

MULTI-DRUG RESISTANT ENTERIC FEVER IN CHILDREN

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ABSTRACT:

Objective: To see the sensitivity pattern of Salmonella and response of the patients to antimicrobial therapy.

Design: A prospective random study.

Place and duration of study: Study was carried out in pediatric A unit at PGMI/Lady Reading Hospital, Peshawar from March, 1993 to February, 1994.

Materials and methods: All clinically suspected cases of enteric fever were investigated but inclusion criterion was positive blood and/or bone marrow cultures. After history, examination and investigations, patients were randomly started on amoxycillin or chloramphenicol (first line antibiotics). Those who did not respond to either within 7 days, were switched over to either ofloxacin (in children above 5 years of age) or one of the third generation cephalosporins (second line antimicrobials) according to culture results. The antimicrobial to which the patient responded was continued for 2 weeks. Patient were followed up for one month for detection of adverse drug reaction (if any).

Results: Eighty six patients were investigated but only 50 had positive culture and these were included in study analysis. The organism isolated were S.typhi in 49 cases (98%) and S. paratyphi A in one case (2%). The single S.paratyphi A isolate was sensitive to all the antimicrobials tested. Out of 49 isolates of S. typhi, only 5 (10.2 %) were sensitive to all antityphoid chemotherapeutic agents, while 44 (89.8%) showed resistance against multiple drugs. Clinically, 22 (44%) patients showed satisfactory response to primary antibiotics, while remaining 28 (56 %) patients had to be switched over to either quinolones (above 5 years of age) or third generation cephalosporins. Response to these agents was good with defervescence within 7 days.

Conclusion: Third generation cephalosporins appear as treatment of choice for multidrug resistant typhoid fever in children, although their cost and parenteral administration are drawbacks. Quinolones are the most effective drugs against typhoid fever but there is risk of epiphyseal damage in children. In this study this side effect was not noted, although sample size was a small one. Their use can still be recommended in multidrug resistant enteric fever in children above 5 years.

Key Words: *Multidrug resistant Enteric fever, Third generation cephalosporins, quinolones.*

INTRODUCTION:

Enteric fever is a common illness of children and young adults. Frequently these people are the main wage earners in the family. This magnifies the socio-economic impact of the disease on the community

(1). The industrialized and more prosperous countries have, to a great extent, controlled this illness by improving standards of public health; but the disease continues to be a major public health problem in less developed countries including Pakistan (2). The emergence of drug resistant strains of Salmonella has made the treatment of enteric fever more difficult. After sporadic initial cases, a major outbreak of chloramphenicol-resistant typhoid occurred in Mexico in 1972 with many fatalities. Since then chloramphenicol-resistant strains have been reported from many other parts of the world including India, Pakistan, Vietnam and United Kingdom. The last 2 decades have also witnessed the appearance and spread of multidrug-resistant (MDR) strains of *S. typhi*. Infection with these strains is associated with longer duration of illness and higher morbidity and mortality, (2,3,4) it is occurring at higher incidence throughout South Asia than previously thought particularly in younger children (5,6,7)The present study was carried out to see the sensitivity patterns of Salmonella causing enteric fever and the response of the patients to antimicrobial therapy.

MATERIALS AND METHODS:

This study was carried out in Pediatric A unit at Postgraduate Medical Institute, Lady Reading Hospital, Peshawar from March, 1993 to February, 1994. It was a prospective and random study. All clinically suspected cases were investigated but inclusion criterion was positive blood and/or bone marrow cultures. On admission, complete history and thorough physical examination were recorded. For blood culture, 5-10 ml of blood was taken from a peripheral vein and for bone marrow culture, 0.5-1 ml of bone marrow from iliac crest. The samples were inoculated in heart-brain infusion broth at 37 C for 7 days. Culture bottles were examined daily for turbidity and subcultured on blood and Mac-Conkey agars. Antimicrobial sensitivity was tested by Kirby-Bauer disk diffusion method. The results were interpreted as fully sensitive (4+), partially sensitive (2+) and resistant (R) according to the interpretative standards. Sensitivity was tested for chloramphenicol, amoxycillin, ampicillin, cotrimoxazole, cefotaxime, ceftriaxone, cefoperazone, ceftazidime, ciprofloxacin and ofloxacin.

Other investigations performed included complete blood count, urine examination, widal test, chest radiogram, slide for MP and liver function test. Montoux test, brucella test, HBs Ag, G-6-PD assay, CSF analysis, and C.T. scan were also performed wherever indicated. On admission, patients were started on either amoxycillin or chloramphenicol randomly. These drugs were continued or changed to a second antimicrobial agent according to the response of the patient and results of the cultures. Those patients, who were on amoxycillin and had not responded to it, were switched over to chloramphenicol, while those, who were on chloramphenicol initially with no response, were given either ofloxacin (in children above 5 year of age) or one of the third generation cephalosporins. The age divisible was arbitrary. The drugs to which the patient responded, was continued for 2 weeks. Patients were discharged from the ward

after defervescence and were called back for follow up and for detection of adverse of adverse drug reaction (if any) after completion of therapy. Repeat and follow up cultures were not performed.

RESULTS:

Eighty six patients were admitted as suspected cases of enteric fever during the study period, but only 50 of these had positive blood and /or bone marrow cultures and they were included in the study analysis. All of the patients were from Peshawar and nearby districts with no clustering of cases in any particular area. The organisms isolated were *Salmonella typhi* in 49 cases (98 %) and *S. paratyphi A* in one case (2 %). The single isolate of *S. paratyphoid A* was sensitive to all of the antimicrobials tested except cotrimoxazole. Out of 49 isolates of *S. typhi*, 5 (10.2 %) were susceptible to all the primary antibiotics used against typhoid, while 44 (89.8 %) showed resistance against multiple drugs. All of these were resistant to chloramphenicol, ampicillin and cotrimoxazole and some were also resistant to some of the third generation cephalosporins. All of these isolates were fully sensitive to ciprofloxacin and ofloxacin, while sensitivity to individual drugs of third generation cephalosporins varied between 57 % and 79 % (table I). Initial treatment was amoxycillin in 11 patients and chloramphenicol in 39 patients on the discretion of the attending physician. In 22 (44%), the response to the above drugs was satisfactory, even though the culture reports showed 16 of these infections to be due to multidrug-resistant *Salmonella typhi*. These patients were afebrile within 7-9 days. In the remaining 28 patients (56%), there was no or minimal response to the initial therapy and the culture reports showed the causative organisms to be resistant to these drugs. Therefore these patients, according to the culture reports, were switched over to ofloxacin (12 patients), ceftriaxone (9 patients), cefoperazone (3 patients), cefotaxime (2 patients) and ceftazidime (2 patients). Third generation cephalosporins were preferred in children below 5 years of age, while ofloxacin was given to children above 5 years of age. The response to these drugs was good and the patients became afebrile within 7-8 days after start of therapy. Time of defervescence is shown in Table II. There was no death due to typhoid fever during the study period. Complications included encephalopathy, neurological signs, hepatitis, G.I. bleeding and hemolysis due to G-6-PD deficiency. All of these responded well to conservative treatment.

Table I. In vitro sensitivity pattern of *S. typhi* (n = 49).

No.	Drug.	Sensitive (4 +) No. (%)	Partially sensitive (2+) No. (%)	Resistant No. (%)
1	Chloramphenicol.	5(10.2 %)	1(2.04 %)	43(87.76 %)
2	Ampicillin.	5 (10.2 %)	2 (4.08 %)	42 (85.72 %)
3	Amoxycillin.	5 (10.2 %)	1 (2.04 %)	43 (87.76 %)

4	Cotrimoxazole.	5 (10.2 %)	0 (0 %)	44 (89.80 %)
5	Ceftriaxone.	39 (79.59 %)	5 (10.2 %)	5 (10.2 %)
6	Cefotaxime.	36 (73.47 %)	9 (18.37 %)	4 (8.16 %)
7	Cefoperazone	28 (57.14 %)	12 (24.49 %)	9 (18.37 %)
8	Ceftazidime.	34 (69.39 %)	9 (18.37 %)	6 (12 .24%)
9	Ciprofloxacin.	49 (100 %)	0 (0 %)	0 (0 %)
10	Ofloxacin.	49 (100 %)	0 (0 %)	0 (0 %)

Table II. Time of defervescence.

No.	Drug.	Mean (days)	Range (days)
1	Amoxicillin.	6	7-May
2	Chloramphenicol.	5	9-Feb
3	Ceftriaxone.	3.88	7-Feb
4	Cefotaxime.	6.5	8-May
5	Cefoperazone.	6.66	8-Apr
6	Ceftazidime.	4.5	5-Mar
7	Ofloxacin.	3.66	7-Feb

DISCUSSION:

Enteric fever is still endemic in developing world including Pakistan, with epidemics each year in summer and rainy seasons, but the seasonal variation is gradually vanishing. Most of the cases are treated on an ambulatory basis but still it accounts for 5-8 % of total pediatric admissions (2,8). Since the first epidemic of drug-resistant typhoid fever in Mexico in 1972, the incidence of drug resistance in *S. typhi* is increasing all over the world (2,3). In our study, 89.8% of the isolates showed in vitro resistance to multiple drugs (two or more). This figure was 66.6% in another study in Afghan children reported from Peshawar (9), and 10-29% during 1986-1989 in Karachi (2). In India, the reported incidence is 50-84% in various areas and it is rising (10,11). These have also been reported from various other parts of the world (12, 13). However in the past few years, the MDR typhoid epidemic appears to be receding, with rates averaging 20-30% (14). All of our isolates were fully sensitive to ofloxacin and ciprofloxacin, while sensitivity to individual drugs of third generation cephalosporins varied between 57% and 79%. Numerous factors are responsible for emergence and spread of multidrugresistant strains. One factor in nontyphoidal *Salmonella* is administration of low doses of antibiotics to farm animals for growth promotion (15). The unrestricted over-the counter usage of antimicrobial agents in most of the developing countries (including Pakistan) has also contributed significantly to this problem. Another factor is transfer

of resistance from one bacteria to the other by R plasmids (4,16). Resistance is dispersed in cells by dissemination of transposons, in strains by the transfer of R plasmids and in human and animal hosts by the spread of resistant strains. Whatever the method of acquisition, resistance in Salmonellae can affect the treatment and ultimately the health of both individuals and communities. The problem with these resistant strains is not only drug resistance but also that their virulence is also increased leading to increased morbidity & mortality (16).

In spite of in vitro resistance to amoxycillin and chloramphenicol, 22 (44%) of our patients responded well to these drugs. This is not unusual and has been reported by other workers as well (9). Vice versa, i.e. clinical failure of chloramphenicol in sensitive strains has also been reported (17). There are also reports of in vivo acquisition of resistance to chloramphenicol and cotrimoxazole during treatment (18). In 56% of our patients, response to the above initial drugs was poor and all these isolates were multidrug-resistant. These patients were given either ofloxacin (above 5 years of age) or one of the third generation cephalosporins. This age division was arbitrary. The response to these drugs was good; however time of defervescence was shorter for ofloxacin and ceftriaxone (3.66 and 3.88 days respectively) than cefotaxime, cefoperazone and ceftazidime (6.5, 6.66 and 4.5 days respectively). In a previous clinical study of 100 patients with enteric fever in 1987 in this same unit, all the patients responded well to amoxycillin or chloramphenicol and in those days treatment of enteric fever used not to be as problematic as it now is (8).

Third generation cephalosporins appear as reasonable choice for the treatment of multidrug resistant typhoid fever in children. The overall cure rates with these agents are over 90% with a lower overall relapse rate (3, 19). High biliary concentrations of these antibiotics (particularly of cefoperazone) enhance the killing of organisms persisting in biliary passage and thus reduce the rates of relapse and chronic carriage (3). In our experience, ceftriaxone was the most effective cephalosporin against multidrug resistant typhoid fever. It is now probably the drug of first choice against MDR typhoid fever in children. Its other advantages are that it can be given once daily and shorter courses (3-7 days) may also be effective. However, cost of therapy with third generation cephalosporins is considerably more than chloramphenicol. Another disadvantage is that these agents are to be given parenterally (20).

Quinolones are probably the most effective drugs against typhoid fever, but there is a risk of epiphyseal damage in children. Some workers advocate their use even in children, arguing that the benefits in reducing the morbidity and mortality far outweigh the theoretical risk of cartilage damage reported in younger animals. Over 30 years of uneventful experience with nalidixic acid (a quinolone) in pediatric practice raises the possibility of inter-species difference in arthropathic potential of quinolones (21, 22, 23). Their advantages are that these are cheaper and can be given orally (24). Mandal (22) has used ciprofloxacin in a child of 7 years apparently without any side effects. It has also been used in United

Kingdom in cases of cystic fibrosis (25). Hassan (26) has used ofloxacin in 55 children of various ages with resistant typhoid fever and after 3 years of follow-up could not detect any adverse effects related to joint cartilage. We have used ofloxacin in 3 children of 5-10 years age (other 9 patients were above 10 years of age), and could not notice any significant untoward effects. However, this sample is small. Furthermore long term sequelae are not known. Therefore further studies are needed before these drugs can be safely recommended for use in children. With our small experience, we still recommend their use in multidrug-resistant enteric fever in children above 5 years of age, not responding to conventional drugs.

We have noted recently the increasing use of third generation cephalosporins and quinolones routinely in day-to-day infections. These drugs are given in lower doses and for inadequate duration. This indiscriminate & injudicious use is dangerous and will ultimately result in emergence of resistance. In fact, some of our isolates were already resistant to third generation cephalosporins, although the clinical response was satisfactory, there is a need for efforts to define a more restrictive antibiotic policy in human and veterinary use and to obtain all the necessary data to follow and control the epidemiology of these strains (12).

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