. Overall cases of males were 58.67% and offemale were 41.33%. In each age group male cases were more than female cases.

In symptom analysis all cases presented with fever followed by malaise in 70% cases, anorexia in 66.6% cases, pain abdomen in 60% cases, chills in 58.4% cases, headache in 56.6% cases, vomiting in 55% cases, diarrhoea in 50% cases, cough in 41.6% cases, constipation in 15% cases and joint pain in 5% cases. In less than 2 years age group as shown in table above , the common presentation was fever followed by diarrhoea in 84.2% cases, vomiting in 68.4% cases, cough in 42% cases. Chills, headache and malaise could not be assessed. Joint pain and altered behavior were absent.

In age group between 2 to 10 years all cases had fever followed by malaise in 76.5% cases, pain abdomen in 74% cases, anorexia in 70.3% cases, chills in 65.4% cases, headache in 58% cases, vomiting in 54.3% cases, diarrhea in 48.1% cases, cough in 42% cases, constipation in 17.2% cases and joint pain in 6.17% cases. None had altered behavior.

In present study the total no. of cases were 50 in>10 years age group as shown in table above. All cases presented with fever followed by malaise in 86%

cases, anorexia in 80% cases, headache in 76% cases, chills in 70% cases, pain abdomen in 60% cases, vomiting in 52% cases, cough in 42% cases,diarrhea in 40% cases, constipation in 18% cases and joint pain in 6% cases. None of the cases presented with altered behavior.

In present study the analysis of all cases was done and all the cases were having pyrexia followed by coated tongue in 70% cases, dehydration in 50% cases, hepatomegaly in 43.33% cases, anaemia in 36.66% cases, abdominal tenderness in 25% cases, hepatosplenomegaly in 25% cases, bradycardia in 20% cases, splenomegaly in 14% cases and signs of bronchitis (crepitations) in 10% cases. None of cases presented with rashes, signs of meningitis, delirium and any complications during hospital stay.In less than 2 years of age group, total no. of cases were 19 and all cases had pyrexia followed by dehydration in 52.6% cases; anaemia and hepatomegaly in 26.3% cases; coated tongue, bradycardia, hepatsplenomegaly in 15.8% cases; signs of bronchitis (crepitations) in 10.5% cases andsplenomegaly in 5% cases. None of the cases developed rash, abdominal tenderness (signs of G.I ulceration, perforation, bleeding), delirium, meningitis and any complication during hospital stay.

In age group between 2 to 10 years,total no. of cases were 81. All hadpyrexia followed by coated tongue in 74.1% cases, dehydration in 49.4% cases, hepatomegaly in 45% cases, abdominal tenderness in 40.7% cases, Anaemia in 37% cases, hepatosplenomegaly in 30.9% cases, bradycardia in 20.9% cases, splenomegaly in 14.8% cases and bronchitis in 9.9 % cases..None of the cases had meningitis, delirium ,perforation and rashes. In more than 10 years of age group, total no. of cases were 50 and all cases had pyrexia followed by coated tongue in 84% cases; dehydrations in 50% cases; hepatomegaly in 46% cases; anaemia in 40% cases; hepatosplenomegaly and bradycardia in 20% cases; splenomegaly in 16% cases and abdominal tenderness and signs of bronchitis in 10% cases. None of the cases developed rash, delirium, meningitis and any complications during hospital stay.

In present study minimum duration of fever was 5 days and maximum was 18 days. 8% cases had fever of more than 14 days, 60% cases had fever between 8-14 days and 32% cases had fever for 5-7days. None of cases had fever more than 18 days.

In present study peak temperatures noted throughout the illness was between 101-103^{0}F in 73.3% cases, more than 103^{0}F in 16.7% cases, and 10% cases had maximum temperature of 101^0 F. Maximum temperature noted was 104^{0}F. Mean temperature was 102.6^{0}F.

Table 1: Comparison Of Presenting Symptoms In Different Age Groups.

Table 1A:

Symptoms	< 2 YEARS (n=19)		2 – 10 YEARS (n = 81)		p-value
	Present	Absent	Present	Absent	
Fever	19	0	81	0	
Chills	0	19	53	28	
Headache	0	19	47	34	
Malaise	0	19	62	19	
Vomiting	13	6	44	37	
Pain abdomen	0	19	60	21	
Cough	8	11	34	47	
Diarrhoea	16	3	39	42	
Constipation	0	19	14	67	
Anorexia	3	16	57	24	
Joint pain	0	19	5	76	
Altered behaviour	0	19	0	81	

Table 1 B:

Symptoms	2 – 10 YEARS (n = 81)		> 10 YEARS (n = 50)		p-value
	Present	Absent	Present	Absent	
Fever	81	0	50	0	
Chills	53	28	35	15	
Headache	47	34	38	12	
Malaise	62	19	43	7	
Vomiting	44	37	26	24	
Pain abdomen	60	21	30	20	
Cough	34	47	21	29	
Diarrhoea	39	42	20	30	
Constipation	14	67	9	41	

Anorexia	57	24	40	10	
Joint pain	5	76	3	47	
Altered behaviour	0	81	0	50	

Table 1 C:

Symptoms	**< 2 YEARS (n=19)**		**> 10 YEARS (n = 50)**		**p-value**
	Present	**Absent**	**Present**	**Absent**	
Fever	19	0	50	0	
Chills	0	19	35	15	
Headache	0	19	38	12	
Malaise	0	19	43	7	
Vomiting	13	6	26	24	
Pain abdomen	0	19	30	20	
Cough	8	11	21	29	
Diarrhoea	16	3	20	30	
Constipation	0	19	9	41	
Anorexia	3	16	40	10	
Joint pain	0	19	3	47	
Altered behaviour	0	19	0	50	

Table 2: Comparison Of Physical Signs In Different Age Groups.
Table 2 A:

Clinical Sign	**< 2 YEARS (n=19)**		**2- 10 YEARS (n=81)**		**p-value**
	Present	**Absent**	**Present**	**Absent**	
Pyrexia	19	0	81	0	
Delirium	0	19	0	81	
Bradycardia	3	16	17	64	
Dehydration	10	9	40	41	
Coated tongue	3	16	60	21	
Rash	0	19	0	81	
Anaemia	5	14	30	51	
Abd. tenderness	0	19	33	48	
Hepatomegaly	5	14	37	44	
Splenomegaly	1	18	12	69	
Hepatosplenomegaly	3	16	25	56	
Signs of Bronchitis	2	17	8	73	
Signs of meningitis	0	19	0	81	
Complication	0	19	0	81	

Table 2 B:

Clinical Sign	**2 – 10 YEARS (n=81)**		**>10 YEARS (n=50)**		**p-value**
	Present	**Absent**	**Present**	**Absent**	
Pyrexia	81	0	50	0	
Delirium	0	81	0	50	
Bradycardia	17	64	10	40	
Dehydration	40	41	25	25	
Coated tongue	60	21	42	8	
Rash	0	81	0	50	
Anaemia	30	51	20	30	
Abdominal tenderness	33	48	5	45	
Hepatomegaly	37	44	23	27	
Splenomegaly	12	69	8	42	
Hepatosplenomegaly	25	56	10	40	
Signs of Bronchitis	8	73	5	45	
Signs of meningitis	0	81	0	50	
Complication	0	81	0	50	

Table 2 C:

Clinical Sign	< 2 YEARS (n=19)		>10 YEARS (n=50)		p-value
	Present	Absent	Present	Absent	
Pyrexia	19	0	50	0	
Delirium	0	19	0	50	
Bradycardia	3	16	10	40	
Dehydration	10	9	25	25	
Coated tongue	3	16	42	8	
Rash	0	19	0	50	
Anaemia	5	14	20	30	
Abdominal tenderness	0	19	5	45	
Hepatomegaly	5	14	23	27	
Splenomegaly	1	18	8	42	
Hepatosplenomegaly	3	16	10	40	
Signs of Bronchitis	2	17	5	45	
Signs of meningitis	0	19	0	50	
Complication	0	19	0	50	

LABORATORY FINDING

Table 3: Laboratory profile

Lab Parameter	Levels	No. of Case (%)
HB	Anaemia (<11g %)	55(36.66)
	Hb (>11g%)	95(63.33)
TLC	Leucocytosis(>11000/cum^3)	15(10)
	Count (4000-11000/cum^3)	110(73.3)
	Leucopenia(<4000/cum^3)	25(16.6)
Polymorphs	Neutrophil count (>65%)	38(25)
	Neutrophil count (50-65%)	43(28.33)
	Neutrophil count (<50%)	70(46.66)
Eosinophils	Eosinophil count (<1%)	0 (0)
	Eosinophil count (1-4%)	118 (78.33)
	Eosinophil count (4-6%)	33(21.66)
Lymphocytes	Lymphocyte count (<20%)	15(10)
	Lymphocyte count (20-45%)	120(80)
	Lymphocyte count (>45)	15(10)
Widal test	TO,TH ≥1:120 Significant	113(75)
Blood Culture +VE	----------	45(30)

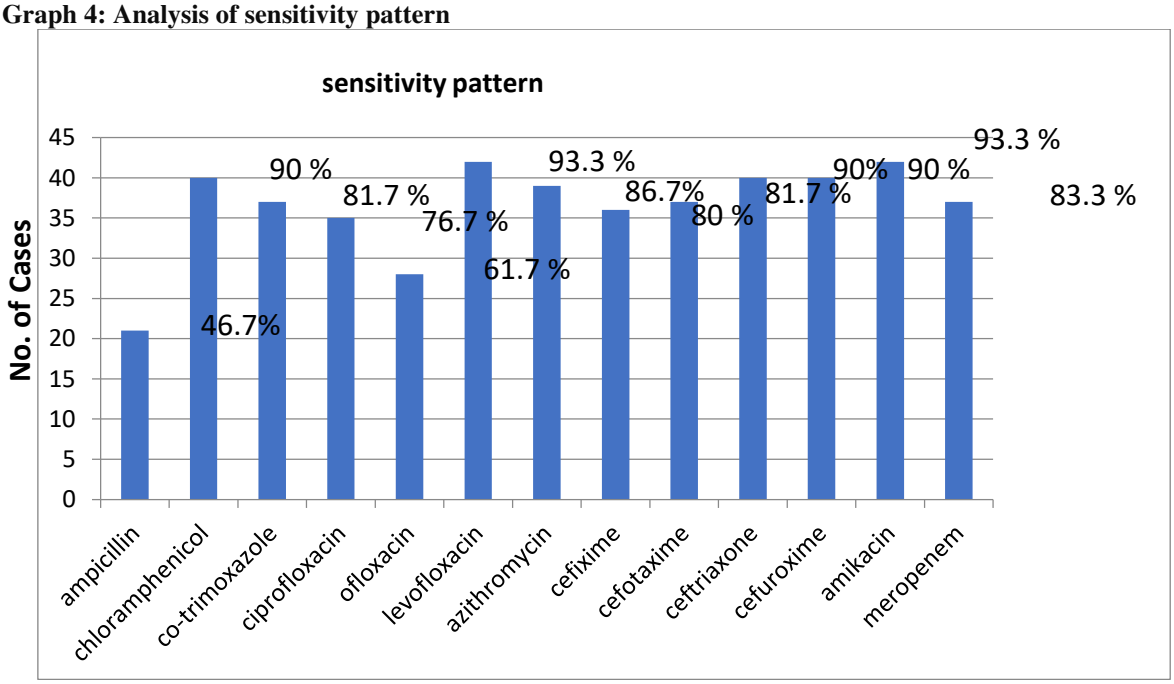
In laboratory investigation 36.6% (55) cases had anaemia with hemoglobin less than 11gm%, the lowest level found was 7.5gm% in 1 year old child. 16.6% cases had leucopenia and 73.3% cases had TLC within normal range and 10% cases had leucocytosis. 78.3% cases had eosinophil count in range of 1-4% and 21.6% cases in range of 4-6%.Widal test was done in all the cases in 2nd week but only 52% cases showed positive result.

Table 4: Antibiotic sensitivity and resistance pattern in vitro.

Antibiotics	Sensitivity		Resistance	
	No. of case	%	No. of case	%
Ampicillin	21	46.7	24	53.3
Chloramphenicol	40	90	5	10
Co-trimoxazole	37	81.7	8	18.3
Ciprofloxacin	35	76.7	10	23.3
Ofloxacin	28	61.7	17	38.3
Levofloxacin	42	93.3	3	6.7
Azithromycin	39	86.7	6	13.3
Cefixime	36	80	9	20
Cefotaxime	37	81.7	8	18.3
Ceftriaxone	40	90	5	10
Cefuroxime	40	90	5	10
Amikacin	42	93.3	3	6.7
Meropenem	37	83.3	8	16.7

Sensitivity pattern of isolates S.typhi as shown in table above against the first line drug – Ampicillin was found to be sensitive in 46.7% cases, Chloramphenicol in 90% cases and Co-trimoxazole in 81.7% cases.Quinolones like Ciprofloxacin was found to be sensitive in 76.7% cases, Ofloxacin in 61.7% cases, Levofloxacin in 93.3% cases(not done against Nalidixic acid). In macrolides group, Azithromycin was found to be sensitive in 86.7% cases and among 3rd generation cephalosporins, sensitivity was seen for Ceftriaxone in 90% cases, Cefotaxime in 81.7% cases, Cefixime in 80% cases and Cefuroxime in 90% cases. Amikacin was sensitive in 93.3% casesand Meropenem in83.3%cases.

Graph 4: Analysis of sensitivity pattern



Resistance pattern of isolates *S.typhi* as shown in table above : Among the first line drug, Ampicillin was found to be resistant in 53.3% cases which was highest in present study, Chloramphenicol in 10% cases and Co-trimoxazole in 18.3% cases. Quinolones like-Ciprofloxacin was found to be resistant in 23.3% cases, Ofloxacin in 38.3% cases and Levofloxacin in 6.7% cases. In macrolides group Azithromycin was found to be resistant in 13.3% cases and in 3rd generation Cephalosporins – Cefixime was found to be resistant in 20% cases, Cefotaxime in 18.3% cases, Cefuroxime in 10% cases and Ceftriaxone in 10% cases. Amikacin was resistant in 6.7% and meropenem in 16.7% cases.

ANALYSIS OF RESISTANCE PATTERN

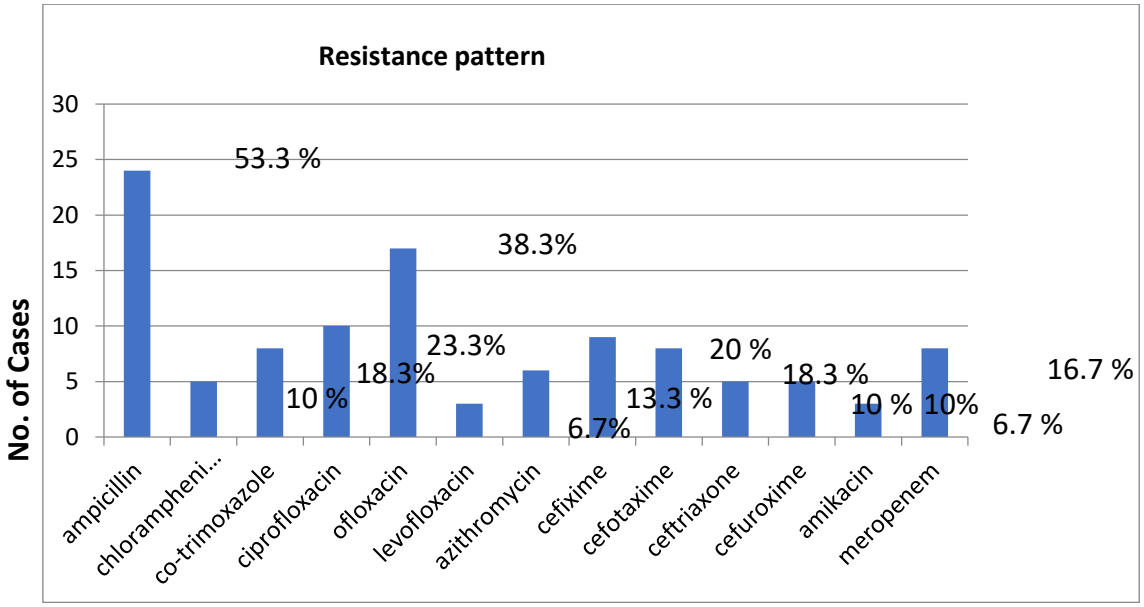


Table 5: Response to treatment

Onset of defervescence	Frequency	Percentage (%)
2-3 Days	22	48.33
4-5 Days	19	43.33
6-7 Days	4	8.33

Onset of defervescence shows the response of treatment, in this study suspected case of enteric fever was started on intravenous Ceftriaxone and it was sensitive in 90% of cases and showed good result. In 48.3% cases, onset of defervescence was 2-3days, in 43.3% cases it was 4-5days and only in 8.3% cases the onset of defervescence was 6- 7days. Mean duration for onset of defervescence was 3.8 days.

DISCUSSION

Typhoid fever is a common infectious disease presenting as anacute multisystem febrile illness in children. This is a detailed study of 150cases who were admitted in Department OfPaediatrics, Nalanda Medical College and Hospital, Patna, Bihar, between December 2017 –December 2019. Analysis of all the 150 cases regarding presenting symptoms, clinical signs, investigations and in vitro antibiotics sensitivity/resistance pattern and treatment response were done.

AGE INCIDENCE

In present study 19 (12.66%) children were below 2 years , 81 (54%) children were between 2 to 10 years and 50 (33.33%) children were between 10 to 15 years. Similar age distribution was observed by Garg *et al.*[15] but 55% were in age group 5-14years as reported by Singla *et al.*[15], Punjabi *et al*[17].

SEX INCIDENCE

In present study 88 (58.67%) cases were boys and 62 (41.33%) cases were girls. Similar male preponderance (1.42M:1F) has been reported by Garg *et al.*[15] But in Kumar *et al.*[18]study 78% were male which is higher than present study and 22% female which is lower than present study. In Mathura K C *et al*[19]study similar incidence was seen.

DURATION OF FEVER

In present study fever was presenting symptom in all the patients which was more of continuous type, the shortest duration of fever observed was 5 days in one patient who was admitted on day 3 of fever, and longest duration was 18 days. 60% cases had fever for 8-14 days and 32% had fever for 5-7days with mean duration of fever was 8.7±1.93 days, none of cases had fever more than 18 days. Similar finding has been reported in Garg *et al.*[15].

TEMPERATURE

In present study maximum temperature noted was 104 ^{0}F. 10% of patients had temperature upto101 ^{0} F and 73.3% caseshad temperature between 101.1-103^{0}F and 16.7% cases had more than 103^{0}F. Mean temperature observed in our study was 102.63±0.83^{0}F.

CLINICAL SYMPTOMS

In present study fever was seen in all the cases with majority of them having continuous type, followed by malaise(70%), anorexia(66%), chills(58%), headache(57%), vomiting(55%), diarrhoea(50%), cough(42%), abdominal pain(60%) and in few cases constipation and joint pain.

Following table shows the incidence of various clinical symptoms that we came across in the present study and for comparison the results of Chowta[20] 2005, Kakaria A *et al.*[21] 2014, Gupta S *et al.*[22]2009, Shahriar K, *et al.*[23]*2002*, Kumar A *et al.*[18]2017. Studies were taken which are asfollows.

Table 6: Comparison of clinical symptoms.

Symptom	Present study in %	Chowta[20] 2005.in %	Kakaria A *et al.*[21] 2014.in %	Gupta S *et al.*[22] 2009 in %	Shahriar K. *et al*[23] 2002 in%	Kumar A *et al.*[18] 2017 in%
Fever	100	100	100%	100	100	100
Chills	58.4	-	26	-	80	-
Headache	56.6	18	26	30.9	75.4	59
Malaise	70	2.3	-	-	73.3	-
Vomiting	55	20.4	44	33.3	20	28
Pain abdomen	60	11	64	18.5	29	20
Cough	41.66	6.8	-	24.7	35.4	-
Diarrhoea	50	20.4	28	24.7	27.7	27
Constipation	15	9.1	-	-	23	-
Anorexia	66.66	-	-	-	-	-
Joint pain	5	-	-	-	1.5	-
Alter behaviour	0	-	-	-	4.6	-

CLINICAL SIGNS

In present study all cases had pyrexia which was continuous in type, classical stepladder rise of temperature was not seen, similar findings were reported in several studies as shown in the following table.

Common finding were coated tongue in 70% cases but in studies of Shahriar *et al.*[23], R K Arora *et al*.[24], Rajiv k *et al.*[25]it was 32-35%**.** Higher incidence may be due to poor oralhygiene.

Anemia was observed in 36.6% cases which were similarly observed in other studies conducted by Shahriar *et al.*[23]Kakaria *et al.*[21]R K Arora *et al.*[24].

Hepatomegaly was seen in 43.3% cases which was similar to finding in other studies like Kakaria*et al.*[21] and R K Arora *et al*.[24].In comparison to these studies hepatomegaly was found to be high (88%) in study by Rajiv k *et al.*[25]and it was low(17%) in study by Shahriar K *et al.*[23].

In present study splenomegaly was found in 14% case which was different from findings of studies conducted by Shahriar *et al.*[23] Kakaria*et al*[21]**,** R K Arora *et al.*[24]. Bradycardia was found in 20% cases which is lesser in comparison with Kakaria*et al*[21]studies, in his study it was 34% and common in more than 5years age group. Other signs observed were dehydration due to diarrhoeaand in few cases signs ofbronchitis.

In present study other signs like rose spots and icterus were not noted. Complications like GI bleeding, ulceration, altered sensorium, meningitis were not noted.

Table 7: Comparison of physical signs.

Clinical Sign	Present study in %	Shahriar K, *et al*[23]*2002* in %	Kakaria A *et al.*[21] 2014 in %	R.K.Arora, *et al.*[24] 1992 in %	Rajiv K, *et al.*[25] 2018 in %
Pyrexia	100	100	100	100	100
Delirium	0	9.2	-	0	1 case
Bradycardia	20	-	34	-	11.2
Dehydration	50	26.2	-	-	+
Coated tongue	70	32.3	-	33	35.4
Rash	0	3	6	0	0
Anaemia	36.6	37	42.9	57.2	26
Abdo. tenderness	0	12.3	-	-	+
Hepatomegaly	43.3	16.9	42	45.6	88
Splenomegaly	14	23	36	90	46
Sign Bronchitis	10	13.8	-	8.7	32.2
Sign meningitis	0	4.6%	-		-
Complication	0	+	-		30.6

LABORATORY FINDINGS

Blood counts : In present study 36.6%(55) cases had anaemia with haemoglobin less than 11gm%, the lowest haemoglobin level found was 7.5gm% in 1 year old child. The lowest TLC noted was 1700 and highest TLC noted was 15400. 16.6% cases had leukopenia and 73.3% caseshad TLC within normal range and 10% cases had leucocytosis. 78% cases had eosinophil count in range of 1-4% and 21.6% had in range of 4-6% with none of cases eosinopenia (<1%).

Leucocytosis was seen in 3.6% cases and leukopenia in11.4% cases in Jog S et al.[26]study while Leucocytosis was seen in 8.7% and leukopenia in 2.2% of cases in Mathura KC et al.[19]study.

Widal reaction- In present study all the 150 cases had their Widal test done and rising titre and a titre of 'H'1:120 and 'O'1:120 and above are taken as positive. 78 cases (52%) showed significant positive reaction which is lesser as compared to 89% in study by Sudharshan RC[27]. 48 % cases were Widalnegative .It could be due to early test sampling or intake of antibiotics before hospitaladmissions.

Blood culture cases: Blood culture was positive in 45 cases (30%).

IN VITRO SENSITIVITY PATTERN

In the present study antibiotic sensitivity/resistance was tested for all the cuture positive cases with Ampicillin, Chloramphenicol, Co-trimoxazole, Ciprofloxacin, Ofloxacin, Levofloxacin, Azithromycin, Cefixime, Cefotaxime, Ceftriaxone and Amikacin.

Ampicillin, chloramphenicol, co-trimoxazole were considered as first line drug in past and resistance to all these three drugs is known as multidrug resistant typhoid fever (MDRTF).

In present study first line drug Ampicillin was sensitive in 46.7% cases, Chloramphenicol in 90% cases and Co-trimoxazole in 81.7% cases which indicate re- emergence of sensitivity of these first line drug which is comparable with Geetika D *et al.*[28] and Gopal *et al.*[29]studies and it indicates the sensitivity against first line drugs is increasing. The incidence of MDRTF is high in studies by Sudharshan RC[27](53%) and Rajiv K, *et al.*[25], this high incidence may due to indiscriminate use of antibiotics.

In quinolone group of antibiotics, ciprofloxacin were sensitive in 76.7%, ofloxacin in 61.7% and levofloxacin in 93.3% cases. In recent studies of Sudharshan RC[27], Geetika D *et al.*[28]Gopal *et al*.[29]it has been shown that the quinolones group of drugs has

very high sensitivity. Review of literature found no study done on sensitivity of levofloxacininenteric fever, but it was observed to be 93.3% sensitive in present study. The less susceptibility of ciprofloxacin and ofloxacin may be due to resistant strain, inappropriate dosage and duration of use of drugs and endemicity.

In present study azithromycin was sensitive in 86.7% cases, but it is 100% sensitive in study by Geetika*D et al*.[28].

Among 3rd generation cephalosporins, oral drug Cefixime is sensitive in 80% cases, which is 100% sensitive in Sudharshan RC[27]study. I.V antibiotics like cefotaxime is sensitive in 81.7% cases which is comparable with Gopal *et al*.[85]but 99% sensitivity has been reported by Geetika D *et al*.[28]. Ceftriaxone is 90%sensitive in present study and the results are similar to Sudharshan RC[27], Geetika D *et al*.[28], Gopal*et al*.[29]and Rajiv K *et al*.[25].

Among aminoglycosides, Amikacin was sensitive in 93.3% cases which was similar to Rajiv K *et al*.[81]study, 100% sensitivity was observed in Geetika D *et al*.[28]study.

Table 8: Comparison of in vitro sensitivity pattern.

Antibiotics	% Sensitivity in Present Study	Sudharsh anRC[27] 2014 in %	GeetikaD *et al*[28] 2013 in%	Gopal *et al*[29] 2011in %	Rajiv K *et al.*[25] 2018 in %
Ampicillin	46.7	11.7	-	-	25.8
Chloramphenicol	90	35.8	99.1	97.5	33.4
Co-trimoxazole	81.7	4	91.1	97.5	31.1
Ciprofloxacin	76.7	100	97.	94	74.1
Ofloxacin	61.7	-	99	92	92.8
Levofloxacin	93.3	-	-	-	
Azithromycin	86.7	-	100	-	-
Cefixime	80	100	-	-	-
Cefotaxime	81.7	-	99	79	76.3
Ceftriaxone	90	100	100	98.5	97.8
Cefuroxime	90	-	-	-	-
Amikacin	93.3	-	100	-	91.3
Meropenem	83.3	-	-	-	-

LIMITATION

- Bacteriophage typing facility is not available in our setup to differentiate between S.typhi and S. paratyphiA,B,C.
- Nalidixic acid sensitivity test is not available in our hospital, which is considered as surrogate marker of quinolonessensitivity/resistance
- Facility to determine the minimum inhibitory concentration (MIC) of different antibiotic is not available to assess the increasing or decreasing susceptibility of isolate against differentantibiotics
- More number of culture positive cases wererequired
- Prolonged follow up of cases could have given better results
- Single centre study

CONCLUSION

- Fever with chills, malaise, headache, vomiting, coated tongue, anorexia, cough, diarrhoea, hepatosplenomegaly, anaemia were the common clinical manifestations of enteric fever.
- Normal to raised leucocyte count is common finding, in few cases leukopenia, neutropenia arefound.
- Widal test, though a good screening test but it has poor specificity for diagnosis. If done early gives false negative results which can be confirmed by bloodculture.
- The incidence of MDRTF was less. We have observed that there was re- emergence of strains with high sensitivity to previously used first line antibiotics chloramphenicol (90%) and co-trimoxazole (82%) but less with ampicillin(47%).
- In quinolone group, there was decrease sensitivity with Ofloxacin (62%) and ciprofloxacin (77%), but levofloxacin sensitivity (93.3%) was very high may be because it has not been used indiscriminately in past and was a reserved drug. So Levofloxacin can be used as second line antibiotic in MDRTF and relapsecases.
- In cephalosporin group, ceftriaxone sensitivity is high and it is in use since last two decades with goodresults.
- An adequate trial for antibiotics like chloramphenicol or oral co-trimoxazole can be tried before starting injectable antibiotics due to increased emergence of sensitivity to these drugs.

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