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Third Generation Cephalosporins in Multi-Drug Resistant Typhoid Fever

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Enteric fever caused by *Salmonella typhi (S. typhi)* is still rampant in most developing countries. Chloramphenicol, cotrimoxazole and amoxycillin have been the standard first line drugs for this disease(1). The continuing emergence of antibiotics resistance of these drugs has been causing considerable concern amongst microbiologists and physicians. The recent emergence of multi drug resistant *Salmonella typhi* (MDRST) strains has necessitated a reappraisal of therapeutic options, in such cases. We report our experience with use of third generation cephalosporins-ceftriaxone and cefotaxime in such cases.

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Material and Methods

Eleven bacteriologically confirmed cases of typhoid fever admitted in the pediatric wards of our Institute constituted the study group. In all these cases the *S. typhi* isolates had *in vitro* resistance to chloramphenicol, co-trimoxazole and amoxycillin, compelling the treating pediatrician to opt for cefotaxime or ceftriaxone as the therapeutic alternative. These strains accounted for 95% of total isolates during this period. The duration of antimicrobial therapy was based on standard recommendation pertaining to their use in enteric fever(1). Statistical analysis was done using Student's 't-test'.

Results

The clinical profile of these patients is detailed in *Table I*. There were 8 males and 3 females and their ages ranged from 1.5 years to 11 years with a mean of 5.2 years. All these children presented with remittent, moderate to high grade fever of durations ranging from 1 to 30 days (mean 14.7 days). All, except one of these patients had previously received one or more antimicrobials (ampicillin, amoxycillin, chloramphenicol, co-trimoxazole, cephalothin, gentamicin) for suspected enteric fever. Failure to respond or an inadequate therapeutic response necessitated referral. The disease had remained uncomplicated even though the duration of symptoms was over 2 weeks in nearly 50% of the cases. The salient characteristics of the therapeutic options chosen are tabulated in *Table II*.

TABLE I–*Clinical Profile of Patients*

S. No.	Age (yrs) & sex	Duration of fever prior to admission (days)	Prior anti-microbial therapy	Therapeutic option chosen	Duration of therapy	Deferve-scence (days)	Relapse (Yes/No) interval of days
1.	7.0 M	30	Amp, CMP, CoT	Cefotaxime	14	10	No
2.	1.5 M	15	CoT, CMP, Genta	Cefotaxime	14	11	No
3.	2.0 M	1	Amp, Genta	Cefotaxime	7	3	No
4.	11.0 F	7	Amp, Genta	Cefotaxime	11	7	No
5.	5.0 F	23	CMP, Amoxy, CoT	Cefotaxime	17	11	No
6.	4.5 M	20	CMP, CoT	Ceftriaxone	7	2	No
7.	2.5 M	9	None	Ceftriaxone	7	4	No
8.	6.0 M	9	CoT, Cephal.	Ceftriaxone	7	5	Yes, 21 days
9.	6.0 M	7	CoT, Genta	Ceftriaxone	6	3	No
10.	6.0 F	11	CMP, Cephal	Ceftriaxone	10	3	No
11.	6.0 M	30	CMP, CoT	Ceftriaxone	10	3	No

Key: M = male; F = female; CoT = co-trimoxazole; CMP = Chloramphenicol; Amp = Ampicillin; Genta = gentamicin; Amoxy = Amoxycillin; Cephal = Cephalothin.

TABLE II–*Salient Characteristics of Therapeutic Options Used*

Therapeutic option	Dose (mg/kg/day); frequency and route of administration	No. of patients	Age-Mean (Range) in yrs	Duration of treatment* Mean (Range) in days	Duration of fever prior to admission Mean (Range) in days	Deferve-scence** Mean (Range) in days
(*a*) Ceftriaxone	50-80; q 12 hrly, IV	6	5.16 (2.5-6)	8.4 (6-10)	14.3 (7-30)	3.3 (2-5)
(*b*) Cefotaxime	100-150; q 6 hrly, IV	5	5.3 (1.5-11)	12.6 (7-17)	15.2 (1-30)	8.4 (3-11)

Statistical analysis by Student's 't-test'* $p < 0.004$; ** $p < 0.005$.

The shortest periods of defervescence were observed with ceftriaxone–a mean of 3.33 days with a range of 2 to 5 days ($p<0.005$). In contrast, lysis of temperature in 3 of the 5 children treated with cefotaxime occurred on the 10th or 11th day of initiating therapy. Ceftriaxone was administered for a shorter period (mean 8.4 days) in comparison to cefotaxime (12.4 days).

The duration of follow up in these cases ranges from 3-6 months. Only one child (Case 8) who was treated with a 7 days

course of ceftriaxone relapsed. This occurred 21 days after completing therapy and the second *S. typhi* isolate demonstrated a similar multidrug resistant pattern. He responded to oral ciprofloxacin and remains well off treatment.

Discussion

Typhoid fever remains a common cause of morbidity and mortality in developing countries. This problem has been further compounded by the recent emergence of MDRST. Besides the conventional primary drugs, a wide range of antimicrobials have been found to be effective against *S. typhi*. These include tetracycline, aminoglycosides, cephalosporins and more recently the quinolones(1,4,5). Clinical experience with these agents has been described in isolated case reports and few prospective studies have been performed.

The third generation cephalosporins have been the most widely used and with an overall clinical cure rate of 90%. Of these the maximum clinical experience has been with cefotaxime, administered in 4 divided doses for a minimum of 10 days or until 3 days after defervescence(1). A recent report has shown that a shorter course of ceftriaxone (50-80 mg/kg/day for 5-7 days) is equally efficacious(1,2). Moreover, ceftriaxone can be given as a single daily intramuscular injection(6). Although the third generation cephalosporins have a disadvantage of their high cost, in case of ceftriaxone this is partly offset by a shorter duration of treatment and hospital stay.

Of the various third generation cephalosporins cefotaxime was used in 5 and ceftriaxone in 6 patients. There was no significant difference between the two subgroups as far as the age of the patients and the grade of fever and concerned. The most encouraging results were obtained with ceftriaxone in which the period of defervescence and duration of therapy was the shortest ($p<0.005$ and $p<0.004$, respectively). However, one child (Case 8) relapsed within 3 weeks of cessation of therapy. The period of defervescence and duration of therapy was longer with cefotaxime. A combination of cephalexin and gentamicin has been found to be effective against MDRST. However, we resorted to the use of third generation cephalosporines as a substantial number of patients had already received either of the drugs perior to referral without any response. Coprofloxacin seems a promising alternative in developing countries but well controlled perspective trials are required before it can be recommended in pediatric age group.

The emergence of multi-drug resistant *S. typhi* is indeed a perplexing trend and calls for a reappraisal of our antibiotic policies. Cefotaxime and ceftriaxone are effective therapeutic alternatives in such cases, the results being particularly encouraging with the latter.

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