ENTERIC FEVER - CULTURE AND SENSITIVITY PATTERN AND TREATMENT OUTCOME

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ABSTRACT

One hundred cases of enteric fever in the age group of 6 months to 12 years were analysed with respect to culture sensitivity pattern and treatment outcome. Patients were divided into 5 treatment groups - chloramphenicol, amoxycillin, trimethoprim-sulfamethoxazole + furazolidine, gentamicin + cephalexin and ciprofloxacin. Out of 91 culture positive cases, 100% were sensitive to ciprofloxacin followed by gentamicin (84.9%), cephalexin (83.6%), furazolidine (36.6%), trimethoprim-sulfamethoxazole (34.1%), chloramphenicol (34.0%) and amoxycillin (23.8%). In 60 cases resistant to chloramphenicol, resistance to other drugs varied from 20 to 88.3%. The treatment response was 100% to ciprofloxacin, 72.7% to chloramphenicol, 50% to gentamicin + cephalexin, 38.5% to trimethoprim-sulfamethoxazole + furazolidine and 12.5% to amoxycillin. Out of 48 cases who did not respond to initial regimen, 33 were treated successfully with ciprofloxacin and remaining with other drug regimens. Time taken for defervescence was shortest with gentamicin + cephalexin (4.6 ± 2.0 days) followed by ciprofloxacin (6.1 ± 2.5 days) and chloramphenicol (6.4 ± 3.5 days). There were 3 deaths in this study.

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KEY WORDS : Typhoid; Drug resistance microbial; Clinical trials.

Introduction

Typhoid fever is an acute infectious disease caused by *Salmonella typhi* and can be considered to be endemic in developing countries like India [1]. Chloramphenicol was the gold-standard in the treatment of typhoid fever till the emergence of resistant *Salmonella typhi* strains. Consequently drugs like trimethoprim-sulfamethoxazole, ampicillin and amoxycillin were evaluated for chloramphenicol resistant strains. Of late, there has been an emergence of multidrug resistant *Salmonella typhi* strains (MDRST) with the incidence ranging from 10-83% [2]. This communication describes our observations on the sensitivity pattern and treatment outcome in children suffering from typhoid fever.

Material and Methods

One hundred proven cases of typhoid fever between 6 months to 12 years of age, admitted over a 18-month period formed the study group. Diagnosis was confirmed by blood/bone marrow culture and/or four-fold rise or 1 : 160 titre of antibodies against TO antigen by Widal test.

Five mL of blood was taken under sterile conditions and added to 45 mL of brain heart infusion with sodium polyanethol sulfonate. This was incubated for 24 hours at 37°C and then plated on to MacConkey and blood agars. Growth was looked for after 24-48 hours incubation at 37°C. If subcultures were negative, primary broth cultures were subcultured on Wilson and Blair medium for a total period of 10 days.

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Bone marrow aspiration was done from iliac crest and 0.5 mL of aspirate was cultured in similar media. *Salmonella typhi* were identified by standard biochemical and serological tests. Sensitivity tests were carried out by Stokes disc diffusion tests. Patients were divided into five treatment groups.

1. Chloramphenicol - 75 mg/kg/day.
2. Amoxycillin - 100 mg/kg/day.
3. Trimethoprim-sulfamethoxazole (10 mg/kg of trimethoprim) + Furazolidine (20 mg/kg/day).
4. Gentamicin (5 mg/kg/day) + Cephalexin (75 mg/kg/day).
5. Ciprofloxacin - 20 mg/kg/day.

Antibiotic therapy was withheld for 48 hours pending antibiotic sensitivity reports unless patient was extremely toxic where empirical therapy was started by allotting randomly to one of the above treatment groups. Subsequent antibiotic therapy was dictated by the clinical response as well as the in vitro sensitivity report. Cases diagnosed only by Widal test were similarly randomly allotted to one of the treatment groups. Culture positive patients were randomly allotted to one of the groups to which they were sensitive. Treatment was continued for 14 days or till 5 days after the patient became afebrile whichever was later.

Treatment was changed to alternative regimen when there was no response for 7 days or clinical condition deteriorated or the patient developed any complications.

Observations

There were 68 male and 32 female children. Maximum cases (51%) were seen in 6-9 years age group. The youngest child was 6 months old. Widal test was found positive in 40% cases. Out of a total of 91 culture positive cases, 16 (17.6%) were only blood culture, 45 (49.5%) were only bone marrow culture and 30 (32.9%) were both blood and bone marrow culture positive.

Sensitivity pattern revealed 34% cases sensitive to chloramphenicol, 23.8% to

amoxycillin, 34.1% to trimethoprim sulfamethoxazole and 36.6% to furazolidine. In contrast, 100% were sensitive to cefotaxime and fluoroquinolones followed by gentamicin (84.9%) and cephalexin (83.6%) (Table 1). Sixty cases resistant to chloramphenicol also revealed resistance to other drugs i.e. MDRST. 88.3% were resistant to amoxycillin, 80% to trimethoprim-sulfamethoxazole and 76.7% to furazolidine. Only 20% were resistant to gentamicin and 20.3% to cephalexin. No resistance was found to cefotaxime and fluoroquinolones (Table 2).

TABLE 1
Antibiotic sensitivity pattern of *Salmonella typhi* isolates (n=91)

Drug	Total No.	Sensitive
Chloramphenicol	91	31 (34.0)
Amoxycillin	63	15 (23.8)
Trimethoprim-sulfamethoxazole	82	28 (34.1)
Furazolidine	82	30 (36.6)
Gentamicin	73	62 (84.9)
Cephalexin	73	61 (83.6)
Cefotaxime	56	56 (100.0)
Norfloxacin	60	60 (100.0)
Ofloxacin	52	52 (100.0)
Ciprofloxacin	86	86 (100.0)

(Figures in the parentheses indicate percentage)

TABLE 2
Sensitivity pattern of chloramphenicol resistant strains (n=60)

Drug	Total No. tested	Sensitive	Resistant
Amoxycillin	60	7 (11.7)	53 (88.3)
Trimethoprim-sulfamethoxazole	60	12 (20.0)	48 (80.0)
Furazolidine	60	14 (23.3)	46 (76.7)
Gentamicin	60	48 (80.0)	12 (20.0)
Cephalexin	59	47 (79.7)	12 (20.3)
Cefotaxime	41	41 (100.0)	—
Norfloxacin	56	56 (100.0)	—
Ciprofloxacin	60	60 (100.0)	—
Ofloxacin	51	51 (100.0)	—

(Figures in parentheses indicate percentage)

TABLE 3
Treatment modalities and outcome

Treatment regimen employed	Initial treatment		Non responders to initial treatment	
	No. of cases	Successful response(%)	No. of cases	Successful response (%)
Chloramphenicol	33	24 (72.7)	6	6 (100)
Amoxycillin	24	3 (12.5)	0	0 —
Trimethoprim - sulfamethoxazole + furazolidine	26	10 (38.5)	3	3 (100)
Gentamicin + cephalixin	10	5 (50.0)	6	6 (100)
Ciprofloxacin	7	7 (100.0)	33	33 (100)

The response to treatment with various regimens was found to be - ciprofloxacin 100%, chloramphenicol 72.7%, gentamicin + cephalixin 50%, trimethoprim-sulfamethoxazole + furazolidine 38.5% and amoxycillin 12.5% only. Out of 48 cases who did not respond to treatment initially, 33 were treated with ciprofloxacin, 6 each with chloramphenicol and gentamicin + cephalixin and 3 with trimethoprim - sulfamethoxazole + furazolidine. The drugs in these 48 cases were not allotted randomly in view of the complications of the disease they were having (Table 3).

Defervescence was earliest with gentamicin + cephalixin (4.6 ± 2.0 days) followed by ciprofloxacin (6.1 ± 2.5 days) and chloramphenicol (6.4 ± 3.5 days) (Table 4). Time taken for defervescence with gentamicin + cephalixin was significantly less compared to amoxycillin and trimethoprim - sulfamethoxazole + furazolidine ($p < 0.05$), but there was no significant difference when compared with chloramphenicol and ciprofloxacin ($p > 0.05$). There were 3 deaths in this study.

Discussion

In the present study, maximum cases were seen in 6-9 years age group (51%). Widal test was positive in 40% cases. Arora et al [3] found high Widal test titres in only 13.5% cases. In contrast Sood and Taneja [4] found high titres in 62.1% and Panja et al [5] in 100% cases. Amongst 100 cases, 91 were diagnosed on the basis of blood/bone marrow

TABLE 4
Average duration of therapy prior to defervescence with different antibiotics

Drug	Duration (days)
Chloramphenicol	6.4 ± 3.5
Amoxycillin	7.5 ± 2.1
Trimethoprim - sulfamethoxazole + furazolidine	7.0 ± 2.2
Gentamicin + cephalixin	4.6 ± 2.0
Ciprofloxacin	6.1 ± 2.5

culture. Almost similar culture pattern has been reported by Mehta et al [6]. In our study 34% cases were sensitive to chloramphenicol and 100% to cefotaxime and fluoroquinolones. Sensitivity varied from 23.8% to 84.9% for other drugs. Incidence of MDRST was found 60% whereas other workers reported the incidence varying from 10-84% [2,3,7,8]. Resistance to the commonly used drugs reported in other studies is 48.5% to 98.0% for trimethoprim-sulfamethoxazole, 49.1% to 84.5% for ampicillin and 2.17% to 48.8% for furazolidine [3,7,9,10]. These findings are almost similar to our study.

With the emergence of MDRST strains, treatment of typhoid fever in children has become increasingly difficult. Chloramphenicol cured 72.7% of our cases. Anand et al found a clinical response in only 31% [9] which was much lower than the response of 88.3% to 100% reported by other authors [11-13]. Response to trimethoprim-sulfamethoxazole + furazolidine was seen in

38.5% and to amoxycillin in only 12.5% cases. A poor response to amoxycillin even in sensitive cases was reported by Nalini et al [14]. A very high in vitro sensitivity has been reported to gentamicin [3,7,9]. However aminoglycosides have limited efficacy against *Salmonella typhi* in vivo because they reside within phagolysosomes which have extremely low pH [8]. A combination of gentamicin with cephalexin resulted in an efficacy of 50.0% in our study. Anand et al [9] found 60% efficacy when they used gentamicin alone. Sporadic reports of use of aminoglycosides in combination with other drugs are available in literature [8]. Seven patients were initially started on ciprofloxacin on the basis of in vitro sensitivity and all showed response. Thirty three patients who failed to respond to initial treatment protocol were administered ciprofloxacin with 100% response. No adverse effect of ciprofloxacin was observed by Arora et al [3] in 54 cases during one year follow up.

Duration of therapy prior to defervescence was longest (7.5 ± 2.1 days) with amoxycillin and shortest (4.6 ± 2.0 days) with gentamicin and cephalexin. Hill et al [13] reported that with chloramphenicol, there was a conspicuous general improvement both subjective and objective within 48 hours and defervescence usually took place within 4 days. Mean duration of response varies between 4-6 days with trimethoprim-sulfamethoxazole and 6.8 - 8 days with amoxycillin [12,15,16]. Arora et al [3] found no clinical response to gentamicin despite 100% in vitro sensitivity. Response to ciprofloxacin may be seen as early as 3.6 - 4.6 days [17-19]. However Nachhatar Singh et al [20] found that norfloxacin and ciprofloxacin took as long as two weeks for response.

It is concluded that ciprofloxacin was the most effective in treatment of typhoid with 100% response and amoxycillin was least effective with only 12.5% cure rate.

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