ENTERIC FEVER: A CHANGING PERSPECTIVE

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ABSTRACT

All the cases of enteric fever admitted between 1988-1992 were studied. There was a gradual rise in the number of admitted cases. Central nervous system (CNS) complications like encephalopathy (14.9%), meningitis (8.8%), seizures (8.5%) and cerebellitis (3.4%) were noted more during 1991 and 1992. Other complications like myocarditis (4.6%), hepatitis (9.5%) and gastrointestinal bleeding were noted in increasing numbers during 1991-1992. Multidrug resistant (MDRT) cases were 46.3% in 1991 and 33.5% in 1992. There was a significant difference in the time taken for defervescence (a gradual rise) between the years but between the individual drugs there was no such significant difference. Deaths were noted only in 1991 and 1992 in cases of MDRT with complications. There has been an increase in resistance of S. typhi to commonly used drugs like ampicillin, chloramphenicol and cotrimoxazole. S. typhi resistant to ciprofloxacin was cultured in 2 cases each from 1990-1992. Further, the time taken for defervescence with ciprofloxacin also showed a gradual rise from 3.5 days in 1990 to 6.2 days in 1992. Nevertheless, ciprofloxacin is still the drug of choice for treatment of complicated cases of MDRT.

Key words: *Typhoid fever, Multidrug resistant typhoid, Ciprofloxacin resistance.*

Enteric fever is an important pediatric problem in developing countries. Emerging drug resistance of *S. typhi* to conventionally used antimicrobials and increasing number of typhoid fever cases every year reflect the socioeconomic and sanitary status of the community. The clinical presentation of typhoid fever changes from epidemic to epidemic(l). This study was undertaken to compare the clinical features, complications, drug therapy and mortality pattern of multidrug resistant typhoid fever with cases of the previous years prior to the emergence of drug resistance.

Material and Methods

All the cases of enteric fever admitted in the Pediatrics Department of JIPMER hospital between January 1988 and December 1992 constituted the study material. The clinical diagnosis was confirmed by blood, bone marrow, stool, urine or CSF culture, positive widal test, rising titre of antibody by four fold or O and H antibody positive in dilutions of 1 : 160 or more. Cases with doubtful rise in antibody titre in presence of chronic liver disease, autoimmune disorders and immunization with typhoid vaccine were excluded from the study group. Details regarding age, sex, presenting features, complications, laboratory investigations and hospital course were recorded in a premade proforma for the year 1990, 1991 and 1992. Data regarding the previous 2 years were retrospectively studied from the medical records section of the hospital.

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Results

The total number of cases admitted in the last 5 years from 1988 to 1992 and their age and sexwise distribution is given in *Table I.* The total number of cases admitted with typhoid fever in 1988 were 11 (males 6, females 5), in 1989 24 cases (males 11, females 13), in 1990 60 cases (males 27, females 33), in 1991 147 cases (males 72, females 75) and in 1992 152 cases (males 74, females 78). Seventy one cases presented with fever of less than one week duration (21.26%), 197 cases with fever of 1 to 2 weeks (47.58%), 105 cases with fever of 2 to 4 weeks (27.98%) and 19 cases with fever of more than 4 weeks duration (7.24%). Clinical symptoms and signs are shown in *Table II.* The complications observed, involving various systems are given in *Table III.* Echolalia, facial palsy, hallucination, hyperkinesis, arthritis and arthralgia were noted in one case each and photophobia and dysarthria in 2 cases each during 1992 only. Widal test alone was positive in 170 cases (53.4%), blood culture alone in 66 cases (14.1%), widal and blood culture were positive in 141 cases (32.2%) and bone marrow culture was positive in 8 cases (2.1%).

Widal positivity was noted even on day 1 (1 case), day 2 (2 cases) as well as on day 3 and 4 of illness (*i.e.,* fever) (3 cases each). Maximum culture positivity (blood culture) was noted in the first week of illness. Blood culture positivity was more in the years 1990 to 1992 and the organism was isolated from bone marrow when other cultures were sterile in some cases. Eosinopenia (0-4%) was encountered in 75% of cases. However, occasional cases of eosinophilia (>10%) were also noted. TLC ranged from 4000-11,000 in 70% of cases. However, TLC counts >20,000/ cu mm were noted in 7.9% of uncomplicated typhoid cases. Associated urinary tract infection (culture positive) was observed in 14.1% of cases. *E. coli* was the commonest (53.8%) followed by *Klebsiella* (15.4%), *Pseudomonas* (11.5%) and *S. typhi* (7.7%). *Table IV* shows the drug sensitivity pattern while the time taken for defervescence with the appropriate drug is given in *Table V.* The resistance pattern of *S. typhi* to various drugs (1988-1992) has been depicted in a graphical form in *Fig. 1.* The two way classification method was used to find the difference in time taken for defervescence between the various drugs and in different years. There was no significant

TABLE I-*Age and Sex Distribution of Cases*

Parameter		1988	1989	1990	1991	1992	Total
Total cases	11		24	60	147	152	394
<1 year	0		1 (4.1)	0	1 (0.7)	0	2
1-5 years	3	(27.3)	10 (23.3)	14 (23.3)	47 (32.0)	43 (28.3)	117
>5 years	8	(72.7)	13 (54.1)	46 (76.7)	99 (67.3)	109 (71.7)	275
Males	6	(54.5)	11 (45.8)	27 (45.0)	72 (49.0)	74 (48.7)	190
Females	5	(45.5)	13 (54.2)	33 (55.0)	75 (51.0)	78 (51.3)	204

Figures in parentheses denote percentages.

TABLE II-*Clinical Signs in Enteric Fever*

Clinical signs	1988-1990	1991-1992
Toxemia	7 (7.3)	81 (27.0)
Splenomegaly	20 (21.1)	196 (65.5)
Hepatomegaly	26 (27.3)	185 (61.9)
Respiratory signs	11 (14.4)	63 (21.0)
Typhoid rash	1 (1.1)	-
Constipation	1 (1.1)	11 (3.7)
Diarrhea	1 (1.1)	52 (17.4)
Vomiting	11 (11.5)	119 (40.1)
Ahdomina1 distention	9 (9.4)	60 (20.6)
Toxic ileus	3 (3.1)	3 (1.0)

Figures in parentheses denote percentages.

difference between individual drugs in each year but in between the years there was a significant difference in the time taken for defervescence, *i.e.,* there was a gradual rise from 1988 to 1992. No deaths were noted during 1988-1990 due to typhoid fever. Six cases in 1991 and 7 cases in 1992 expired due to typhoid fever.

Discussion

The incidence of typhoid fever below 5 years of age is on an increase and has been reported to vary from 10.7-23.9% by some workers(2-4). In our study, 30.5% of children affected were below the age of 5 years. Both sexes seemed to be almost equally affected. Most of the cases were admitted during die second week of illness. All the cases had fever as the presenting feature with or without other symptomatology, except one patient in 1992 who presented as a case of

TABLE III-*Complications of Typhoid Fever*

CNS complications	1988-90	1991-92	Other complications	1988-90	1991-92
Encephalopathy	6 (6.3)	43 (14.4)	Gastro-intestinal bleeding	2 (2.1)	30 (10.0)
Meningitis	2 (2.1)	16 (5.5)	Peripheral circulatory failure	3 (3.1)	30 (10.0)
Seizures	5 (5.2) (3 general 1 focal 1 febrile)	19 (6.3) (14 general 1 hemi-seizure 4 febrile)	Hepatitis	-	19 (6.4)
			Cholecystitis	-	3 (1.0)
Aphasia	1 (1.1)	11 (3.5)	Myocarditis	-	12 (4.0)
Deafness	–	2 (0.7)	Pleural effusion	1 (1.1)	4 (1.3)
Retrobulbar neuritis	-	1 (0.3)	Peritonitis and perforation		2 (0.4)
Cerebellitis	2 (2.1)	8 (2.7)	Pancytopenia		1
			Thrombocytopenia with anemia		3 (1.0)

Figures in parentheses denote percentages.

TABLE IV-*Drug Sensitivity Pattern of S. typhi*

	1988	1989	1990	1991	1992
Total cases	11	24	60	147	152
Ampicillin (S)	3/4 (75.0)	4/4 (100.0)	12/27 (44.4)	34/106 (32.0)	21/74 (28.4)
Chloramphenicol (S)	4/4(100.0)	3/4 (75.0)	12/29 (41.4)	34/105 (32.4)	21/74 (28.4)
Ciprofloxacin (S)		-	9/11 (81.8)	103/105 (98.0)	72/74 (97.3)
Cotrimoxazole (S)	-	-	-	13/47 (27.7)	17/34 (50.0)
Furazolidone (S)	-	-	-	55/60 (91.7)	52/57 (91.3)
Cefotaxime (S)	-	-	-	98/101 (97.0)	73/74 (98.7)
Total MDRT cases ($\geq$ 2)		-	16 (26.7)	68 (46.3)	51 (33.5)
Ampi + Chloram-phenicol (R)	-	-	16 (26.7)	59 (40.0)	45 (29.6)
Two drugs (Other than Ampi + Chloro		-	-	9 (6.1)	6 (3.9)
Three drugs (R)	-	-	1 (1.6)	1 (0.7)	12 (7.9)
Four drugs (R)	-	-	-	2 (1.4)	2 (1.3)

Figures in parentheses denote percentages.

TABLE V-*Time Taken for Defervescence*

Drug	1988	1989	1990	1991	1992
Ampicillin	4.0	3.6 (±1.4)	7.0 (±2.1)	6.0 (±2.6)	5.9 (±3.3)
Chloramphenicol	5.4 (±2.4)	3.2 (±1.4)	5.7 (±3.2)	3.7 (±2.3)	7.4 (±2.9)
Cotrimoxazole	1.0	3.5 (±1.7)	5.7 (±2.4)	5.4 (±2.7)	6.9 (±3.8)
Furazolidone	-	-	7.0	4.8 (±2.8)	5.2 (±2.6)
Ciprofloxacin	-	-	3.5 (±1.5)	6.5 (±2.8)	6.2 (±2.3)
Cefotaxime	-	-	8.0 (±4.3)	5.5 (±6.3)	-

Figures in parentheses give range.

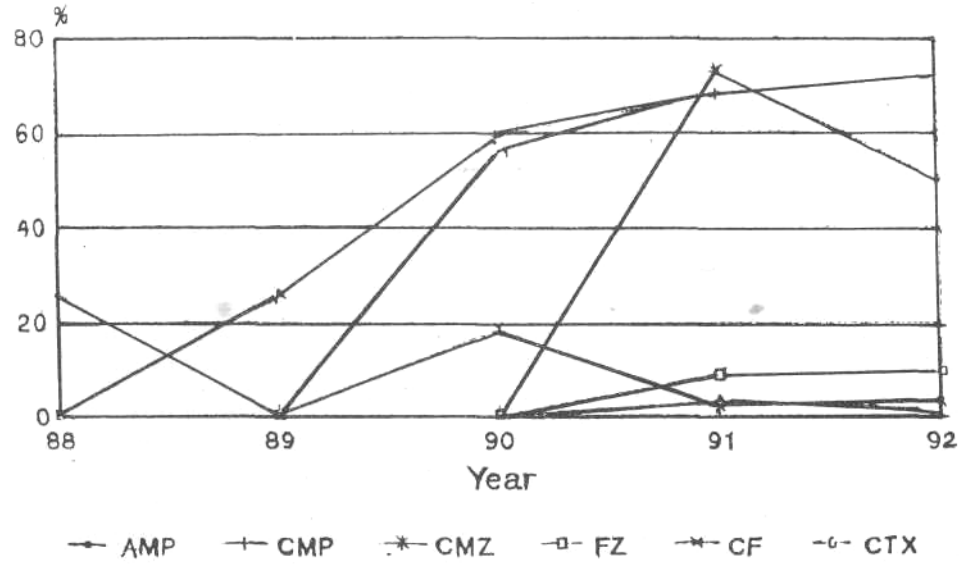

Fig.1. Resistance pattern of S. typhi to various drugs (1988-92).

gastroenteritis without fever. Sinclair *et al.(5)* found 1% of cases without fever. Associated nonspecific features like vomiting and diarrhea were noted with increasing frequency in multidrug resistant typhoid (MDRT) during 1991 and 1992. Cough, respiratory signs, tender, tympanitic abdomen and hepatosplenomegaly were commonly associated with typhoid fever as reported in other studies(2-4,6-8). Pleural effusion as a complication was noted more frequently in MDRT cases. In 1992, parotitis was noted in 2 cases, myositis and impaired hearing in 1 case each. Relative bradycardia wasnoted in 3 cases in 1992, 2 of which were 12 years old and one case was 8 years of age.

Peripheral circulatory failure, encephalopathy and maningitis were encountered more frequently during 1991 and 1992. This has been observed in other studies also(9,10). Typhoid encephalopathy was observed even in the 4th and 5th week of illness. Neurological manifestations like seizures, cerebellitis, aphasia and retrobulbar neuritis were encountered mainly in 1991 and 1992. Cerebellitis has also been reported by other workers(8,10,ll). Other rare neuropsychiatric complications seen in adults, *i.e.* encephalomyelitis, pseudobul-bar palsy, peripheral neuritis, catatonic seizures, chorea and palatal palsy(12-14) were not seen in our study.

Hepatitis, cholecystitis and peritonitis with perforation were observed with high frequency in 1991 and 1992 and were not seen during the previous 3 years (1988-1990). Typhoid hepatitis has also been observed by other workers(15-17). In our study cholecystitis associated with typhoid fever was noted in 1.4% of cases. Incidence of cholecystitis in typhoid has been reported to be around 2.8% cases(18,19). Gastro-intestinal bleeding was more commonly noted in MDRT cases.

The incidence of typhoid myocarditis has been reported to vary from 12%(20,21). In our study the incidence of myocarditis in typhoid fever was 3.4 and 4.6% in 1991 and 1992, respectively. Before that none of the cases admitted had myocarditis.

Pancytopenia was observed in 2 cases during 1991 and thrombocytopenia in a total of 3 cases during 1991-1992. These cases presented with bleeding from multiple sites (GI tract, ear, nose and gums): Thrombocytopenia as a part of typhoid has also been noted by other workers(22). Isolated hematemesis and/or malena in the absence of thrombocytopenia and hepatic dysfunction were also observed in MDRT cases.

One patient presented with features suggestive of nephritis in the form of facial puffiness, oliguria, borderline hypertension and RBC and granular casts in urine in 1992. Typhoid nephritis has also been noted by other workers(22,23). There was a high incidence of CNS complications and gastrointestinal bleeding among the MDRT cases. Encephalopathy was the commonest CNS complication noted. Myocarditis, peripheral circulatory failure and nephritis were less common.

In the present study, Widal positivity was noted even during the first 4 days of illness (in 1992). Maximum positivity was noted in the first week of illness (31.6%) in the year 1992. Culture positivity varied from 21-50% in our study. In another study blood culture positivity was reported to be around 41.7%(4), CSF culture was positive only in one case in 1991.

There was a sharp rise in the incidence of drug resistance to conventionally used antimicrobials (ampicillin, chloromycetin and cotrimoxazole). Most of the isolates were sensitive to ciprofloxacin and furazolidone but two isolates each of S. *typhi* in 1990-1991 and 1992 were resistant to ciprofloxacin.

The defervescence period with ampicillin, cotrimoxazole and ciprofloxacin showed a rise from 1988 to 1992, whereas with chloramphenicol the average time taken for defervescence was shorter in 1991 but rose again in 1992. Cefotaxime and gentamicin had very limited therapeutic utility *in vivo* inspite of very high *in vitro* sensitivity.

Deaths due to typhoid fever were noted only in 1991 and 1992. Mu1tidrug resistant typhoid fever with hepatitis, meningitis, encephalopathy and gestrointestinal bleeding were associated with higher mortality. Only 12-15% of children with neurological symptoms died during 1991-92. One death occurred due to hepatitis with peripheral circulatory failure in 1991. In 1992, 3 deaths occurred due to intractable hypotension and one due to myocarditis. Deaths due to typhoid could not be prevented inspite of therapy with ciprofloxacin (the sensitive drug) for more than 48 hours.

Increased incidence of MDRT with emerging resistance to ciprofloxacin as well as a gradual increase in the time taken for defervescence with the sensitive drug. poses a serious challenge to the clinical management of typhoid. Varying period of presentation of typhoid encephalopathy specifically from endemic areas of Japanese B encephalitis in South India puts the clinician in a diagnostic dilemna. Attention should be paid towards raising the standard of sanitation and potable water supply to reduce the alarmingly high number of typhoid cases in the community. Oral typhoid vaccine holds a new promise in this direction.

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