ORIGINAL ARTICLES

MULTI DRUG RESISTANT *SALMONELLA TYPHI* INFECTION : CLINICAL PROFILE AND THERAPY

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ABSTRACT

Multiple drug resistant Salmonella typhi infection was observed in thirty five recent cases among forty eight children with bacteriologically proven enteric fever. Incidence of complications such as shock, myocarditis, encephalopathy and paralytic ileus was higher among these. A combination of cephalexin and gentamicin was successfully used in the management of these children.

Key words: *Salmonella typhi, Drug resistance*

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The emergence of chloramphenicol resistant *Salmonella typhi* is of concern to pediatricians the world over, more so in the tropical countries(1). The alternative drugs suggested for treatment of resistant salmonella infection include cotrimoxazole and amoxycillin(2). We recently noticed an unanticipated upsurge in the incidence of typhoid fever due to *Salmonella typhi* strains, resistant to the three commonly used drugs, *viz.*, chloramphenicol, co-trimoxazole and amoxycillin. This is of serious concern for pediatricians in India both from the therapeutic considerations and public health aspects.

This communication highlights our observations on (*a*) the clinical profile of patients with typhoid fever due to multidrug resistant *Salmonella typhi* infections, and (*b*) alternate approaches in management.

Material and Methods

Forty eight consecutive culture proven typhoid fever cases who had not received any antibiotics prior to admission were analysed. A detailed history, clinical profile, complications at the time of admission and during the course of hospital stay were recorded. A complete hemogram, *X*-ray chest, Widal reaction and blood cultures for salmonella were obtained in all children. When clinical suspicion of typhoid fever was strong and blood culture was sterile, salmonella were cultured from bone marrow aspirates (five cases).

Glucose citrate broth and taurocholate broth were used for culture for salmonella. Subcultures were done on blood agar and

McConkey's agar on day one, two and seven(3). Growth from solid media was identified by biochemical reactions and by slide agglutination using monospecific somatic and flagellar specific phase antisera(4). Antibiotic sensitivity testing on Muller-Hinton agar was done by Stokes disc diffusion method(5). The concentration per disc of the following antibiotics was 10 μg gentamicin, cephalexin, norfloxacin, co-trimoxazole, amoxycillin and furazolidone. In the case of chloramphenicol, both 10 μg and 30 μg discs were used.

Patients were initially treated with chloramphenicol (75 mg/kg/day). After blood culture reports were available, amoxycillin (100 mg/kg/day) was started in chloramphenicol resistant *Salmonella typhi* infection who were sensitive to amoxycillin. All triple drug resistant salmonella strains (resistant to chloramphenicol, co-trimoxazole and amoxycillin) were sensitive to cephalexin and gentamicin. These patients were treated with cephalexin (75 mg/kg/day) and gentamicin (5 mg/kg/day) for fourteen days. The period of defervescence and relief in toxemia was recorded after starting alternate antibiotics. Since a combination of potentially nephrotoxic drugs was used, estimation of blood urea and serum creatinine was done initially and after one week. Patients were kept under observation in ambulatory clinic for a period of two weeks after discharge.

Results

Salmonella typhi isolated in 13 cases were sensitive to chloramphenicol (Group-I). Isolated chloramphenicol resistance was seen in seven children (Group-II) and 17 had salmonella infection resistant to chloramphenicol and cotrimoxazole (Group-III). Eleven children had enteric fever resistant to chloramphenicol, cotrimoxazole and amoxycillin (Group-IV). A disquieting feature in 1990, compared with the year 1989, was a significantly higher proportion of triple drug resistant cases (*Fig.*). The clinical features and complications of all 48 children with enteric fever are summarised in *Tables I & II.*

Age and duration of fever at the time of admission was not significantly different amongst the four groups. It was noted that 2 patients in Group III and 2 patients in Group IV had palpable spleen as against 9 in Group I and 3 in Group II. Quick defervescence and relief of toxemia was seen after addition of cephalexin and gentamicin in ten triple drug resistant patients. The mean time taken for defervescence in these patients was significantly lower (4.00 $\pm$ 1.18 d) compared to patients in Group I and Group III ($p < 0.01$). Blood urea and serum creatinine levels were unaffected in these patients. Of two deaths, one had infection resistant to two drugs and the other to three drugs. Both the patients had presented in a state of shock at the time of admission and expired within 24 hours before results of blood culture were available. Twelve cases were lost to follow up (5 of Group II and 7 of Group III). Of the remaining cases followed for 2 weeks none had relapse.

Discussion

In the present study, 72.8% of blood culture positive *Salmonella typhi* were resistant to chloramphenicol. The figures vary between 38.6 and 83.0% in other reports from India(1,2,6). Of the chloramphenicol resistant strains, 48.5% were resistant to co-trimoxazole and 31.4% to co-trimoxazole and amoxycillin. The triple

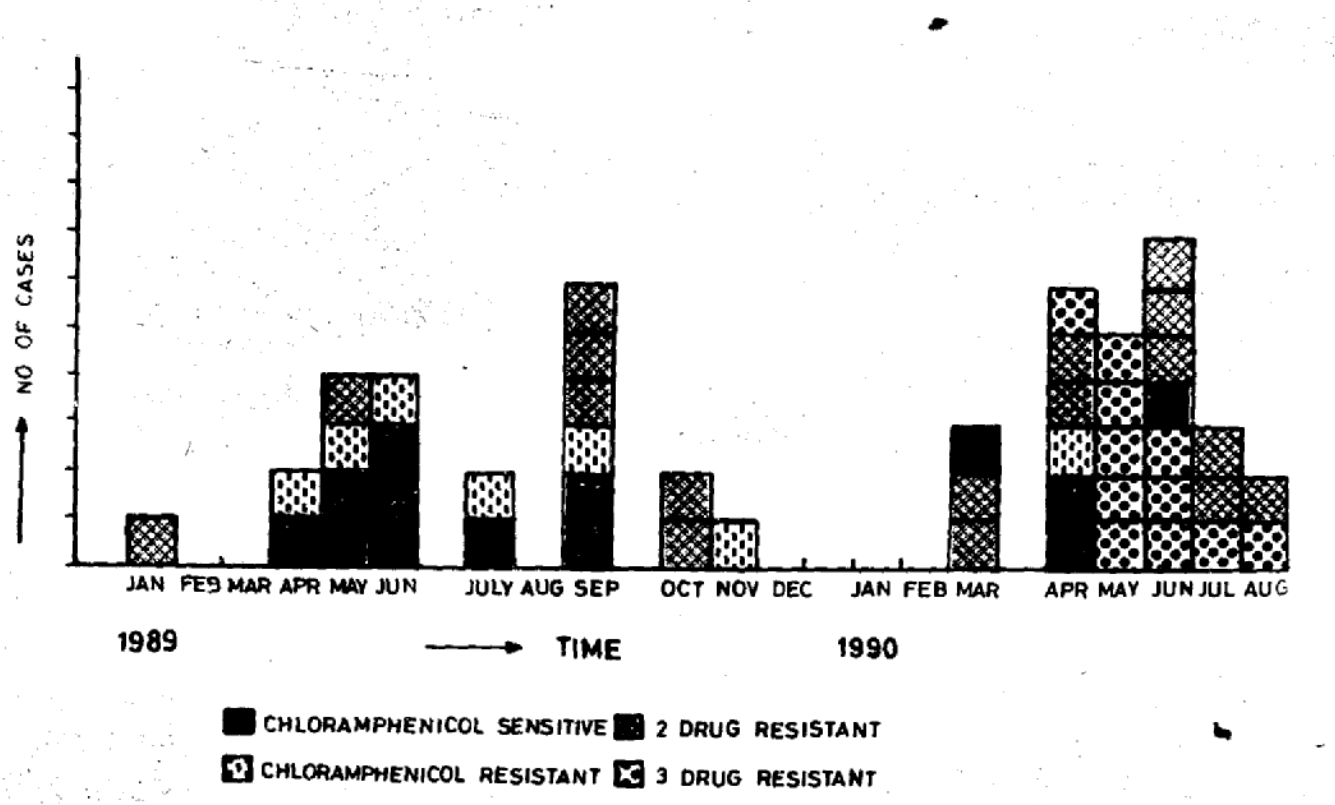

Fig. Seasonal distribution of patients with enteric fever.

TABLE I—*Clinical Features of Enteric Fever*

Features	Group I Chloromycetin sensitive (n=13)	Group II Chloromycetin resistant (n=7)	Group III Chloromycetin + Cotrimoxazole resistant (n=17)	Group IV Chloromycetin + Cotrimoxazole + Amoxycillin resistant (n=11)
1. Age (yrs)	7.2 ± 2.6	7.14 ± 1.67	5.12 ± 3.33	6.6 ± 3.41
2. Sex	M = 5 F = 8	M = 2 F = 5	M = 10 F = 7	M = 7 F = 4
3. Duration of fever at admission (days)	9.23 ± 6.73	14.43 ± 8.44	13.06 ± 9.85	10.18 ± 4.83
4. Splenomegaly	9	3	2	2
5. Hepatomegaly (>2.0 cm)	4	3	6	2
6. Defervesence of fever on alternative antibiotics (days)	6.75 ± 2.34	6.28 ± 1.25	6.94 ± 2.44	4.00 ± 1.18

TABLE II—*Complications of Enteric Fever*

Features	Group I Chloromycetin sensitive (n=13)	Group II Chloromycetin resistant (n=7)	Group III Chloromycetin + Cotrimoxazole resistant (n=17)	Group IV Chloromycetin + Cotrimoxazole + Amoxycillin resistant (n=11)
1. Shock	0	0	2	1
2. Gastrointestinal hemorrhage	2	1	3	3
3. Loose motions and vomiting	5	1	1	1
4. Encephalopathy	3	1	5	8
5. Paralytic ileus	0	0	1	2
6. Pneumonia	2	5	2	1
7. Maculo-papular rash	0	0	1	1
8. Arthritis	0	0	1	0
9. Myocarditis	0	0	0	2
10. Death	0	0	1	1
11. Hepatitis	0	0	1	2
12. Parotitis	0	0	0	1

drug resistance seems to be on the increase of late. In 1990, 52.9% of salmonella isolated in our hospital were resistant to chloramphenicol, amoxycillin and co-trimoxazole. In a recent epidemic witnessed in Calcutta, 89.7% isolates of salmonella were resistant to co-trimoxazole and 78% were resistant to chloramphenicol(6).

Twenty two out of forty eight cases in the present study were in age group 0-5 years (45.8%). This is higher than 13.5% in a recent report from South India but comparable to 53.3% reported from Delhi(7,8).

Life threatening complications such as shock, encephalopathy and myocarditis were seen more often in multi drug resistant patients (Groups III & IV). However, this phenomenon was not observed in previous studies, which report a low incidence for these complications(1,6,7).

The antibiogram in the cases of multidrug resistant *Salmonella typhi* revealed, that these strains were sensitive to cephalexin, gentamicin, norfloxacin and furazolidone. Norfloxacin was not used, in our study, as safety of this drug is not well established in pediatric population, though there are suggestions for its use in life threatening situations(9). Gentamicin when used alone showed clinical efficacy in 60% of susceptible *Salmonella typhi* infections(6). There is paucity of literature for use of cephalexin alone in the management of typhoid fever. Since majority of the triple drug resistant cases in our study were too sick and toxic, a combination of cephalexin and gentamicin was used. All patients suffering from triple drug resistant *Salmonella typhi* infection successfully responded to this mode of therapy.

The city of Delhi witnessed an outbreak of cholera and gastroenteritis in year 1988. Since then amoxycillin, co-trimoxazole and chloramphenicol were extensively used in the treatment of these disorders. The emergence of multiple drug resistance of *S. typhi* to above drugs has been appreciable after this outbreak.

The drug resistance of *S. typhi* is mediated by transferable 'R' plasmid. This plasmid is acquired by conjugation with coliform organisms(1,10,11). Coliforms rapidly acquire resistance to the above mentioned drugs. In areas endemic for both gastroenteritis and typhoid fever, this resistance 'R' plasmid is easily transferred to *Salmonella typhi*. This probably accounts for the current upsurge of multi-drug resistant *S. typhi* infection(12).

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