# Therapeutic Re-appraisal of Multiple Drug Resistant Salmonella Typhi (MDRST) in Pakistani Children

T. Hazir,S. A. Qazi,K. A. Abbas,M. A. Khan ( The Children Hospital, Pakistan Insititute of Medical Sciences, Islamabad. )

## Abstract

**Background:**The emergence of multi drug-resistant Salmonella typhi (MDRST) in many developing countries including Pakistan, has led to a search for suitable alternatives to conventional therapy. Quinolones have been found to be an effective alternative for the treatment of MDRST, in adults as well as in children.
**Methods:**The efficacy of various therapeutic regimens currently used for the treatment of Typhoid was analysed.. Children 1 month to 12 years of age admitted to the Children's Hospital from 1990 to 1993 with fever and Salmonella typhi isolated from blood cultures were included in this retrospective analysis.
**Results:**The cumulative prevalence of Multiple Drug Resistant Salmonella typhi (MDRST) was 67.2%. Only 32.8% of isolated Salmonella typhi were susceptible to chloramphenicol and amoxicillin. The cumulative cure rate with conventional therapy (chloramphenicol or amoxicillin) was 47.4% and 53.6% children needed a change of therapy. The average hospital stay for the non-responders to conventional therapy was 9.2 days as compared to 7.7 days for the responders. The average hospital stay of the patients treated with a third generation cephalosporin was 12.7 days. Patients treated with ofloxacin, a flouroquinolone drug, did not need a change of therapy. The average hospital stay of the patients treated with flouroquinolones was 6.2 days.
**Conclusion:**There was a high prevalence of multiple drug resistant typhoid fever in hospitalized children, leading to a high failure rate with conventional therapy. This resulted in frequent change of therapy, delayed defervesence and prolonged hospital stay. The flouroquinolones were found to be the most effective drug against MDRST (JPMA 52: 123, 2002).

## Introduction

Typhoid fever has been treated with chioramphenicol or amoxicillin for many years. The emergence of multi drug - resistant Salmonella typhi (MDRST) in many countries like India[1], Korea[2], Mexico[3], Central Africa[4] and Pakistan[5], has successfully led to a search for suitable alternatives to conventional therapy. Clinical experience with third generation cephalosporin drugs has shown a cure rate of 82-97% in MDRST disease[6]. The quinolone group of drugs has been found effective in the treatment of adults with MDRST with cure rates of 100%[6-8]. There are a number of published reports where this group of drugs has been used in children for the cure of MDRST without any evidence of significant arthropathy[9-16].
Since 1990 the prevalance of MDRST at the Children's Hospital, Islamabad, has been on

the rise. We have analysed the therapeutic outcome of various drugs used for the treatment of typhoid fever from 1990 to 1993 at the Children's Hospital, Islamabad.

## Patients and Methods

The Children's Hospital Islamabad is a 200-bed tertiary care hospital. Besides sick children from Islamabad Capital Territory (ICT) and the twin city of Rawalpindi, it receives complicated cases from a large geographic area of northern Pakistan. All children 1 month to 12 years of age admitted to the Children's Hospital from 1990 to 1993 with fever and Salmonella typhi isolated from blood cultures were included in this retrospective analysis.

### Case identification

Two milliliters of blood was inoculated into 20 ml of Brain Heart infusion broth and incubated at 37°C. Subcultures were carried out at 48 and 72 hours on blood agar and MacConkey (Difco-Detroit, Michigan, USA). Colonies were identified biochemically by IMVICK or API 20E systems. Confirmation of Salmonella typhi was done serologically by using antisera (WeUcome Diagnostics -Dartford, UK). In vitro susceptibility was done by disc diffusion using Kirby Bauer method.

### Therapy

All the patients were started on one of the four antibiotics at the time of admission. Children started on the conventional therapy of chloramphenicol or amoxicillin were designated as group I (Table 1). Both the drugs were used at the dosage of 100 mg/kg given intravenously in four divided doses. Children who were given on ofloxacin and a third generation cephalosporin at the time of admission were designated as group II and 111 respectively (Table 1). Cefotaxime and ceftriaxone were given intravenously at a dosage of 100 mg/kg and 80 mg/kg in 8 hourly and 12 hourly divided doses respectively. Ofloxacin was administered in twice daily oral dosages of 10 mg/kg/day. Children who failed to respond to the conventional therapy of chloramphenicol/amoxicillin and were changed to ofloxacin or a third generation cephalosporin were included in group II and III respectively while analyzing cumulative cure rates (Table 2).

In majority of patients the criteria for starting a third generation cephalosporin or ofloxacin at the time of admission were: failure to respond to conventional therapy of chloramphcnicol or amoxicillin on an outpatient basis; a positive culture report showing growth of MDRST or poor clinical condition and/or presence of serious complications at the time of admission.

Infection was considered cured if the clinical signs and symptoms resolved and the patient was afebrile for a period of 48 hours. Failure was defined as lack of defervercence after 7 days of institution of a particular drug in adequate therapeutic dosage and when no other cause of fever could be identified. Defervescence time was defined as the number of days starting from initiation of therapy the patient took to become afebrile for a period of 24 hours. Hospital stay was defined as the number of days the patient remained admitted in the ward, starting from the day of admission and excluding the discharge day. Average cost of therapeutic course was calculated in Pakistani rupees (US$) for a child weighing 15 kilograms given the recommended therapeutic dosage for a period of 10 days for ofloxacin and 14 days for third generation cephalosporin and chloramphenicol. The cost was estimated using Islamabad market prices for chloramphenicol ceftriaxone

and ofloxacin. Average hospital cost was obtained from Children's Hospital accounts department, which is the amount spent by the hospital for each child per day .adniitted in a general ward with routine care. This includes nursing care, food, laboratory investigations, physicians time and other administrative costs. The organism was deemed as multiple resistant if it showed in vitro resistance to chioramphenicol, amoxicillin and cotrimoxazole.

Socio-economic status was considered to be low if the monthly income of the family was less than 2000 Pakistani rupees (52.6 U S$). A monthly income of rupees 15000 (394.7 US$) or more was classified as high socioeconomic status.

The data was entered into EPI INFO-5 programme. Univariate analysis was carried out for various clinical parameters. Bivariate analysis was conducted between therapeutic groups, antimicrobial susceptibility of Salmonella typhi and other clinical and therapeutic indicators. The Barlett's test for homogeniety of variance shows the variances in the sample proportion to differ, so non parametric test of Kruskal-Wallis (equivalent to chi-square) was used for comparison between groups.

## Results

One hundred and nineteen children admitted between 1990 and 1993 were included in this retrospective analysis. All had blood culture positive for Salmonella typhi and all were febrile at the time of admission. The cumulative incidence of MDRST over a four year period was 67.2%. The incidence of MDRST rose from 53% in 1991 to 70% in 1993.

Using the definitions specified, the therapeutic response to various antibiotics used for the treatment of these patients was analysed. For analysis purposes these patients were divided into three groups depending upon the initial antibiotic used. There were no significant differences regarding age, sex and socioeconomic background of all groups (Table 1).

**Table 1. Comparison of demographic characteristics of typhoid (n=119).**

| Characteristics | Therapeutic Regimens | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Conventional Therapy n=97 | | Ofloxacin n=15 | | Third Generation Cephalosporin n=7 | | Total | |
| | No. | % | No. | % | No. | % | No. | % |
| Sex | | | | | | | | |
| Male | 61 | 62.9 | 11 | 73.3 | 7 | 100.0 | 79 | 66.4 |
| Female | 36 | 37.1 | 4 | 26.7 | - | - | 40 | 33.6 |
| Age in years | | | | | | | | |
| 0-2 | 10 | 10.3 | 2 | 13.3 | - | - | 12 | 10.1 |
| >2-5 | 32 | 33.0 | 4 | 26.7 | 3 | 42.9 | 39 | 32.8 |
| >5-12 | 55 | 56.7 | 9 | 60.0 | 4 | 57.1 | 68 | 57.1 |
| Socioeconomic Status | | | | | | | | |
| Lower | 40 | 41.2 | 7 | 46.6 | 4 | 57.1 | 51 | 42.9 |
| Middle | 51 | 52.6 | 6 | 40.0 | 3 | 42.8 | 60 | 50.4 |
| Upper | 6 | 6.2 | 2 | 13.3 | - | - | 8 | 6.7 |

Thirty nine non-responders to conventional therapy were started on ofloxacin and 12 on an injectable third generation cephalosporin. All 39 who were changed to ofloxacin responded (Table 1). Whereas 9 of 12 (75.0%) of the latter group showed satisfactory results. The three who Ninety seven patients were started on conventional therapy (chloramphenicol= 85 and amoxicillinl2) at the change of therapy was required in 51 (52.6%) patients (Table 1). Mean defervescence time for responders in this group was 7.2 days. The mean hospital stay for this sub- group of primary responders to conventional therapy was were started on7.7 days (Table 2).
failed to respond to a third generation cephalosporin were then given ofloxacin and were cured (Table 1). The average hospital stay of non-responders to conventional therapy, who were started on a third generation cephalosporin was 9.2 days (Table 2).

**Conventional therapy group**

This consisted of 15 patients who were started on ofloxacin at the time of admission (Table 1) and 39 non-responders in group I who were switched over to ofloxacin. All 54 patients (100%) responded with average defervescence time of 2.9 days. The mean hospital stay of these patients was 6.2 days (Table 2).

**Table 2. Cure rates, defervescence time, hospital stay and costs of three therapeutic regimens.**

| Therapeutic regimens | Cure rates % | Mean defervescence time (days) | Mean hospital stay (days) | Average cost of medicines pak. rupees (US$) SD | Approximate cost of hospital stay pak. rupees (US$) SD |
|---|---|---|---|---|---|
| Conventional therapy Responders (n=46) (Non-responders excluded from analysis.) | 47.4 | 7.2±10.0 | 7.7±3.2 | 995.8±580 (US $26) | 3.737.0±1432 (US $ 98.3) |
| Ofloxacin Total (n=54) | 100.0 | 2.9±1.5 | 6.2±3.0 | 236.0±99 (US$ 6.2) | 3,060.0±1363 (US$ 80.5) |
| Third generation cephalosporin Total (n=18)* | 72.2 | 6.8±1.5 | 12.7±6.4 | 8817.3±5831 (US $ 232) | 5040.0±2871 (US $ 132.6) |
| P-value** | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |

* One patient died and was excluded from analysis.
** Kruskal-Wallis H one way analysis of variance

**Third generation cephalosporin group**

This included seven patients who were started on an injectable third generation cephalosporin at the time of admission (Table I) and 12 patients in group I who were switched over to this group after failure to respond to the conventiOnal therapy. One patient expired within 48 hours of admission. Five patients (26.3%) needed a change of therapy; thirteen (68.42%) were cured. The overall failure rate with third generation cephalosporins was 3 1.58%. The mean defervescence time of the primary responders was 6.8 days with average hospital stay of 11.8 days (Table 2).

**Cost of therapy**

The average cost for 14 days of treatment for primary responders with conditional therapy was 995.8 Pak. rupees(US$ 26). A 10 day course with ofloxacin was on an average 236.0 Pak. rupees (U.S $6.2) and for the injeclable third generation cephalosporin it was 88173 Pak. rupees (USS 232) (Table 2). The approximate average cost of a hospital stay is also given in Table 2 for all groups of patients.

## Discussion

Chioramphenicol was first used in the treatment of typhoid fever in 194817. Response to treatment of typhoid fever with chloramphcnicol was so consistent that despite reports of clinical efficacy of many other drugs, none was seriously considered as an alternative. However with the emergence of MDRST, chloramphenicol is becoming less effective for the treatment of typhoid fever. Our data show a very high in vitro resistance with chioramphenicol and amoxicillin in hospitalized patients. More than half the patients in our series who were started on conventional therapy. required a change of drugs due to treatment failure. This resulted in prolonged hospital stay and delay in defervesence leading to prolonged morbidity and increase in the treatment costs.

Third generation cephalosporins have proved effective in the treatment of MDRST in adults as well as children. Treatment failure with third generation cephalosporin was considerably less, but these patients required longer hospitalization due to parentral mode of administration of medication. Moreover, the cost of 10 days treatment with third generation cephalosporins is phenomenal and far exceeds the monthly income of an average Pakistani family. If the cost of hospitalization is also included in the cost of therapy, the total amount becomes exorbitant by local standards, thereby making third generation cephalosporins a non-viable option for the treatment of typhoid fever in a country like Pakistan. The experience with oral third generation cephalosporin, cefixime, at the moment is limited but seems to have a definite advantage over parentral preparations. When compared to ofloxacin it is still five times more expensive (Pak. rupees 6.0/Kg vs Rs.l.35IKg), has a higher failure rate (4-8%) and a longer defervescence time (5-8 days) according to the studies available so far[18].

Ofloxacin, with its 100% cure rate, lower expense..— and shorter duration of hospital stay appeared to be the most promising antibiotic for the treatment of MDRST. There are no substantial reports proving the cartilage toxicity of floroquinolones in children. Nalidixic acid having the most arthropathogenic potential out of all quiuolones has been used extensively in children since its approval by the U.S Food and Drug Administration (FDA) in the early 1960's. Its widespread use has not confirmed this complication[20]. The adverse drug reactions reported due to flouroquinolones in children are no more frequent than in adults. Their safety is comparable to other drugs being commonly used in children[20-24]. The most comprehensive monitoring for probable arthropathogenicity in children treated with floroquinolones for a period of 3 months carried out by Schaad and colleagues[25] revealed no abnormalities suggestive of arthropathy at 6 month follow-up. In view of all the trials carried out so far, the clinical efficacy of flouroquinolones outweighs its adverse effects in the paediatric age group. In countries where MDRST poses a serious threat to the health of the community, its use seems to be justified.

However, keeping in view the rapid development of resistance with flouroquinolones, great caution must be exercised in prescribing this drug indiscriminately. Its use in typhoid fever should currently be restricted to the cases with either confirmed MDRST or those having serious complications at the time of admission. Our data has several limitations. It is a retrospective audit of admitted typhoid culture positive patients. No single protocol was being followed by the physicians treating these patients. There was an uneven distribution of patients who were treated with flouroquinolones and third generation cephalosporin drugs, thus making the comparison between the efficacy of the

above two drugs difficult. The main purpose of this study, however ,is not to draw comparisons between various groups but to highlight the fact that there is a need to find a suitable alternative to chloramphenicol therapy for children suffering from Typhoid fever in developing countries .where the incidence of MDRST is very high. Another limitation of our data is relatively small number of patients.

A large number of patients were treated on out-patient basis and many others who were treated as inpatients did not have a positive blood culture because of prior use of antibiotics.

In a developing country like Pakistan where drug resistance would always be a major problem due to indiscriminate use of antibiotics, role of prevention assumes even greater significance. In the absence of a drastic improvement in living and sanitation condition in the near future, the role of at least strict handwashing before eating and after using the toilet is extremely important. The value of vaccination against typhoid fever also cannot be over emphasized. With the availability of oral vaccine having an efficacy of 67-96%[26,27], a more concerted effort should be made to prevent the disease from occurring in the first place by immunizing children.

Our data shows a very high failure rate with chloramphenicol. Since this is a hospital-based inpatient study, community based studies are needed to determine the true incidence of MDRST in various regions to reconsider the role of chioramphenicol as a first line drug in the treatment of typhoid fever in Pakistan.

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