MULTIDRUG RESISTANT TYPHOID FEVER: THERAPEUTIC CONSIDERATIONS

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ABSTRACT

Forty six blood culture positive cases were studied during the current outbreak of multidrug resistant typhoid fever (MRTF). The present outbreak was caused by E_1 phage type and organisms were resistant to all commonly used drugs for the treatment of typhoid fever, viz., chloramphenicol (78%), co-trimoxazole (76%) and ampicillin (68%). Treatment failures with chloramphenicol (45.5%) corroborated well with in vitro resistance. No treatment failure was seen with chloramphenicol and ceftriaxone, when these drugs were used in cases infected with sensitive strains. Among the alternative drugs used in cases with in vitro sensitivity, successful clinical response was seen with ceftriaxone (4/4) and cefotaxime (8/9) as compared to cephalexin (3/5) or a combination of cephalexin and furazolidone (9/12).

Key words: *Multidrug resitant typhoid fever, Phage type, Resistance pattern, Treatment failure.*

The first report of successful treatment of typhoid fever with chloramphenicol dates back to 1948(1) and first resistance was reported in 1950(2). Since then chloramphenicol or multidrug resistant typhoid fever (MRTF) has been reported from many parts of the world, mainly during outbreaks and the organism continued to be sensitive to routinely used antibiotics once the outbreak was over.

Presently we are witnessing an outbreak of multidrug resistant typhoid fever in and around Delhi. The microbiological profile seems to be unchanged even after an year of onset of the outbreak. This study focusses our attention on some of the therapeutic aspects of MRTF.

Material and Methods

Patients admitted with a clinical diagnosis of enteric fever and later confirmed by positive blood culture were included in the study. The cases were admitted in general Pediatric Units of Kalawati Saran Children's Hospital from January to October, 1990 and were managed under supervision of atleast one of the authors. Treatment was started with one of the routinely used antibiotics after samples for widal test and blood culture were collected. The phages used for phage typing were obtained from International Research Laboratory for Enteric phage typing and method used was as described in one of the earlier communica-

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tions from this institution(3). Sensitivity of various antibiotic discs was tested by Stoke's method(4). Other relevant investigations were done as and when indicated.

Based on our earlier sensitivity reports, chloramphenicol, furazolidone, cephalexine and co-trimoxazole were used as first line antibiotics. The decision to use one of these antibiotics was based on clinical condition of the child, drugs used before hospitalization and availability of drug(s) in the hospital. Treatment failure was defined as persistance of high grade fever after taking antibiotic(s) orally/parenterally with a proper dose at appropriate intervals for a period of 7 days.

Results

From January, 1990 to October 1990 *S. typhi* was grown from blood culture of 50 out of 214 patients admitted with a clinical diagnosis of enteric fever. Three patients left the hospital before completion of the therapy and therefore were excluded from the study and one case expired while on treatment. Sensitivity profile and phage types with resistance pattern are shown in *Tables I & II*, respectively. Response to first line antibiotics and alternative drugs used in cases of treatment failure is shown in *Tables III & IV*, respectively. If a child did not respond to alternative drug, he was labelled as a case of treatment failure to that drug or cominbation of drugs if used together. *Table V* shows results of treatment with various drugs when they were used in sensitive cases. Ciprofloxacin was used in one case only, who was a treatment failure with cefotaxine and had *in-vitro* resistance to it.

Discussion

Chloramphenicol was used in the treatment of typhoid fever in 1948 by Woodwards(1) and has been successfully used for the last four decades. However, in

TABLE I—*Sensitivity Pattern of S. typhi*

Drug	Sensitive No. (%)	Resistant No. (%)	Not done
Chloramphenicol	11 (22.0)	39 (78.0)	–
Ampicillin	16 (32.0)	34 (68.0)	–
Co-trimoxazole	12 (24.0)	38 (76.0)	–
Tetracycline	11 (22.0)	39 (78.0)	–
Cephalexin	35 (97.2)	1 (2.8)	14
Furazolidone	37 (100.0)	–	13
Cefotaxime	39 (88.1)	5 (12.4)	6
Ceftriaxone	30 (81.1)	7 (18.9)	13
Augmentin	–	14 (100.0)	36
Amikacin	27 (96.4)	1 (3.6)	22
Gentamicin	32 (64.0)	18 (36.0)	–
Ciprofloxacin	20 (100.0)	–	30

TABLE II—*Distribution of Phage Types According to Resistance Pattern*

Resistance pattern	No. of cases	Phase Type							
		E1	UVS	A	O	Deg vi	vi Neg.	K1	J1
A, C, Co, T, G	17	13	–	2	–	1	1	–	–
A, C, Co, T	16	12	–	3	–	–	–	1	–
C, Co, T, G	1	–	–	–	–	–	–	–	1
C, Co, T	4	1	2	–	1	–	–	–	–
C, T	1	–	1	–	–	–	–	–	–
Sensitive strains	11	6	4	1	–	–	–	–	–
Total	50	32	7	6	1	1	1	1	1

A—Ampicillin, C—Chloramphenicol, Co—Co-trimoxazole, T—Tetracycline, G—Gentamicin.

TABLE III—*Treament Results with First Line Drug(s)*

Drugs	No. of pts treated (n = 46)	No. culture sensitive	No. (%) responded
Chloramphenicol*	22	9	12 (54.5)**
Co-trimoxazole + Furazolidone	13	9,13	7 (53.8)
Cephalexin	3	3	2 (66.7)
Cephalexine + Furazolidone	6	6,6	5 (83.3)
Ampicillin + Gentamicin	2	1,1	

* An additional 17 patients received this drug before hospitalization. In 5 cases, doses were not proper and in another 4 duration was less than 1 week. Remaining may be considered treatment failure.

** Three patients with *in vitro* resistance to chloramphenicol responded.

present series 78% isolates were resistant to this drug *in vitro* and well corroborated with treatment failures. The isolates were resistant to other commonly used alternative drugs, *viz.*, Ampicillin (68%), Co-trimoxazole (76%) and Tetracycline (78%). Augmentin (a combination of clauvulanic acid and amoxycillin) was projected as a good alternative based on *in vitro* study(5) and clinical response in other betalactamase producing Gram negative organisms(6-8). However, in the present study, all strains tested against this antibiotic were resistant.

Current outbreak of MRTF is caused by E_1 phage type which used to be a much less common strain in Northern India constituting only 10.5 to 26.7% strains and was still less common in South India. Phage type A, the most prevalent strains of yester years, was seen in 6 (12%) patients only whereas E_1 constituted 64% of the cases.

TABLE IV–*Treatment with Alternative Drugs in Cases of Treatment Failure**

Drugs used	Treatment failure	Alternative antibiotics used					
		Chloram-phenicol	Cefo-taxime	Ceftri-axone	Cepha--lexin	Cephalexin +Furazoli-done	Cipro-floxa-cin
Chloramphenicol	10	–	4 (4)	2 (2)	–	4 (2)	–
Co-trimoxazole + Furazolidone	6	–	4 (2)	–	2 (1)	–	–
Cephalexin	2	1 (1)	1 (1)	–	–	–	
Cephalexin + Furazolidone	3	–	1 (1)	2 (2)	–	–	–
Ampicillin + Gentamicin	2	–	–	–	–	1 (1)	–
Cefotaxime	2	–	–	–	–	1 (1)	1 (1)

* Includes treatment failure of first line drugs as well as drug used after sensitivity report. Total number is more than actual number of patients as some had treatment failure with more than one drug.

(Figures in parenthses represent number of patients responded to alternative drugs).

TABLE V–*Treatment Results of Patients Treated with Drugs having in vitro Sensitivity**

Drugs	Number of patients treated*	Patients responded No.	%	Mean duration of deferves-cence (days)	Duration of defer vescence (days)
Chloramphenicol	11	11	100.0	6.3	3-11
Cefotaxime	9	8	88.9	10.9	7-21
Ceftriaxone	4	4	100.0	6.5	6-7
Cephalexin	5	3	60.0	5.7	4-7
Cephalexin + Furazolidone	12	9	75.0	6.9	4-8
Co-trimoxazole + Furazolidone	9	7	77.8	6.4	4-10
Ciprofloxacin	1	1	100.0	4.0	4

* Includes drugs used as first line or after availability of culture reports.

** Total number of patients treated is more then 46 as some patients did not respond to drugs having *in vitro* sensitivity and were treated with more than one drug.

Only one patient of phage type 'O' was seen which was almost as common as E_1 in past years(9). Another report of MRTF from Calcutta(10) showed phage type 51 to be the responsible strain for the outbreak. This is a serious feature of these outbreaks as these strains continue to intermingle due to population migration(9) and can lead to outbreak in places where the strain was not found earlier.

Majority of multidrug resistant strains belonged to one phage type (E_1) which, therefore, seems to be responsible for the current outbreak. The resistance to various drugs is attributed to the presence of plasmids which are auto transferable(5). An occasional case of multidrug resistance was seen in other phage types. This might reflect spread of some resistance plasmid to other phage types. A similar phenomenon was seen in Vietnam(11) in late seventies.

Alternative drug therapy for MRTF is an issue of paramount importance particularly because most of the suggested alternatives are expensive, some of them have to be administered parenterally and are not recommended for pediatric practice. Excellent therapeutic response to chloramphenicol and ceftriaxone was seen wherever organisms were sensitive *in vitro*. There was statisfactory response to cefotaxime and combinations of Furazolidone with cephalexin and cotrimoxazole (*Table V*). However, in view of a very high resistance *in vitro* to chloramphenicol and cotrimoxazole (*Table II*) which corroborated well with treatment failures, these drugs can't be used as first line drug during the outbreak of MRTF. Cephalexin, because of its good *in vitro* sensitivity and fair response *in vivo* when used in combination with furazolidone, holds some promise for ambulatory treatment of enteric fever. Ceftriaxone has been advocated for the treatment of sick hospitalized children or as a single intramuscular injection on outdoor basis(12,14). Even though this drug was successful in all the 4 resistant cases, no definite conclusions can be drawn regarding its superiority because of small number of cases studied.

Ciprofloxacin had sensitivity against all 20 strains tested. Quinolone group of drug have been found effective in treatment of enteric fever in adults(10,15) with a cure rate of 100% but presently are not recommended for use in pediatric patients because of its possible side effects on growing cartilages. However, preliminary data from ongoing trials suggest that the newer quinolones are safe in children(16,17). These observations are further endorsed by some of the clinical studies in children with no adverse clinical, hematological or biochemical effects(18). Since this drug was used in only 1 of our patients, no meaningful conculsions can be drawn.

Response to treatment of typhoid fever with chloramphenicol used to be so consistent that despite the reports of clinical efficacy of many other drugs, none was seriously used as an alternative. Cephalexin, which had shown promising results against *Salmonella* infection in earlier years of its advent(19), used in combination with furazolidone, may be useful alternative for some patients with '*in vitro*' resistance to chloramphenicol.

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