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Dr. Bushra Nasreen
Assistant Professor,
Department of Paediatrics,
VRK Women Medical College,
Teaching Hospital and
Research Centre, Hyderabad,
Telangana, India

Corresponding Author:
Dr. Bushra Nasreen
Assistant Professor,
Department of Paediatrics,
VRK Womens Medical
College, Teaching Hospital and
Research Centre, Hyderabad,
Telangana, India

A study on changing trends in the management of Entric fever

Dr. Bushra Nasreen

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Abstract
Aim and Objective: To study the changing profile of enteric fever with reference to clinical features and complications and also study the response of enteric fever to various drugs.
Methodology: The present study was carried out of 75 cases of enteric fever and admitted to the paediatric department of Dr VRK Womens hospital and Princess Durru Shehvar Hospital from March 2018 to September 2018, Cases diagnosed as enteric fever. In all cases, a detailed Clinical history, complete physical examination, family history, history of Contact with patient of enteric fever, the type of water supply, post immunisation Status of enteric fever were asked. Only those cases with a rising litre by slide agglutination or Positive tube agglutination more than 1:80 or Positive blood culture reports were included in this study to know the clinical profile. Children between the ages of 0-12 years were selected for the study.
Results: 75 cases of enteric fever in children up to 12 years of age formed the study group. 67% were boys and 33% were girls. The youngest patient in our study was 9 months old. Fever was seen in all cases. The fever was high grade, continuous in 60% and intermittent in 40% cases. General malaise and weakness were seen in all cases. Tongue coating was noticed in all cases. Splenomegaly was seen in 82.4% cases and hepatomegaly was seen in 58.4% cases. The widal agglutination by slide method showed rising titers in 49 cases. The tube agglutination was positive in 26 cases. Cases which showed positive results with both slide agglutination test and tube agglutination were 10. Blood culture was positive in 5 cases. The initial treatment started was amoxycillin in 27 cases. Amoxycillin was changed to cipro floxacillin in 11 cases and it was changed to ceftriaxone in 6 cases and amoxycillin was changed to chloramphenicol in 2 cases.
Conclusion: Finally concluded that, this study on enteric fever shows the changing trends in the clinical features and management. Ceftriaxone and Cipro floxacillin were found to be very effective.

Keywords: Cipro floxacin, widal, amoxycillin, agglutination, spleenomegaly, hepatomegaly

Introduction
Typhoid fever continues to be a common and serious infections disease in India in general and in this part of the Hyderabad city in particular due to the poor sanitation, unsatisfactory personal hygiene and low socio economic status [1-3].
Although the morbidity and mortality was reduced significantly by introduction of Chloramphenicol, relapses, drug resistance and complications continue to pose problems. In recent years enteric fever has assumed severe proportions and is with varied pattern of presentation but most disconcerting of all is the resistance of the disease and standard therapy [4-6].
Hence it was decided to undertake this study to evaluate the exact incidence of enteric fever, to study efficacy of diagnostic methods and to study the primary and secondary line of drugs in the treatment of enteric fever.

Epidemiology
Typhoid fever effects 500 per 1 lakh population in developing countries like India. The typhoid bacillus infects only humans and infected patients excrete salmonella typhi in respiratory secretions, urine and faeces for variable time. Direct or indirect contact with an infected person (sick or chronic carrier) is necessary for infection. Water borne outbreaks occur due to poor sanitation and direct faecal oral spread due to poor personal hygiene, unsatisfactory sanitary facilities and unpredictable supply of safe drinking water. The infected person during acute stages of illness excrete 10^6 - 10^9 salmonellae per gram of stools which is the main source of contamination of food or water [5-10].

Aim of study
1. To study the changing profile of enteric fever with reference to clinical features and complications.

2. To study the response of enteric fever to various drugs.

Materials and Methods

The present study was carried out of 75 cases of enteric fever and admitted to the paediatric department of Dr VRK Women's hospital belonging to Moinabad, Azeez Nagar, Chevella in Rangareddy district. Some patients were seen in Princess Durru Shehvar Hospital from March 2018 to September 2018, Cases diagnosed as enteric fever were the residents of purani Haveli, Talab Katta. Dabeerpura, mughalpura, Eidi bazaar areas of old Hyderabad city. Infected person exceeds 10^6-10^9 salmonella per grams of stools. In all cases, a detailed Clinical history, complete physical examination, family history, history of Contact with patient of enteric fever, the type of water supply, post immunisation Status of enteric fever were asked. Only those cases with a rising litre by slide agglutination or positive tube agglutination more than 1:80 or Positive blood culture reports were included in this study to know the clinical profile. Children between the ages of 0- 12 years were selected for the study. After admission to the ward, 5ml of blood was collected and inoculated in 5m1 of 0.8% bile broth and sent for culture and sensitivity. The culture was concluded negative only when there was no growth even after the end of one week. Blood was collected for complete blood picture, Widal test, peripheral smear for malarial parasite.

Biochemical analysis

Complete urine analysis was done and urine culture sent for salmonella [18-20]. Skiagram of the chest was taken in those patients with respiratory symptoms or to rule out tuberculosis.

Plain X-ray abdomen in erect posture was taken in suspected cases of intestinal perforation and toxic ileus.

Ultrasonography of the abdomen was done in some cases.

No patient underwent peritoneal lavage.

Lumbar puncture was done in cases with signs and symptoms of central nervous System.

All the findings were recorded in a prepared proforma.

All patients were treated with antipyretic paracetamol as 10-15mg per Kg per day orally.

Tepid sponging was done in cases of high fever.

Intravenous fluids, blood transfusion, B complex supplementations were used wherever necessary.

Results

75 cases of enteric fever in children up to 12 years of age formed the study group. 67% were boys and 33% were girls. The youngest patient in our study was 9 months old.

Table 1: Sex distribution (n = 75)

Sex	Number	%
Male	51	68
Female	24	32

Table 2: Age incidence

Age incidence	Number	%
0-2 yrs	10	13.3
2-4 yrs	18	24
4-6 yrs	15	20
6-8 yrs	12	16
8-10 yrs	10	13.3
10-12 yrs	10	13.3

Table 3: Clinical manifestations

Clinical features	Number	%
Fever	75	100
Tongue coating	75	100
General Weakness	75	100
Splenomegaly	62	82.6
Hepatomegaly	44	58.6

Table 4: Complications

Complications	Number	%
Gestrintestinal Bleeding	10	13.3
Ileus	5	6.66
Encephalopathy	4	5.33
Intestinal perforation	2	2.66
Death	2	2.66
Acute cerebralaralaxia	2	2.66

Table 5: Effectiveness of drugs used

Drugs	Number	%
Amoxycillin		
Total	27	100
Not Effective	8	29.62
Effective	19	70.37
Chloramphenicol		
Total	8	100
Effective	1	12.5
Not Effective	7	87.5
Ciprofloxacillin		
Total	12	100
Effective	11	91.66
Not effective	1	0.8
Ceftrioxone		
Total	28	100
Effective	27	96.4
Not Effective	01	3.5

Table 6: Showing response to drugs

No. of cases	Widal positive	Chloramphenicol	Amoxycillin	Ciprofloxacillin	Ceftrioxone	Average days
27	27	-	+	-	-	6-7days
08	08	+	-	-	-	5-7days
12	12	-	-	+	-	5-7days
28	28	-	-	-	+	4-6days

Clinical features

Fever was seen in all cases. The fever was high grade, continuous in 60% and intermittent in 40% cases. General malaise and weakness were seen in all cases. Tongue coating was noticed in all cases. Splenomegaly was seen in 82.4% cases and hepatomegaly was seen in 58.4% cases.

Investigations

The widal agglutination by slide method showed rising titers in 49 cases.

The tube agglutination was positive in 26 cases. Cases which showed positive results with both slide agglutination test and tube agglutination were 10. Blood culture was

positive in 5 cases.

Treatment

The initial treatment started was amoxycillin in 27 cases. It was found to be effective in 8 cases. These patients did not relapse on follow-up. Amoxycillin had to be changed to other drugs when clinical symptoms did not improve and fever persisted after 5 days.

Amoxycillin was changed to cipro floxacillin in 11 cases and it was changed to ceftriaxone in 6 cases and amoxycillin was changed to chloramphenicol in 2 cases. All these patients were given these drugs for a total of 8 days. The average period of effervescence was 5 to 7 days.

Chloramphenicol was used as a primary drug in 8 cases. It was found to be effective in 1 case. In 7 cases it had to change to other drugs. It was changed to ceftriaxone in 2 cases and 5 cases were changed to cipro floxacillin. The patients were given treatment with these drugs for duration of 10 days.

Cipro floxacillin was used a primary drug in patients with severe toxic manifestations, older children and in those who could not afford ceftriaxone which was more costly. It was found to be effective in 11 out of 12 cases. In 1 case it was changed to ceftriaxone as the fever did not subside after 5 days.

No case showed any complications after 2 to 3 months of follow up.

Ceftriaxone was used initially in 28 cases. Most of the patients became a febrile on 4^{th} to 5^{th} day. Only in 1 case it was found to be ineffective and so it was changed to cipro floxacillin.

Complications noted during the course of disease were:

a) Ileus in 3 cases.
b) Peritonitis in 1 case.
c) Intestinal perforation in 1 case.
d) Gastrointestinal bleeding in 6 cases manifesting as hematemesis and melena.
e) Acute cerebellar ataxia in 1 case.
f) Death in 1 case due to in intestinal perforation in case in which chloramphenicol was used.

Enteric fever

Management-antimicrobial therapy choice for empiric antibiotic therapy is guided by various factors

a) Severity of illness
b) Inpatient/out-patient therapy
c) Presence of complications
d) sensitivity pattern of S.typhi/Para Typhi

Antibiotics for outpatient treatment

a) Oral cefexime-20 mg/kg/day
b) Azithromycin 20 mg/kg/day
c) Chloramphenicol- 50 mg/kg/day
d) Amoxycillin-100 mg/kg/day

Total duration of therapy with above drugs is 14 days except for azithromycin where 7 day therapy is recommended.

Criteria for inpatient treatment and Treatment with parenteral antibiotics

a) Persistent vomiting
b) Severe Diarrhea
c) Abdominal distruction
d) Systemic or local complications

Drugs

Third generation cephalosporins

Drugs of first choice

a) Ceftrixone-100 mg/kg/day in BID dose
b) Cefotaxime-100-150 mg/kg/day in BID dose or TID dose
c) Cefaperazone-50-100 mg/kg/day In BID dose

Treatment of carriers

Healthy/Intermittent carriers

Harbour infections without suffering from disease as bacilli persist in gall bladder or Kidney. Treatment-Prolonged treatment with quinolones or cephalosporins may requires cholecystectomy.

Carrier state is more common in a children. Floroquinalones given for 4 weeks is recent treatment for carriers. Sometimes Cholecystectomy is needed for those who have relapsed after therapy or who cannot tolerate antimicrobial therapy. In some cases of relapse Rifampicin along with Trimethoprim- Sulphamethaxazole helps to avoid cholecystectomy.

Prevention

Most effective methods are improving hygiene (personal) sanitation and waste disposal and safe drinking water. Vaccination is a major preventive strategy. Administration of VI polysaccharide vaccine 0.5 ml 1M every 3 years to all children's above 2 years till age of 18 years is helpful.

Specific treatment for complicated/severe enteric fever

Paracetmol given as 10-15 mg/kg/day QID for all fever patients.

For fully sensitive

a. Ceftrioxones as 1 line 80-100 mg/kg/day IV, 10-14 days
b. Flouroquinalones as II line –Oflaxcin/ Ciprofloxacin 15 mg/kg/day for 10-14 days.

Uncomplicated cases-Cefixime 15-20 mg/kg/day, 10-14 days

Multi drug resistant

a. Fluroquinalones as I line
b. Cefotaxime as II line

Quinalone resistant

Ceftroxones as I line

Azithromycin (20 mg/kg/day oral single dose for 7 days) or Gatifloxacin as II line (10 mg/kg/day for 7 days)

Treatment of multidrug resistant salmonella typhi

Ceftrioxine 80-100 mg/kg/day IV BID or OD-10-14 days

Cefotaxime 100 mg/kg/day IV BID, 10-14 days.

Cifrofloxacin-Effective with low relapse rate and prevent typhoid carrier state.

Azithromycin is used as second line.

The patients were admitted to the ward and followed up for any complications.tie of defervescence.

The patients were followed for 2-3 months for detection of any relapse of typhoid fever.

Parenteral treatment should be continued till defervesences has occurred. Oral intakes have improved & complications impaired. The mean time of defervescense with ceftrioxone is usually 5-6 days can be up to 10 days. Following

defervescense therapy is can be changed to oralcefeximes 20 mg/kg/day to complete total duration of 14 days.

Supportive therapy

Includes bed rest, adequate nutrition, attention to fluid and electrolyte balance, antipyrates for fever. Paracetmol as 10-15 mg/kg/day 4 th or 6 th hourly.

Patients with mental changes (Delurium, Stupor or Coma) are treated with Dexamethasone initial dose of 3mg/kg followed by 1mg/kg every 6 hours up to 48 hours.

Enteric fever complicated with intestinal haemorrhage needs intensive care monitoring with blood transfusion in some cases.

Intestinal perforation with peritonitis should be managed with appropriate antibiotics Ceftrioxone plus Mentranidazole IV fluids with isotonic crystalloid, blood and oxygen if needed & surgical repair preferably within 6 hours.

Treatment of relapse

Most common cause of relapse is third generation cephalosporins especially if shorten duration of therapy is used. Culture is obtained and may be treated with same drugs as used for primary therapy in the right dose and for right duration. If quinalones were used before if Nelidixic acid sensitive. Ciprofloxacin or Oflaxacin should be used for treatment of relapse. Azythromycin is another good option for relapse treatment.

Capsular polysaccharide unconjugated vacccine

It is found to be very effective and can be used in younger children less than 2 years where oral vaccine is contraindicated.

Oral vaccine

It has been tries using killed vaccine as enteric coated or live vaccine containing streptomycin dependent strain. S. typhi Ty21a strain has a stable mutant lacking the enzyme UDP galactose 4 – epimerase (GAL-E mutant and is used as live vaccine.The newly licenced vaccine (VIVOTIF) is oral live attenuated preparation [12-14]. Typhi21A vaccine is effective in 67-82%. Adverse reactions are rare. Three enteric coated capsules on alternate days are given. It is not recommended for children less than 6 years due to limited experience. Infants and toddlers do not develop immune response with this preparation. It should not be used in patients who are immunodeficient. Vaccines are recommended to individuals with intimate exposure to a documented carrier or for control of outbreaks [19].

Newer vaccine

Vaccine against typhoid made from Vi capsular polysaccharide with or without protein conjunction given orally as 3 doses on alternate days only for children who are more than 6 years.

Discussion

Enteric fever is a systemic clinical syndrome produced by salmonella organisms. It encompasses the terms typhoid fever caused by salmonella typhi, and paratyphoid fever caused by S. paratyphi [7-9].

A.S. schottmuelleri (formerly S. paratyphi B) S. hirschfeldii (formerly S. paratyphi C) and occasionally other salmonella types like S. dublin, S. berrilly, S. sendai, S. enteritidis, S. typhimurium, S. astbourne, S. saintpaul, S. oranienburg and S. panama. Enteric fever has virtually disappeared from most of the developed countries. However, it continues to be a major health problem in all states of India. The present morbidity reported from various regions of India varied from 109 to 2219 per 1,00,000 population [6]. The problem has become worse due to the emergence of multidrug resistant salmonella typhi. With the frequent use of antibiotics, the old text book picture of enteric fever appears to have changed and newer presenting features have come to light.

Because humans are the only natural reservoirs of S. typhi, direct or indirect contact with an infected person (sick or chronic carrier) is necessary for infection. Ingestion of foods or water contaminated with human feces is the most common mode of transmission. Waterborne outbreaks due to poor sanitation and direct fecal-oral spread due to poor personal hygiene are seen in India. Congenital transmission of enteric fever can occur. The clinical profile of the disease is variable among different age groups. Younger the child, more non-specific the signs and symptoms. The younger children show more features of septicemia and the school age children and adolescents present with more localized symptoms.

Enteric fever is endemic in all parts of India. The proportion of typhoid to paratyphoid fever is about 10:1. Paratyphoid B is rare and C is very rare. The disease occurs at all ages but is probably most common in the 5-20 years age group. The age incidence is related to the endemicity of the disease and the level of sanitation.

The majority of our cases were from low socio-economic classes,

The youngest patient in our study was 9 months old.

Most of the cases belonged to the age group 2-4 years which is similar to the study by previous studies [10]. Fever was seen in 100% cases which was continuous and high grade associated with chills and rigors in almost 60% of cases. Bhutta 14) shows continuous fever in 45% cases [3]. Intermittent fever was seen in 40% cases. High grade fever of 5-10 days duration was commonest presentations also reported by other workers earlier [12-15]. Non-specific symptoms of diarrhea, vomiting and anorexia were noted frequently at initial presentation in these children as also reported in previous studies [8, 29]. Splenomegaly was seen in 82.4% cases which resembles to earlier reports.

Hepatomegaly was seen in 58.4% cases. Similar results were reported by Bhutta in his study (60%) [15]. No specific pattern was observed in the total leukocyte count in our study. Relative eosinopenia 0-1% was the commonest observation (80%) in the study of peripheral smear which has also been reported earlier [9, 18, 19]. The overall blood culture positivity in our study was 6.6%. Similar results were reported by Kundu *et al*. [15], which may be attributed to antibiotic therapy prior to hospitalization. In our study, typhoid encephalopathy with normal cerebrospinal fluid was seen in 2.6% cases which is similar findings seen earlier. Acute cerebellar ataxia was seen in 1.1% cases with a normal CSF examination similar to case reported by Buckle *et al*. [1].

Amoxicillin was effective in 10% of the cases and failure rates were 25% while chloramphenicol was effective in 3% cases and failure rates were 93%. Amongst the newer drugs, Cipro floxacillin is effective in 96% cases so also ceftriaxone with 96% efficiency.

The clinical response to Cipro floxacillin as indicated by the period of differences averaging 5 days was satisfactory thus requiring shorter hospital stay compared to chloramphenicol group as shown in the earlier studies [3]. Although the clinical safety of Cipro floxacillin in children is controversial, careful use of this drug in life threatening cases, older children, patients with severe toxicity or MDRST may be justified. Oflaxacin also can be used at some dose of 15 mg/kg 1 day for 5-7 days and if found multidrug resistant for 10-14 days is effective.

Moreover, the orthopathic side effects are seen with higher dose when used for prolonged periods in adults. Most of the studies done so far in children have not documented skeletal toxicity. Azithromycin at a 20 dose of 20 mg/day can be given for 7 days.

The initial clinical diagnosis of enteric fever I young children is largely dependent on high index of suspicion. It should be considered in the differential diagnosis of fever of unknown origin.

Conclusion

This study on enteric fever shows the changing trends in the clinical features and management. Ceftriaxone and Cipro floxacillin were found to be very effective. There were no complications during the treatment and relapse after 2 to 3 months of follow-up.

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Conflict of interest

None

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