

WHAT AFTER CIPROFLOXACIN AND CEFTRIAXONE IN TREATMENT OF SALMONELLA TYPHI

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ABSTRACT:

Objective: To determine resistance pattern of *Salmonella typhi* in blood cultures.

Design: Laboratory-based observational study.

Material and Methods: Blood samples processed during the period of one and half year in the laboratory of Fatima Memorial Hospital for culture sensitivity were followed. Sensitivity of *Salmonella typhi* isolates was checked to 20 different antibiotics. Report of culture and sensitivity pattern was recorded.

Results: Amongst the 86 isolate 45 were found to be resistant to 2 or more first line anti-salmonella drugs. Eighteen multi-drug resistant *Salmonella typhi* (MDRST), isolates were detected. Four of the MDRST isolates were resistant to each of ciprofloxacin and ceftriaxone, and two were resistant to both of these drugs. Resistance was 19.2% to ciprofloxacin and 17.5% to ceftriaxone. Sensitivity to meropenem was 100% and to imipenem 98.6%.

Conclusion: Pattern of *S. typhi* resistance is changing rapidly. MDRST and strains resistant to ciprofloxacin and ceftriaxone are a major threat in developing world. Proper steps must be taken to avoid emergence of *Salmonella typhi* strains resistant to most of the pertinent antibiotics.

KEY WORDS: *Salmonella typhi*, Multi-drug Resistant *Salmonella typhi* (MDRST), Typhoid Fever.

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INTRODUCTION

Typhoid fever is a systemic infection caused by *Salmonella Enterica* serotype typhi. This is a highly adapted human specific pathogen and possesses remarkable mechanism for persistence in host. Most of the disease burden occurs in developing countries due to poor sanitary conditions.¹ In 1948 chloramphenicol was introduced and a severe, debilitating and fatal disease was transformed to a readily treatable condition. Resistance started to develop within

two years of the drug introduction and until 1972 chloramphenicol resistant *S. typhi* became a major problem.² Outbreaks of chloramphenicol resistant salmonella occurred in Mexico, India, Vietnam, Thailand, Korea and Peru. These strains were also found to be resistant to sulfonamide, tetracycline and streptomycin. Amoxicillin and trimethoprim-sulphamethoxazole were effective alternatives till the end of 1990's when strains resistant to all the first line anti-salmonella drugs used at that time, were reported. Multi-drug resistant salmonella typhi (MDRST) is defined as *Salmonella typhi* resistant to all first line antibiotic i.e. chloramphenicol, ampicillin, and trimethoprim-sulphamethoxazole. Multiple outbreaks of infections with these resistant strains occurred in India, Pakistan, Bangladesh, Vietnam, Middle East and Africa.³⁻⁵ This resistance rarely develops during course of treatment but instead results from clonal dissemination of individual multi-drug resistant *S. typhi* or from transfer of R-plasmid.⁶ Recently however there are reports from some areas, of strains, fully susceptible to all first line drugs.⁷

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Therfall and Ward have reported that *S.typhi* with decreased sensitivity to ciprofloxacin is endemic in several Asian countries, and incidence of such strains has increased in travelers from the Indian subcontinent. They suggested 3rd generation cephalosporins such as ceftriaxone or cefotaxime as possible alternatives and in their study it was assured that all strains were sensitive to these drugs.⁸

Reduced susceptibility to flouroquinolones has become a major problem mostly in Asia.^{9,10} Outbreak with such strains affected eight thousand people and killed 150 people in Tajikistan in 1997.¹¹ Isolates responsible for this outbreak were found to have MIC of flouroquinolone ten times to that of those fully susceptible to the drug. This decreased susceptibility is resulting in treatment failure.^{12,13}

There are sporadic reports of high resistance to ceftriaxone as well.¹⁴ At the moment the emergence of resistant strains to two major second line drugs like ciprofloxacin and ceftriaxone is posing a major problem.

METHODS

Blood samples received in the laboratory of Fatima Memorial Hospital for culture during the study period of one and half year, were followed and sensitivity of isolates positive for *Salmonella typhi* was checked to 20 different antibiotics. These antibiotics included ampicillin, amikacin, amoxicillin, augmentin, aztreonam, cefipime, ceftazidime, ceftriaxone, cefotaxime, cefixime, cefaclor, cefuroxime, ciprofloxacin, chloramphenicol, gentamicin, imipenem, meropenem, piperacil, tobramycin and trimethoprim-sulphamethoxazole.

Age, sex, duration of ailment, diagnosis and any prior use of antibiotics were not taken into account. All of the isolates were not checked to all the antibiotics mentioned. Percentage of isolates regarding resistance and sensitivity was calculated and results obtained.

RESULTS

During the study period a total of 86 blood culture isolates were found positive for *Salmonella typhi*. Out of these isolates 45 were resistant to 2 of 3 first-line anti-salmonella drugs

(ampicillin, trimethoprim-sulphamethoxazole and chloramphenicol). Twenty-eight isolates were checked to all three first-line anti-salmonella drugs and 18 isolates (64.28%) were found resistant to all three drugs (Multi-drug Resistant *Salmonella typhi* [MDRST]). Of these MDRST isolates, 4 were resistant to ceftriaxone, 4 to ciprofloxacin and two isolates were resistant to both ceftriaxone and ciprofloxacin.

Resistance to Trimethoprim/Sulphamethoxazole was found in 94.2% and in chloramphenicol 65.3%, similarly resistance to cefuroxime was 53.1% in cefaclor 49.2% and in augmentin 42.5%. Sensitivity and resistance to other antibiotics is also mentioned in (Table-I).

Sensitivity to both ampicillin and chloramphenicol was found in 10 isolates, three isolates were sensitive to ampicillin and trimethoprim-sulphamethoxazole, and one isolate was found sensitive to all three first-line anti salmonella drugs. A total of 65 isolates were checked to 2 or more first line anti-salmonella drugs and only 12 isolates were sensitive to 2 or more of three first line anti-salmonella drugs.

DISCUSSION

Salmonella typhi, a potentially lethal organism was successfully managed with introduction of chloramphenicol. Since then emergence of resistant strains began and now MDRST has become a real challenge especially in the developing world. There have been reports from different parts of the world about resistance pattern. Most reports from developing countries are showing MDRST strains. Strains resistant to even second line anti-salmonella drugs like ciprofloxacin and third-generation cephalosporin are being increasingly reported.¹⁵ Patients in United Kingdom and United States detected with strains resistant to all three first-line drugs (MDRST), ciprofloxacin and ceftriaxone reported travel to the developing world especially southeast Asia.^{14,16}

Ackers and colleagues performed susceptibility testing on 350 isolates and found 16% of the isolates to be MDRST. No resistance was

Table-I: Salmonella typhi resistance pattern to individual drugs.

	Name	No of Cases	No of case Sensitive	% Sensitive	No of case Resistant	% Resistance
1.	Amikacin	73	64	87.7	9	12.3
2.	Amoxicillin	79	75	93.7	4	6.3
3.	Ampicillin	75	24	32	51	68
4.	Augmentin	40	23	57.5	17	42.5
5.	Aztreonam	50	14	28	36	72
6.	Cefaclor	59	30	50.8	29	49.2
7.	Cefipime	19	18	94.7	1	5.3
8.	Cefixime	20	3	15	17	85
9.	Cefotaxime	76	60	78.9	16	21.1
10.	Ceftazidime	73	62	84.9	11	15.1
11.	Ceftriaxone	78	64	82.1	14	17.9
12.	Cefuroxime	64	30	46.9	34	53.1
13.	Chloramphenicol	49	17	34.7	32	65.3
14.	Ciprofloxacin	52	42	80.8	10	19.2
15.	Gentamicin	63	54	85.7	9	14.3
16.	Imipenem	71	70	98.6	1	1.4
17.	Meropenem	67	67	100	0	0
18.	Pipracil	27	10	37	17	63
19.	Tmp/Sxt	52	3	5.8	49	94.2
20.	Tobramycin	39	30	76.9	9	23.1

Tmp/Sxt: Trimethoprim-sulphamethoxazole.

reported to ciprofloxacin, ceftriaxone, gentamicin and kanamycin.¹⁶ Nadeem and colleague in 2004 reported from Quetta, Pakistan that 69% of isolates were found to be MDRST.¹⁸ In yet another report from Bahawalpur, Pakistan: 53.8% of isolates were found MDRST and all strains were sensitive to fluoroquinolones and third-generation cephalosporins.¹⁷ In this study, 28 isolates were checked against all three first-line anti-salmonella drugs of which 18 isolates turned out to be MDRST which makes up 65% of isolates.

Studies by Ackers et al.,¹⁶ Tehmina et al.¹⁷ and Nadeem et al.¹⁸ demonstrated all the isolates including MDRST to be fully susceptible to ciprofloxacin and ceftriaxone while data in our study showed that out of 18 MDRST four of the isolates were found resistant to ciprofloxacin, four resistant to ceftriaxone and two of them were found resistant to both of these drugs. Overall resistance to ciprofloxacin in our study is found to be 19.2% and to ceftriaxone being 17.9%.

Threlfall and Ward showed decreased sensitivity to ciprofloxacin and they suggested possible alternatives as ceftriaxone and cefotaxime, and reassured that organisms were fully susceptible to these drugs. But in our study not only resistance to ceftriaxone is noted but 21.1% out of 76 isolates were found resistant to cefotaxime as well. Cases of Salmonella typhi resistant to ciprofloxacin and ceftriaxone have been reported from Bangladesh.⁸ An out-break of *S. typhi* resistant to ciprofloxacin has already been reported in 1997 from Tajikistan.¹¹ Our study and that from Bangladesh both favor ever changing pattern of Salmonella resistance and hence the importance of proper selection and usage of antibiotic.

In some areas strains fully susceptible to all first-line anti-salmonella drugs have re-emerged.⁷ In our study 12 out of 65 isolates checked against two or more first-line anti-salmonella drugs were sensitive to at least two first-line drugs and one isolate was found sensitive to all three first-line drugs. Ackers and

colleagues did not show resistance to gentamicin and kanamycin while in our study 14.3% resistance to gentamicin and 12.3% resistance to amikacin is demonstrated. Cefixime, one of the anti-salmonella drugs showed 85% resistance.

If we closely look at the results only meropenem showed 100% sensitivity and imipenem showed 98.6% sensitivity, both of which may be next possible alternative to drug resistant anti-salmonella isolates.

This study as well as previous studies are clearly indicating ever changing pattern of altered resistance in *Salmonella* typhi isolates. Strains resistant to second-line anti salmonella drugs are being increasingly reported. Mostly these resistant strains are reported from developing countries. Main reason for this is irrational use of antibiotics. Doctors, patients and government all are equally held responsible for this.¹⁹

In some reports aztreonem and imipenem are potential third-line anti-salmonella drugs,²⁰ and our study is showing 72% of 50 isolates to be resistant to aztreonem.

CONCLUSION

We are fast heading toward a situation where emergence of a fastidious, highly resistant salmonella isolate is quite likely. What is required is good choice, proper dosage, proper duration of therapy and rational prescribing of antibiotics. Possible use of costly drugs like meropenem and imipenem for multi-drug resistant salmonella is going to have a huge burden on individual as well as state's economy. Hence, the need is for continued surveillance of resistant strains and proper selection and use of antibiotics.

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