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DIAGNOSTIC AND THERAPEUTIC PROTOCOL IN TREATMENT OF ENTERIC FEVER IN CHILDREN

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ABSTRACT

Present study was done for retrospective analysis of Diagnostic and treatment protocol for management of suspected and probable cases of Enteric fever in children.

Methods: Observational descriptive study conducted on data of case papers of Enteric fever patients admitted & treated during January 2015 to January 2016. In the pediatric population in the age group of 2 to 20 years at NKPSIMS, Digdoh, Hingna, Nagpur.

Results: Out of the 41 children with enteric fever, male to female ratio was 1.3:1 with common age group between 11-20 years. Maximum i.e. 20 cases are from urban areas, 13 from Rural and 8 are from Suburban area. *S typhi* was isolated in … cases while S. *paratyphi* in … cases. Clinical features of *S. typhi* and *S. paratyphi* were indistinguishable. None of the children were immunized for Typhoid fever. Fever with or without chills are the commonest symptoms. Average duration of stay is 6.8 days and a No relation of age of child with hospital stay during treatment of typhoid fever cases. No significant relevance of pre hospital duration of fever with patient's hospital stay & hence response to antibiotic treatment. Significant Co-morbidities have not been seen .Blood culture though a gold standard test is of limited use in resource limited scenario, especially in children with prior antibiotics treatment. Ceftriaxone as a solo drug is effective in the treatment of majority of patients of enteric fever.

Conclusion: Public health interventions to minimize human carrier contact, improvement in environmental sanitation, improved personal hygienic measures including health care behavior strategies, typhoid vaccination and rational antibiotic selection based on sensitivity pattern to prevent resistance will help to reduce the morbidity and mortality of this global health problem.

KEYWORDS :

Introduction

Enteric fever is a systemic infection caused by the bacteria Salmonella enterica serovar Typhi (S.typhi -80%) and Salmonella enterica serovara Paratyphi (S. paratyphi A, B and C).

Disease is transmitted by feco-oral route, through contaminated food & water. Huge burden of disease is present in Indian population for want of Environmental sanitation, Safe food & drinking water. Rising trend of using "Fast food" from Eateries, Tourist places & Pilgrimage centers; promotes high Enteric fever incidence. Negligible vaccination coverage act as "Fuel for Fire" and is responsible for population susceptibility to the disease. High incidence of Multi drug resistance in last few decades increases morbidity, mortality and cost of therapy.

Because of the provision of clean water and good sewage system, it is a sporadic disease in developed countries and today, most of the burden of the disease is limited to the developing countries where standards of hygiene and sanitation remain poor[1].

The global estimate of incidence of enteric fever caused by S. typhi is over 21 million causing 700,000 deaths each year and more than 5 million new infections are caused by S. paratyphi A [2,3].

The timely appropriate management of typhoid fever, can considerably reduce both morbidity and mortality. General supportive measures like use of antipyretics, maintenance of hydration, appropriate nutrition and prompt recognition and treatment of complications are extremely important for a favorable outcome. The child should continue to have normal diet and no food should be restricted.

In areas of endemic disease 90% or more of typhoid cases can be managed at home with proper oral antibiotics and good nursing care[4]. Close medical follow up is necessary to look for development of complications or failure to respond to therapy. Patients with persistent vomiting, inability to take oral feed, severe diarrhea and abdominal distension usually require parenteral antibiotic therapy preferably in a hospital.

Antimicrobial Therapy

Since 1990s *Salmonella typhi* has developed resistance simultaneously to all the drugs used in first line treatment (chloramphenicol, cotrimoxazole and ampicillin) and are known as Multi Drug Resistant typhoid fever (MDRTF). There are some reports of reemergence of fully susceptible strain to first line drugs[5]. But these reports are few and unless antibiotic sensitivity testing shows the organisms to be fully susceptible to first line drugs they are not advocated for empirical therapy in typhoid.

Fluoroquinolones are widely regarded as the most effective drug for the treatment of typhoid fever[1]. But unfortunately, some strains of *S. typhi* have shown reduced susceptibility to fluoroquinolones[6,7]. On routine disc testing with the recommended break points, organisms showing susceptibility to fluoroquinolones show poor clinical response to actual treatment. These organisms when tested by disc testing with nalidixic acid show resistance. So in other words resistance to nalidixic acid is a surrogate marker which predicts fluoroquinolones failure and can be used to guide antibiotic therapy. The resistance to fluoroquinolones may be total or partial. The nalidixic acid resistant *S typhi* (NARST) is a marker of reduced susceptibility to fluoroquinolones.

With the development of fluoroquinolones resistance third generation cephalosporin were used in treatment but sporadic reports of resistance to these antibiotics also followed[8]. Recently, Azithromycin is being used as an alternative agent for treatment of uncomplicated typhoid fever[9]. Aztreonam and imipenem are also potential third line drugs which are used recently[1].

There is now considerable amount of evidence from the long term use of fluoroquinolones in children that neither they cause bone or joint toxicity nor impairment of growth.

Ciprofloxacin, ofloxacin, perfloxacin and fleroxacin are common fluoroquinolones proved to be effective and used in adults. In children the first two are only used in our country and there is no evidence of superiority of any particular fluoroquinolones. Norfloxacin and nalidixic acid do not achieve adequate blood concentration after oral administration and should not be used. Fluoroquinolones have the advantage of lower rates of stool carriage than the first line drugs[10]. However, fluoroquinolones are not approved by Drug Controller General of India to be used under 18 years of age unless the child is resistant to all other recommended antibiotics and is suffering from life threatening infection. Of the third generation cephalosporins oral

Cefixime has been widely used in children[11 - 13]. Amongst the third generation cephalosporins in injectable form ceftriaxone, cefotaxime and cefoperazone are used of which ceftriaxone is most convenient. Fluoroquinolones like ofloxacin or ciprofloxacin are used in a dose of 15 mg/kg of body weight per day to a maximum of 20 mg/kg/day.

Of the oral third generation cephalosporins, oral cefixime is used in a dose of 15-20 mg per kg per day in two divided doses. Parenteral third generation cephalosprins include ceftriaxone 50-75 mg per kg per day in one or two doses; cefotaxime 40-80 mg per kg per day in two or three doses and cefoperazone 50-100 mg per kg per day in two doses. Azithromycin is used in a dose of 10-20 mg per kg given once daily.

Fluoroquinolones are the most effective drug for treatment of typhoid fever. For nalidixic acid sensitive *S. typhi* (NASST) 7 days course is highly effective. Though shorter courses are advocated but they should be reserved for containment of epidemics. For nalidixic acid resistant *S. typhi* (NARST) 10-14 days course with maximal permitted dosage is recommended. Courses shorter than seven days are not satisfactory.

In case of uncomplicated typhoid oral third generation cephalosporin *e.g.*, cefixime should Imepenem may also be used. Combination therapy though practiced all over needs substantiation with adequate data from studies.

Aims and Objective

- Present study was planned for retrospective analysis of Diagnostic and treatment protocol for management of suspected and probable cases of Enteric fever in children admitted at NKPSIMS, Digdoh, Hingna, Nagpur in the year 2015-2016.
- To find out Age & sex wise population distribution.
- Common symptoms and signs.
- Laboratory tests useful for diagnosis
- Any complication occurred during the disease course.
- Treatment protocol used during the period.
- Efficacy of treatment protocol used.

Materials & Methods

- Observational descriptive study conducted on data of case papers of Enteric fever patients admitted & treated during 2015-16 at NKPSIMS, Digdoh, Hingna Road, Nagpur.
- Incomplete case papers were rejected from the study project.
- Relevant data entered in the study proforma.
- Demographic, Clinical and Lab data was entered in MS-Excel sheet.
- Descriptive and Analytical statistical tests were done using MS-Excel, SPSS-21 & Minitab statistical package.
- Chi sq. test for categorical data; Student "t" test and Pearson correlation coefficient test for continuous variables was used.
- p value of < 0.05 was considered as significant.

Observations & Results

1. Age & sex wise distribution of Enteric fever cases.

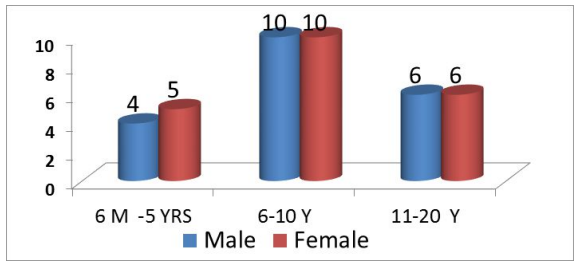
Chi sq. = 0: indicating no significant difference in groups.

Age	Male n , M, SD	Female n , M, SD	Total n & (%) percentage
< 1 yr.	0	1,	1 (2%)
1-5 yrs.	4, 2.775 (0.45)	4, 4.2 (0.62)	8 (20%)
6-10 yrs.	10 8.260 (1.46)	10, 8.165 (1.72)	20 (48%)
10-20 yrs.	6 14.200 (1.14)	6, 14.000 (1.26)	12 (30%)
Total (n)	20	21	41

n-no of participate , M- Mean , SD- Standard diversion, %- Percentage

However Age wise analysis suggest maximum cases i.e. 78 % in Children between **6-20 yrs.** Age groups. This observation emphasizes the relation between eating habits, access to outside Food and incidence of Typhoid fever.

2. Age & sex wise distribution of Enteric fever cases



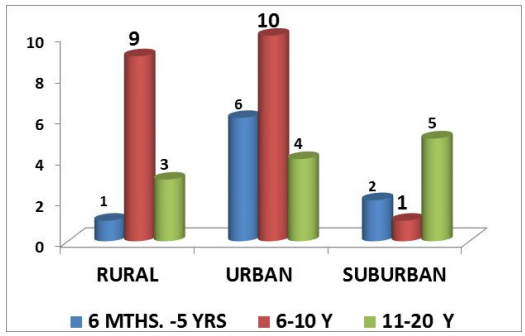
3. Age vs Residence distribution of sample

Age	RURAL	URBAN	SUBURBAN	Total
6 M -5 YRS	1	6	2	9
6-10 Y	9	10	1	20
11-20 Y	3	4	5	12
TOTAL	13 (32%)	20 (49%)	8 (19%)	41

%- Percentage, p<0.05

- Maximum i.e. 49 % are from urban areas & rest from Rural and Suburban area.
- Chi-Sq = 8.883, DF = 4, P-Value = 0.064 (not significant)
- 6 cells with expected counts less than 5.

4. Age vs Residence distribution of sample



5. Relation of Hospital stay in days with the patient's Age

Age	Mean, (SD)
< 1 yr (n = 1)	9 days
1-5 yrs (n = 8)	6.75 (1.75)
6-10 yrs (n = 20)	5.1 (1.29)
10-20 yrs (n = 12)	6.4 (3.47)
Total (N) = 41	

— Mean , SD- Standard diversion

"t" = 0.007 & 0.11; r= 0.004 : indicating no significant difference in groups. Indicates No relation of age of child with hospital stay during t/t of typhoid fever cases

6. Relation of Pre-Hospitalization duration of fever with the patient's hospital stay

Relation of Pre-admission duration of Fever with Hospital stay was assessed by finding a correlation coefficient.

- Pearson correlation coefficient is (r) = 0.042 ;
- p-Value = 0.796
- Indicating no significant relevance of pre hospital duration of fever with patient's hospital stay & hence response to antibiotic treatment.

7. Immunization status

- National immunization schedule vaccines
  - Received optimum for age in 15 subjects (36%)
  - Not received in 26 subjects (64%)
- Typhoid vaccines not received in all 41 subjects.
- Hence a need for low cost effective vaccines.

8. Weight profile and duration of hospital stay

- Tabulation of weight profile of patients was done.
- And then compared with 50th percentile of IAP standards.
- Percentage of 50th IAP percentile was calculated.
- Relevance of nutritional status with recovery from Enteric fever in the form of Hospital stay was calculated.
- There was inverse relation of hospital stay with weight of the child. r = -0.13; however statistically non-significant ($p < 0.2$ in one tailed test)

9. Blood Culture & Widal Test Report

TEST	-VE n (%)	+VE n (%)
BLOOD CULTURE	36 (88%)	5 (12%)
WIDAL TEST : TO 1: 80	-	7
WIDAL TEST: TO 1: 120	-	8
WIDAL TEST: TO 1: 160	-	13
WIDAL TEST: TO 1: 320	-	3
WIDAL TEST: TH 1: 120 & MORE	-	12
TOTAL WIDAL TEST TO > 1: 80 +ve	-	31 (75%)

10. Antibiotics given to Enteric fever Diagnosed cases

Parameters	Blood culture confirmed cases	Widal Test +ve cases	Clinically diagnosed (Culture & Widal test – ve cases)	Total (N)
n	5 (12%)	25 (61%)	11 (27%)	41
Mean hospital stay (Days)	5.8	6.16	5.36	
Antibiotics Mono Dual Multi	 0 5 0	 12 13 0	 6 4 1	 18 (44%) 22 (54%) 1 (2%)

Antibiotics: Mono:-Either Ceftriaxone or Cefixime
Dual:-Ceftriaxone + Amikacin or Azithromycin
Multi:-Ceftriaxone + Amikacin + Azithromycin or Ofloxacin

Summary

- Enteric fever is quite common in children between 2 to 18 yrs. of age. Highest no. is found in 10-20 yrs. group. None of the children were immunized for Typhoid fever.
- Fever continuous with or without chills are the commonest symptoms. Significant Co-morbidities have not been seen in the present study.
- Blood culture though a gold standard test, is of limited use in resource limited scenario, especially in children with prior antibiotics treatment.
- Ceftriaxone as a solo drug is effective in treatment of majority of patients of Enteric fever.

Conclusions

- Enteric fever carries a huge burden of the disease in all developing countries like India.
- Improvement in environmental sanitation and hygienic practices are warranted to reduce the disease burden.
- Public health interventions to minimize human carrier contact, Improvement in environmental sanitation, improved personal hygienic measures including health care behavior strategies, typhoid vaccination and rational antibiotic selection based on sensitivity pattern to prevent resistance will help to reduce the morbidity and mortality of this global health problem.
- But due to paucity of infrastructure, it carries distant goal.

Limitations of Study

- Retrospective study: No control over variables to be studied.
- Bone marrow culture: Not done (Review of literature suggest limited efficacy; in suspected malignant & immuno-compromised individuals).

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