MULTIDRUG RESISTANT TYPHOID FEVER: STUDY OF AN OUTBREAK IN CALCUTTA

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ABSTRACT

Of 103 cases of typhoid fever admitted to the Pediatric Wing of our hospital during the months of August 1989 to April 1990, 82.5% were resistant to chloramphenicol, ampicillin and co-trimoxozole. Nearly 87% children were in the age group of 3-10 years. Fever was present in all and splenomegaly in 90.2% cases. Urinary retention during the course of illness was present in 2 cases. The positivity rate of blood culture, bone marrow culture and Widal test was 83.7, 100 and 13.5%, respectively. Majority of the strains were of Phage 51-Type I. For the treatment of multidrug resistant cases gentamicin and furazolidine proved ineffective. Ciprofloxacin was tried in 85 cases and was found to be effective in all cases with no side effects.

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

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The incidence of typhoid fever continues to be high in developing countries like India where it remains a major health problem. Emergence of chloramphenicol resistant cases(1,2) has been a cause of worry for the civilians since its first report in 1962. However, it is the emergence of multi-drug resistant cases(3-6) which is threatening to become a serious health problem.

In this study we present our experience of the clinical, laboratory and therapeutic aspects of an outbreak of multi-drug resistant typhoid fever in children of Calcutta (West Bengal).

Material and Methods

One hundred and seventeen cases of suspected typhoid fever were admitted to the Pediatric Wing of the Command Hospital, Calcutta during August, 1989 to April, 1990. One hundred and three of these grew *Salmonella typhi* on blood/ bone marrow culture. These cases and the strains of *S. typhi* provided the material for this study. A detailed proforma enlisting various clinical and laboratory parameters was filled in every case. Investigations included complete hemogram, smear for malarial parasite, urine analysis, widal test and blood culture in all cases. Bone marrow aspiration for culture was done in 7 cases where despite strong clinical suspicion of typhoid fever, the blood culture was negative. *X*-ray chest, CSF studies, LFT and other laboratory tests were done in selected cases depending upon the individual case profile.

Blood culture was done in taurocholate broth. Identification of strain was carried out by standard biochemical tests and confirmation by serological tests using polyvalent and monovalent *S. typhi* sera. Drug

sensitivity was tested by Stokes method(7) using standard organisms. MIC was studied by Agar dilution methods. Phage typing was performed at the National Salmonella Research Laboratory, New Delhi. Antibiotics were exhibited as per the antibiotic sensitivity test (AST) in standard recommended dosages and duration. The drug was considered ineffective if the fever did not start coming down even after 10 days of therapy. Alternative drugs were used in such cases.

Results

Peak incidence was seen in the months of September and October (44.6%). Age and sex distribution of the cases is given in *Table I*. Nearly 87% of children were in the school going age (3-10 yrs). Three infants aged 8, 9 and 10 months formed the youngest group.

Presenting complaints are shown in *Table II*. Fever was the main symptom present in 100% cases. Continuous pattern was seen in 56.3% cases and intermittent in 43.7%. Two thirds cases had temperature above 102°F, 22.3% between 100°F and 102°F and in 10.7% it was less than 100°F. Duration of fever prior to admission was as long as 60 days in 4 cases (3.8%) and more than 30 days in 11 cases (10.6%), the average duration being 9 days. Chills were associated in 42.7% cases. Despite prolonged fever, majority of children did not look sick, were bright, active and had good appetite. Relative bradycardia was not a common feature and was seen in older children only. Jaundice was found in one case. Urinary retention during the course of illness was found in 2 cases. CNS manifestations (altered sensorium and abnormal behavior) were seen in 3 cases (2.9%).

The details of the clinical findings are given in *Table III*. Splenomegaly was found in 93 (90.2%) cases. It was less than one cm below costal margin in 62.4%, more than 3.0 cm in 9.7% and between 1 and 3 cm in the rest (27.9%). Consistency was soft in 79.6% and firm in 20.4% cases.

Anemia (Hb less than 10.0) was seen in 27 cases (26.2%). Leucopenia (TLC less than 4000/cmm) in 11 (10.7%) and leucocytosis in 9 (8.7%) cases. BT rings were seen on peripheral smear examination in 3 (2.9%) cases. Platelet count was normal in

TABLE I—*Age and Sex Distribution*

Age (yrs)	Number			Percentage
	Male	Female	Total	
0-1	2	1	3	2.9
1-3	6	5	11	10.6
>3-6	12	16	28	27.2
>6	30	31	61	59.3
Total	50	53	103	100.0

TABLE II— *Clinical Features (Presenting Complaints)*

Symptoms	Number	Percentage
Fever	103	100.0
Chills	44	42.7
Myalgia	43	41.7
Anorexia	41	39.8
Cough	39	37.8
Vomiting	31	30.0
Headache	29	28.1
Loose motions	15	14.5
Arthralgia	11	10.6
CNS manifestations	3	2.9
Epistaxis	2	1.9
Retention of urine	2	1.8
Jaundice	1	1.0

TABLE III—*Clinical Features (Signs)*

Signs	Number	Percentage
Splenomegaly	93	90.2
Pallor	59	57.2
Hepatomegaly	47	45.6
Toxic look	41	39.8
Coated tongue	34	33.0
Nasopharyngitis	26	25.2
Cheilosis/Angular Stomatitis/Apthous ulcers	19	18.4
Relative bradycardia	12	11.6
Bronchitis	9	8.7
Meningismus	2	1.9
Icterus	1	1.0

all patients. The results of blood/bone marrow culture and Widal test are given in *Table IV*. Antibiotic sensitivity pattern is shown in *Table V*. Eighty five cases (82.5%) were resistant to 3 commonly used drugs, *i.e.,* chloramphenicol, ampicilin and co-trimoxozole (CHAC).

MIC carried out on the resistant (R) strains revealed that: (*a*) 68% of ampicillin (R) strains were not inhibited even at concentrations of 356 micrograms/ml; (*b*) 65% of chloramphenicol resistant strains were not inhibited even at 400 micrograms/ml of chloramphenicol; and (*c*) 70% of Co-trimoxozole resistant strains were not inhibited at 160 micrograms/ml of trimethoprim and 1280 micrograms/ml of sulphamethoxozole.

TABLE IV—*Investigations*

	No. of samples	No. of positive samples	%
Blood culture	117	98	83.7
Bone marrow culture	7	7	100.0
Widal test	81	11	13.5

TABLE V—*Antibiotic Sensitivity Test*

Drug	No.	%
	Sensitive	Resistant
Chloramphenicol	14 (13.6)	89 (86.4)
Ampicillin	16 (15.5)	87 (84.5)
Co-trimoxozole	5 (4.8)	98 (9.2)
Furazolidine	26 (54.2)	22 (45.8)
Gentamicin	103 (100.0)	Nil
Ciprofloxacin	103 (100.0)	Nil

Antibiotics used and their therapeutic response is shown in *Table VI*.

Majority of the strains of *S. typhi* were of Phage type 51, biotype I, which is unusual in this part of the world.

Discussion

During a recent epidemic of multidrug resistant typhoid fever (MDRTF) in Calcutta(8), we came across 117 cases in the pediatric age group. Although several reviews are available about epidemiological and cinical features of typhoid fever in children(9-14) our study highlights several unusual and unique features.

Though the school going children were found to be most vulnerable, the younger children including infants were not spared, the youngest baby in our study being 8 months of age. Male preponderance reported in other studies(10,12,13) was not seen in the present study. Fever of variable pattern, grade and duration was the predominant symptom. Its association with chills, cough, lung signs and myalgia in significant number of cases was responsible for its confusion with malaria and respiratory infection resulting in the undue delay

in vivo and *in vitro* sensitivity of *S. typhi* to gentamicin is well known(29). However, we could not find a logical explanation of failure to respond to furazolidine.

Ciprofloxacin has been used in adults to treat enteric fever particularly in patients with multiply resistant organisms(30). However, its use is not recommended in children below the age of 12 years unless the benefit is considered to out-weigh the potential risk(31). After having exhausted the well tried drugs and in the absence of any other drug known to be effective in MDRTF, we went ahead with it's use in 85 children resistant to CHAC and furazolidine. The response rate was gratifying. Toxemia was relieved within 48-72 hours of initiating therapy. Mean period of defervescence was 5.5 days. The drug was given by intravenous route for the first 24-48 hours in 6 very sick children having vomiting. Oral administration was resumed once the vomiting stopped. In all other cases it was given by oral route. The dose used was 10 mg/kg body weight in two divided doses for 10 days. It was extremely well tolerated even by 3 infants less than 1 year of age.

There were no side effects except nausea in 3 (3.8%) and diarrhea in one (1.2%) case. Fifty four children have been followed up for a period of one year, none has relapsed or shown any adverse affects of ciprofloxacin.

Recent studies by Adam(32) and Fontaine(33) indicate that recommendation of not using fluoroquinoline group of drugs in children may be overly cautious and that the risks associated with these drugs in pediatric age group are outweighed by the benefits that accrue in life threatening disease. Our experience supports these findings. However, the drug should be used with discretion keeping a close watch on any adverse effects developing during and in the months following the course of treatment.

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