Reemergence of Chloramphenicol Sensitivity in Enteric Fever

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Abstract

Background: Enteric fever is a global health problem and rapidly developing resistance to various drugs makes the situation more alarming. Drug sensitivity in *Salmonella enterica serovar typhi* and *Salmonella enterica serovar paratyphi A* isolated from 45 blood culture positive cases of enteric fever was tested to determine in-vitro susceptibility pattern of prevalent strains in northern India. **Methods:** Strains isolated from 45 blood culture positive cases of typhoid and paratyphoid fever over a period of three years were studied and their sensitivity patterns to chloramphenicol, ampicillin, ciprofloxacin, ceftriaxone, nalidixic acid, amikacin and ofloxacin were analysed.

Results: Our results show a high sensitivity of both *Salmonella enterica serovar typhi* (96%) and *Salmonella enterica serovar paratyphi A* (100%) to chloramphenicol. Sensitivity to ciprofloxacin and amikacin was 88% and 84% respectively. All the isolates were sensitive to ofloxacin, nalidixic acid and ceftriaxone. Sensitivity of *Salmonella enterica serovar paratyphi A* was 100% to chloramphenicol, ciprofloxacin, ofloxacin, nalidixic acid and ceftriaxone, 95% to amikacin and 30% to ampicillin. Overall 44 out of 45 isolates of *Salmonellae* were sensitive to chloramphenicol.

Conclusion: These findings suggest changing pattern of antibiotic resistance in enteric fever with reemergence of chloramphenicol sensitivity in northern India.

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Key Words : Enteric fever; Chloramphenicol; *Salmonella enterica serovar typhi*; *Salmonella enterica serovar paratyphi A*

Introduction

Enteric (Typhoid) fever is a growing concern worldwide. World Health Organisation (WHO) estimates that there are about 22 million cases of typhoid fever worldwide every year [1]. Antimicrobial therapy markedly reduces the case fatality rate of typhoid fever. Chloramphenicol had been the “gold standard” of therapy since its introduction in 1948. However, *Salmonella enterica serovar typhi* and *paratyphi A* acquired resistance to chloramphenicol and other antimicrobial agents including the fluoroquinolones causing a major setback in the management of typhoid [2]. In this scenario, reports of reemergence of sensitivity of *Salmonella enterica serovar typhi* to chloramphenicol [3], calls for a reappraisal of antibiotic sensitivity pattern of strains prevalent in India. The aim of this study was to analyse drug sensitivity pattern of blood culture positive cases of enteric fever.

Material and Methods

This study was carried out in a service hospital located in northern India over a period of three years. *Salmonella enterica serovar typhi* & *paratyphi A* isolates from 45 blood culture positive cases of typhoid fever were tested to

determine their in vitro susceptibility to various antimicrobial agents. Culture positive typhoid was defined as a febrile episode, which yielded *Salmonella enterica serovar typhi* or *paratyphi A*, on blood culture. Antibiotic sensitivity was tested using Disc diffusion (Stokes) method on Mueller-Hinton Agar (Hi-Media, Bombay, India). Antibiotics discs used were- chloramphenicol-30mcg/disc, ampicillin-10mcg/disc, ciprofloxacin-5mcg/disc, ceftriaxone-30mcg/disc, nalidixic acid-30mcg/disc, amikacin-30mcg/disc, and ofloxacin-5mcg/disc. Commercially available, six mm discs (Hi Media) were used. Minimum inhibitory concentrations (MICs) were not measured.

Results

Out of 45 culture positive patients, *Salmonella enterica serovar typhi* was isolated from 25 patients and *Salmonella enterica serovar paratyphi A* from 20 patients. All patients were adult males in the age group of 16-43 years, with a mean age of 24.7 years. Maximum patients were in the 20-25 years age group.

Table 1 shows the antibiotic sensitivity pattern of various isolates. These results show a high sensitivity of *Salmonella enterica serovar typhi* to chloramphenicol (96%). Sensitivity to ciprofloxacin, amikacin and ampicillin was 88%, 84% and 48% respectively. All the isolates were sensitive to ofloxacin, nalidixic acid and ceftriaxone.

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Table 1

Antibiotic sensitivity of *Salmonella enterica* serovar typhi and *Salmonella enterica* serovar paratyphi A to various antibiotics

Antibiotic	<i>S. enterica</i> serovar typhi	Sensitivity (%)	<i>S. enterica</i> serovar paratyphi A	Sensitivity (%)
Chloramphenicol	24	96	20	100
Ampicillin	12	48	06	30
Amikacin	21	84	19	95
Ciprofloxacin	22	88	20	100
Ofloxacin	25	100	20	100
Nalidixic acid	25	100	20	100
Ceftriaxone	25	100	20	100

All the isolates of *Salmonella enterica* serovar paratyphi A were sensitive to chloramphenicol, ciprofloxacin, ofloxacin, nalidixic acid and ceftriaxone and 95% were sensitive to amikacin. Ampicillin resistance was high with only 30% of isolates showing sensitivity. In five patients of *Salmonella enterica* serovar typhi, though the in-vitro studies showed sensitivity to ciprofloxacin, there was no clinical response for up to a week despite the isolates being nalidixic acid sensitive. The isolates from these patients were also sensitive to chloramphenicol and the patients improved with this drug.

Discussion

Enteric fever continues to be a public health problem in India, being compounded by emerging resistance to antibiotics that were effective earlier. Wide variation in the sensitivity pattern of various strains circulating in different geographic regions in India makes it necessary to assess the sensitivity of typhoid bacilli to antibiotics before instituting therapy. This also calls for compilation of data from specific zones for epidemiological analysis.

Chloramphenicol was the first antibiotic used against typhoid and resistance to this drug developed in seventies and eighties and thereafter to other first line drugs viz. trimethoprim, sulfamethoxazole and ampicillin. In nineties, increasing resistance to ciprofloxacin, which was a good alternative for multidrug resistant (MDR) typhoid fever, emerged in both *Salmonella enterica* serovar typhi and *Salmonella enterica* serovar paratyphi A [4,5]. Resistance to ceftriaxone has also been reported [2].

In India there have been varying reports of resistance of *Salmonella enterica* serovar typhi and paratyphi to various antibiotics. These include - high degree of resistance to chloramphenicol (56.6%), ampicillin (40%), amikacin (50%), gentamicin (43.3%), ampicillin (40%), cotrimoxazole (33.3%), and cephalexin 30% with very low resistance to ceftriaxone and cefotaxime (6.6% each), and 100% sensitivity to ciprofloxacin, from Rajasthan [6], resistance to chloramphenicol and sensitivity to ciprofloxacin from Mumbai [7], 80% of isolates showing resistance to amoxicillin, chloramphenicol and cotrimoxazole along with 100%

sensitivity to ciprofloxacin and ceftriaxone from Ahmedabad [8], and high resistance to amoxicillin, chloramphenicol, ampicillin, co-trimoxazole and ciprofloxacin from Mangalore [9]. Amidst these, there have been reports of reemergence of sensitivity in *Salmonella enterica* serovar typhi to chloramphenicol and other first line drugs [4, 10-13], giving us a reason to analyse and report our data.

MIC is a better predictor of drug sensitivity than disc diffusion method and WHO recommends the use of Kirby-Bauer method. However, Stokes method is more economical. Mackie & McCartney compared all the available disc diffusion methods and finally concluded that the Stokes method is most suitable [14]. Recent studies have compared disc diffusion with MIC methods and have reported 90% correlation for *Salmonella enterica* serovar typhi [11], and only 1 in 200 (0.05%) discordance in enterobacteriaceae [15]. We determined antibiotic sensitivity by Stokes disc diffusion method.

Our study showed 96% sensitivity to chloramphenicol in *Salmonella enterica* serovar typhi and 100% sensitivity in paratyphi A. Only one case of *Salmonella enterica* serovar typhi out of 45 cases of enteric fever was resistant. These results compare favourably with those reported from other parts of India and point towards re-emergence of sensitivity to chloramphenicol in this region also. All the isolates were sensitive to ofloxacin, nalidixic acid and ceftriaxone. Ampicillin resistance was found to be high both in *Salmonella enterica* serovar typhi and *salmonella enterica* serovar paratyphi A.

In five patients of *Salmonella enterica* serovar typhi, though the in-vitro studies showed sensitivity to ciprofloxacin, there was no clinical response up to a week despite the isolates being nalidixic acid sensitive. This observation is in accordance with the findings of Chandel et al [16], who reported that treatment failures did not always correlate with higher MICs to nalidixic acid and ciprofloxacin alone. Their findings suggest that, despite prolonged doses of ciprofloxacin, treatment failures are common with isolates sensitive to ciprofloxacin and nalidixic acid.

Previous generation antibacterial drugs are increasingly being found useful for many diseases [13]. Likewise, chloramphenicol can be a useful and cost effective alternative in select cases. Constant surveillance and antibiotic sensitivity testing is required from different geographical areas in the country, to keep abreast with emerging patterns of drug sensitivity in enteric fever.

Conflicts of Interest

None identified

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CORP NEWS

SCIENTIFIC SESSIONS ON SELECTED PROFESSIONAL PAPERS

56TH ARMED FORCES MEDICAL CONFERENCE: 2008

1. It has been decided to organise two scientific sessions on selected professional papers during the above conference scheduled to be held at the Armed Forces Medical College, Pune in the month of **February 2008**. The details are as under:-
 - a) **Scientific Session on Selected Professional Papers**
 - (i) Medicine and allied subjects including Pathology, Preventive and Social Medicine, Hospital Administration and Nursing.
 - (ii) Surgery and allied subjects including Dental Surgery and Nursing.
2. The scientific sessions mentioned at para 1(a) will include presentation of papers by medical, dental and MNS officers on original work on various aspects of work done in clinical disciplines, development of new diagnostic/therapeutic techniques/equipments/aids etc. Each paper will be allotted 12 minutes including the time for discussion.
3. The criteria for selection of papers, for scientific sessions in general, will be in terms of originality, scientific content and methodology adopted. Rejection of paper should not be regarded as a reflection of its merit, since diversity and balance are also considered in the selection of papers for presentation.
4. Wide publicity may please be given on this subject matter and medical, dental and MNS officers be encouraged to prepare papers of high quality which are worthy of presentation in the above scientific sessions.
5. Papers for presentation should be submitted in an article format as per the guidelines to authors printed in Jan 2007 issue of *Medical Journal Armed Forces India*. The first page of paper must bear a heading **Paper for Scientific Session** [indicating the session (Medicine/Surgery)]. Papers received in conformity with the correct format will only be taken up for consideration. **Seven copies** of each scientific paper are to be submitted through proper channel so as to reach this office latest by **31 Aug 2007**.