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Changing Spectrum of Antibiotic Sensitivity in Enteric Fever- A Six Year Retrospective Study in North India

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ABSTRACT

Enteric fever is a global health problem and rapidly developing resistance to various drugs makes the situation more alarming. Drug sensitivity in Salmonella typhi and Salmonella paratyphi A isolated from 136 blood culture positive cases of enteric fever was tested to determine in-vitro susceptibility pattern of prevalent strains in Northern India. To study the changing spectrum of antibiotic sensitivity in enteric fever. Strains isolated from 136 blood culture positive cases of typhoid and paratyphoid fever over a period of six years were studied and their sensitivity patterns to chloramphenicol, ampicillin, cotrimoxazole, ciprofloxacin, ceftriaxone, cefotaxime, cephalexin, nalidixic acid, amikacin, ofloxacin and azithromycin were analysed using SPSS version 15. A high sensitivity was observed to chloramphenicol for both Salmonella typhi (98.9%) and Salmonella paratyphi A (100%). All the isolateswere sensitive to amikacin and ceftriaxone. Sensitivity to ciprofloxacin, ofloxacin and cefotaxime was 97%, 99% and 99% respectively. Sensitivity of Salmonella paratyphi A was 100% tochloramphenicol, ciprofloxacin, ofloxacin, ceftriaxone and amikacin, 85% to cotrimoxazole, 68% to ampicillin and only 14% to nalidixic acid. In our practice, it was observed that there is a changing pattern of antibiotic resistance in enteric fever with re-emergence of chloramphenicol sensitivity in Punjab. The policy of empirical treatment of enteric fever needs to be rationalized; since increasing rates of antibiotic resistance may ultimately render inexpensive antibiotics obsolete and make it necessary to use expensive newer antibiotics.

Keywords: Antibiotic sensitivity; Chloramphenicol; Enteric fever; Salmonella typhi; Salmonella paratyphi A; Typhoid fever.

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INTRODUCTION

Enteric fever continues to be a global health problem with an estimated 12–33 million cases and 6,00,000 deaths occurring worldwide each year.[1] Antibiotic therapy with Chloramphenicol had been the "gold standard" in enteric fever for decades. However, *Salmonella* acquired resistance to chloramphenicol and other antimicrobial agents causing a major setback in the management.[2] There are reports of re-emergence of sensitivity of *Salmonella typhi* to chloramphenicol emphasising for a reappraisal of antibiotic sensitivity pattern of strains prevalent in India.[2] The aim of this study was to analyse drug sensitivity pattern of blood culture positive cases of enteric fever.

METHODS

A retrospective chart review of all children admitted with enteric fever was carried out atDepartment of Pediatrics,Christian Medical College and Hospital, Ludhiana. The records of all children (0-18 years of age) discharged from the hospital between January 2005 and December 2010 with a diagnosis of enteric fever, typhoid fever or paratyphoid fever were assessed for suitability for inclusion in our study. The inclusion criteria were the presence of signs compatible with enteric fever and isolation of *S. typhi* or *S. paratyphi* A, B, or C from blood or stool cultures or any other site; patients were diagnosed as having typhoid or paratyphoid fever, respectively (i.e., enteric fever). These records were retrieved from the Medical Records Section of the hospital after going through the departmental records using 'enteric fever, typhoid fever or paratyphoid fever' as discharge diagnosis in the search criteria. Only culture proven cases of enteric fever were included in the study. Others were considered as clinically diagnosed or serology (Widal) positive typhoid and were excluded from the study. They were used to calculate the culture positivity. Clinical, laboratory and treatment information was extracted from the medical records on a detailed proforma and analysed using SPSS software version 15. The hospital Ethics Committee had no objection on the retrospective data analysis of the study.

Blood samples collected in brain heart infusion broth/ Bactec bottle, under aseptic precautions from all febrile patients with a clinical diagnosis of enteric fever were sent to Microbiology Laboratory. After overnight incubation at 37°C, subcultures were made on blood agar and MacConkey agar plates at 1, 2 and 5 days to check for growth. Typical lactose non-fermenting colonies were identified as *Salmonella* by standard biochemical reactions.

Antimicrobial susceptibility testing of the isolates was carried out by the Kirby Bauer disc diffusion method according to National Committee for Clinical Laboratory Standards (NCCLS) guidelines. [3] The following antibiotics were used: ampicillin, chloramphenicol, co-trimoxazole, cephalexin, ceftriaxone, nalidixic acid, amikacin, cefotaxime, ciprofloxacin, ofloxacin and azithromycin. *Escherichia coli* ATCC strain 25 922 was used as the quality control strain. The zone of inhibition was measured and compared with critical zone diameter in published tables. Zone size more than 22 mm for cefotaxime, 20 for ceftriaxone and ciprofloxacin, 18 for nalidixic acid, 17 for chloramphenicol, ofloxacin and azithromycin, 16 for ampicillin and amikacin and 15

for cotrimoxazole is considered as sensitive. Isolates with 'intermediate' levels of resistance were included in the percentage of resistant organisms for final analysis. A strain was designated as MDR if it exhibited simultaneous resistance to ampicillin, chloramphenicol and co-trimoxazole.[1] Minimum inhibitory concentrations (MICs) were not measured.

RESULTS

A total of 136 isolates of *Salmonella* spp. were isolated from 408 blood cultures received from children with discharge diagnosis of enteric fever/ typhoid fever/ paratyphoid fever during the study period with a culture positivity of 33.3%. *S*. Typhi was the predominant serotype (107, 78·7%) followed by *S*. Paratyphi A (29, 21·3%).

There were 85 male and 51 female patients (M: F, 1·7:1) as shown in Table I. The highest number of culture- positive cases was in the 5–12 years age group (61, 44·8%). The number of cases <1 year was 7 (5·1%) with the youngest one being 3 months of age. Mean age was 6.14 years.

Table I: Age and Sex distribution

Age Group (Years)	Male	Female	Total
0-1	05	02	07
1-5	36	17	53
5-12	35	26	61
12-18	09	06	15
Total	85	51	136

Salmonella typhihas been the predominant serotype (> 75%) throughout the study period as is depicted in Table II.The sensitivity pattern of salmonella to various antibiotics is shown in Table III. All the Salmonella isolates were sensitive to ceftriaxone, amikacin and azithromycin. Also high sensitivity was observed to chloramphenicol (99.1%), ofloxacin (99%), cefotaxim (99%) and Ciprofloxacin (97.3%). Sensitivity of Salmonella isolates to Cephalexin and ampicillin was 94.2% and 79.1% respectively. Significant number of isolates was resistant to nalidixic Acid with sensitivity of 13.5% only.

Table II: Year wise distribution of cases

Year	Total Isolates	Salmonella typhi		Salmonella Paratyphi A	
		Number	Percentage	Number	Percentage
2005	21	16	76.2%	5	23.8%
2006	24	19	79.2%	5	20.8%
2007	28	21	75.0%	7	25.0%
2008	21	17	81.0%	4	19.0%
2009	18	14	77.8%	4	22.2%
2010	24	20	83.3%	4	16.7%

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Table III: Antibiotic sensitivity pattern of Salmonella Typhi and Salmonella Paratyphi A to various antibiotics

Drug	Sensitive	Resistant	Total	Percentage sensitive
Nalidixic Acid	05	32	37	13.5%
Ciprofloxacin	110	03	113	97.3%
Ofloxacin	97	01	98	99.0%
Amikacin	127	00	127	100%
Ceftriaxone	120	00	120	100%
Cephalexin	65	04	69	94.2%
Cefotaxim	97	01	98	99%
Ampicillin	91	24	115	79.1%
Chloramphenicol	113	01	114	99.1%
Cotrimoxazole	113	10	123	91.9%
Azithromycin	13	00	13	100%

Sensitivity pattern of Salmonella paratyphi has shown a progressive decline in sensitivity to ampicillin over the years. One of the nalidixic acid resistant (NAR) isolates of S typhi showed block resistance to ampicillin, chloramphenicol and cotrimoxazole (multi-drug resistant, MDR).

DISCUSSION

Enteric fever continues to be a major public health problem. The incidence is highest in South-Central Asia and South EastAsia (over 100/1,00,000 cases/year), with the highest burdenof disease in children aged 2-15 years. [4-6] It is one of the commonest major infectious diseases prevalent in India, with annual incidence as high as 760/100,000; 980/100,000 in Delhi. A limited study in an urban slum in India showed one per cent of the children upto17 years of age suffer from typhoid fever every year.[7]

The problem is compounded by emerging resistance to antibiotics that were effective earlier. There exists a wide variation in the sensitivity pattern of various strains of salmonella, necessitating the assessment of salmonella sensitivity to various antibiotics before instituting therapy.

In the current study, *S*. Typhi and *S*. Paratyphi A were responsible for a total of 78·7% and 21·3% cases of enteric fever respectively. The proportion of ***S***. Paratyphi A isolated from enteric fever cases remained almost constant throughout the study period similar to a study from North India.[8]

About one-fifth (26/136) of children were under 2 years of age. The highest incidence of enteric fever was seen in the 5–12 years age group (45%) followed by 1-5yrs (39%) and >12years (11%). After the age of 20, there is reduced incidence probably due to acquisition of immunity from clinical or subclinical infection with increasing age.[9]

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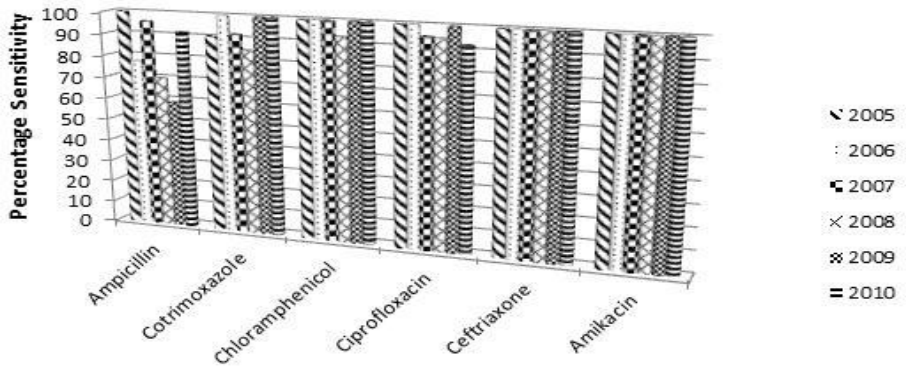
In this era of increasing air travel and global operations, there is also a rising trend of travel-associated typhoid in industrialized countries. It is much more frequently observed in travellers to the Indian subcontinent than to other regions.[10] In the US, the proportion of imported cases had increased from 62% to 81% over two decades (1977–1997).[11] An additional threat for the traveller is the increasing prevalence of nalidixic acid resistance in India and Vietnam. In a recent study, patients with multidrug resistant *Salmonella typhi* and with nalidixic acid resistant *S. typhi* infections were more likely to return from the Indian subcontinent.[11] This resistance can have therapeutic consequences.

Chloramphenicol has been the mainstay of treatment for enteric fever, while ampicillin/co-trimoxazole are other cost-effective primary drugs of choice. Drug resistance to chloramphenicol in *S. typhi* first emerged in the United Kingdom (UK) in the 1950s and subsequently in Greece and Israel followed by the epidemics of MDR *Salmonella* in Mexico, India and other regions.[12] There are two categories of drug resistance: resistance to antibiotics such as chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole (MDR strains) and resistance to the fluoroquinolone drugs.[13] Though the resistance to chloramphenicol increased steadily in India from 1960 onwards MDR salmonella showed a downwards trend. This indicates a re-emergence of chloramphenicol sensitivity in *S*almonella strains (Table II), as reported previously.[12]

The present study showed all salmonella isolates were sensitive to ceftriaxone, amikacin and azithromycin. However the azithromycin sensitivity does not represent the complete picture as the sensitivity testing was done only for a limited time period. Also high sensitivity (99%) was observed to chloramphenicol, ofloxacin and cefotaxim (Figure I).

Figure I: Year-wise antibiotic sensitivity pattern



Another feature of importance was the marked increase in NAR strains (86.5%) in both ***S***. Typhi and ***S***. Paratyphi A.Similar findings have been observed by various authors such as Joshi et al who in their study found NAR in 88% of salmonella isolates and Neopane Ashowing 75% NAR salmonella isolates.[14,15]

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The nalidixic-acid-resistant *S. typhi* (NARST) is a marker of reduced susceptibility to fluoroquinolones compared with nalidixic-acid-sensitive strains. Nalidixic acid itself is never used for the treatment of typhoid. These isolates are susceptible to fluoroquinolones in disc sensitivity testing according to current guidelines. However, the clinical response to treatment with fluoroquinolones of nalidixic-acid-resistant strains is significantly worse than with nalidixic-acid-sensitive strains.[13] As there is a trend for the development of Ciprofloxacin resistance, indiscriminate use of ciprofloxacin or ceftriaxone should be strongly discouraged and they should be used in an event of non-responsiveness to the three conventional agents.

CONCLUSIONS

Hence the sensitivity pattern of causative organism must be sought before instituting appropriate therapy to prevent further emergence of drug resistance. The changing trends in the antibiograms of *S.typhi* and *S.paratyphi A*; probably demands reconsideration for the use of chloramphenicol in typhoid fever, instead of ciprofloxacin or third and fourth generation cephalosporins to prevent the emergence of multidrug resistance. Chloramphenicol can be a useful and cost effective alternative in select cases.

Although improvements in sanitation and water systems are the ultimate solutions to the control of the disease, vaccination should be considered in the near-to-intermediate term. There is a need to review the current strategies for vaccination against enteric fever requiring administration in a manner that confers protection to young children, adolescents and travellers to endemic countries.

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