JOURNAL OF CLINICAL AND DIAGNOSTIC RESEARCH

ORIGINAL ARTICLE

The Re-Emergence Of Chloramphenicol Sensitivity Among Enteric Fever Pathogens In Mangalore

YASHAVANTH R*, VIDYALAKSHMI K**

ABSTRACT

Background: Enteric fever is a global health problem, especially in the developing countries of the tropics. Drug resistance among enteric fever pathogens is a major challenge for the clinicians. Since its introduction in 1948, chloramphenicol (C) remained as the drug of choice for enteric fever. Later, ciprofloxacin (Cf) replaced C, when C-resisitant enteric fever emerged and caused outbreaks in different parts of the world. Fluoroquinlones are replaced by third generation cephalosporins like ceftriaxone (Ci) and cefotaxime (Ce) as the first line therapy nowadays. C-sensitive *Salmonella* serotypes emerged again due to the withdrawal of antibiotic pressure. Therefore, an attempt was made to study the incidence of blood stream *Salmonella* infections and their antimicrobial susceptibility pattern. **Method:** Strains isolated from 188 blood culture positive cases of enteric fever over a period of 1 year and 11 months were studied and their sensitivity pattern to chloramphenicol(C), ampicillin(A), cotrimoxazole(Co), nalidixic acid(Na), ciprofloxacin(Cf), ofloxacin(Of) and ceftriaxone(Ci) were analysed by the disk diffusion method according to the Clinical Laboratory Standard Institute(CLSI) guidelines. The Minimum Inhibitory Concentration (MIC) was determined for chloramphenicol by the agar dilution method according to the CLSI guidelines. **Results:** A total of 188(2.99%) *Salmonella* isolates were obtained from blood culture during the period of 1 year and 11 months. Of these, 77 were *S.typhi* and 111   were *S.paratyphi A*. The present study showed   higher chloramphenicol sensitivity for *S.typhi* (97.4%) and *S.paratyphi A* (100%). The MIC for Chloramphenicol was $\leq$ 4 µg/ml for 187 *Salmonella* isolates. One*Salmonella* isolate showed C - MIC of 64 µg/ml. **Conclusion**: This study has shown the reemergence of chloramphenicol sensitivity among enteric fever pathogens. The results suggest the necessity for the reevaluation of chloramphenicol therapy in enteric fever.

KEYWORDS:
Chloramphenicol, Disk-diffusion, Minimum Inhibitory Concentration, *Salmonella*

*M.D(Microbiology) Department of Microbiology, A.J Institute of Medical sciences, Mangalore, Karnataka (India)
** M.D (Microbiology),
Department of Microbiology, Kasturba Medical College, Mangalore,
Manipal University, Karnataka.
Correspondence Address:Yashavanth Rai, Dept. of Microbiology, A.J.I.M.S, Kuntikana, Mangalore-575004.
Ph:09986297656
e-mail-dryashwanthrai@gmail.com

Introducton:

Enteric fever is a growing concern, worldwide. The World Health Organisation (WHO) estimates that there are about 22 million cases of enteric fever worldwide, every year [1]. Enteric fever continues to be endemic in all parts of India. *Salmonella typhi* and *Salmonella paratyphi A* are predominant types of *Salmonella* which are responsible for the incidence of enteric fever in India [2]. Chloramphenicol had been the "gold standard" therapy since its introduction in 1948. In India, drug resistance to *S.typhi* has been reported since

1960, followed by the first outbreak of multidrug resistant *S.typhi* (MDRST) in Calicut [3]. Since then, MDRST has appeared throughout the world, especially in South America, the Indian subcontinent, Africa and South East Asia [4, 5]. Resistance to commonly used antibiotics such as chloramphenicol, ampicillin and cotrimoxazole has been reported from different parts of India in the last two decades. Fluoroquinolones emerged as the drug of choice for the treatment of enteric fever. There have been increasing cases of clinical failure after the administration of ciprofloxacin (Cf) to patients with enteric fever [6]. Third generation cephalosporins like ceftriaxone and cefotaxime are being used as the first line therapy in the treatment of enteric fever now- a -days [7].

In this scenario, reports of the reemergence of the sensitivity of *S.typhi* and *S.paratyphi A* to chloramphenicol calls for a reappraisal of the antibiotic sensitivity pattern of the strains which are prevalent in India. The aim of this study was to analyse the drug sensitivity pattern of blood culture positive cases of enteric fever.

Materials and Methods:

A total of 6297 specimens were received for blood culture during the study period (August 2005-June 2007), at a tertiary care hospital in Mangalore. All the blood culures were performed by using the BacT- Alert automated blood culture system. The isolates obtained, were identified, based on standard laboratory techniques [8].

Anitbiotic susceptibity of the isolates were determined against 7 antibacterial agents by the Kirby Bauer disk diffusion method. They included ampicillin [10μg], chloramphenicol [30 μg], ceftriaxone [30 μg], ciprofloxacin [5 μg], cotrimoxazole [25 μg], nalidixic acid [30 μg] and ofloxacin [5 μg] [Hi-media Mumbai]. Minimum Inhibitory Concentration [MIC] was determined for chloramphenicol by the agar dilution method. The results were recorded and interpreted as per the recommendations of the CLSI [9].

Results:

A total of 188 [2.99%] *Salmonella* isolates were obtained from 6297 blood cultures. Of these, 77 were *S.typhi* and 111 were *S.paratyphi A*.

[Table/Fig 1] shows the antibiotic sensitvity pattern of *S.typhi* and *S.paratyphi A*. These results show a high sensitivity of *S.typhi* [97.4%] and *S.paratyphi A* [100%] to chloramphenicol. Among the *S.typhi* isolates, susceptibility was found to be 99.87% for ampicillin, 97.4% for cotrimoxazole, 23.4% for nalidixic acid and 100% for ciprofloxacin, ofloxacin and ceftriaxone.

[Table/Fig 1] shows the antibiotic sensitvity pattern of *S.typhi* and *S.paratyphi A*.

Antibiotic (μg/disk)	S. typhi (n=77) No. of sensitive, (%)	S. paratyphi A (n=111) No. of sensitive, (%)
Ampicillin (10)	76 (98.7%)	103 (92.79%)
Cotrimoxazole (25)	75 (97.4%)	111 (100%)
Chloramphenicol (30)	75 (97.4%)	111 (100%)
Nalidixic acid (30)	18 (23.4%)	0 (0%)
Ciprofloxacin (5)	77 (100%)	111 (100%)
Ofloxacin (5)	77 (100%)	111 (100%)
Ceftriaxone (30)	77 (100%)	111 (100%)

Among 111 *S.paratyphi A* isolates, susceptibility was found to be 92.79% for ampicillin and 100% for cotrimoxazole, ciprofloxacin, ofloxacin and ceftriaxone. All *S.paratyphi A* strains were found to be resistant to nalidixic acid by the disk diffusion method.

The MIC of Chloramphenicol was ≤4 μg/ml for 187 *Salmonella* isolates. One *Salmonella* isolate showed an MIC of 64μg/ml by the agar dilution method. This isolate showed multidrug resistance (to A, Co and C by the disk diffusion method).

Discussion:

Enteric fever continues to be a major public health problem in our country, being compounded by the emerging resistance to antibiotics that were effective earlier. Wide variations in different geographical regions in India make it necessary to ensure the sensitivity of the enteric fever pathogen to antibiotics before instituting therapy.

Chloramphenicol was the first antibiotic which was used against typhoid and resistance to this drug developed in the seventies and eighties

and thereafter, to the other first line drugs like trimethoprim, sulfamethaxazole and ampicillin. In the nineties, increasing resistance to ciprofloxacin which was a good alternative for the multidrug resistant enteric fever pathogen emerged in both *S.typhi* and *S.paratyphi A* [10]. Resistance to ceftriaxone has also been reported [11].

In India, there have been varying reports on the resistance of *S.typhi* and *S.paratyphi A* to various antibiotics [12,13]. There have been reports of the reemergence of the sensitivity of *S.typhi* and *S.paratyphi A* to chloramphenicol and other first line drugs [14]. The present study showed 97.4% sensitivity to chloramphenicol in *S.typhi* and 100% sensitivity in *S.paratyphi A*. The MIC of Chloramphenicol was ≤ 4 µg/ml for 187 *Salmonella* isolates; only one isolate had an MIC of 64µg/ml by the agar dilution method. These results are very similar to other reports from other parts of India and point towards the re-emergence of the sensitivity to chloramphenicol in this region also [14, 15].

The significant decrease in chloramphenicol resistant *Salmonella* isolates in Bangladesh suggested the cheaper and the effective first line antibiotic, chloramphenicol, as the drug of choice for the treatment of enteric fever [16].

The previous generation antibiotics are increasingly being found to be useful for the treatment of many diseases. Chloramphenicol can be a useful and cost effective alternative in selected cases. Consistent surveillance and antibiotic susceptibility testing is required in different parts in the country to know the antibiotic sensitivity pattern among enteric fever pathogens. There is a possibility that restricted use can lead to the withdrawal of selective presssure and resistant bacteria will no longer have the advantage of survival in such settings.

Conflict of interest: NO

References

[1] Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ 2004; 82: 346-53.

[2] Gupta B, Kumar U, Khurana S. Multidrug resistant *Salmonella typhi* Ludhiana [Punjab]. Indian J Pathol Microbial 1993; 36(1): 5-7.

[3] Panicker CKJ, Vimla KN.Transferable chloramphenicol resistance in *Salmonella typhi*. Nature 1972; 239: 109-10.

[4] Butler T, Linch N, Arnold K, Pollock M. Chloramphenicol resistant typhoid fever in Vietnam associated with R factor Lancet 1973; ii : 983-5.

[5] El-Sherbini A. An outbreak of typhoid fever resistant to chloramphenicol and other drugs in Gharbeya Govermorate. Egypt J Trop Pediatr 1992; 38:331- 4.

[6] Thelfal EJ, Ward LR, Glunner JA. et.al. Ciprofloxacin resistant *S .Typhi* and treatment failure. Lancet 1999; 353: 1590-1.

[7] Lesser CF, Miller SI. Salmonellosis chapter 156. In. Harrison's Principle of internal medicine; 15th Ed 2001; 1:970-974.

[8] Forbes BA, Sham DF, Weissfeld AS, editiors. Overview conventional methods for bacterial indentification. Chapter B: Baliley and Scott's Diagnostic Microbiology, 10th ed. St.Louis: The CV Mosby Company; 1998.p.167.

[9] Clinical and Laboratory Standards Institute Performance Standards for antimicrobial disc tests; Approved Standards, 9th ed CLSI Document M2-A9, vol. 26 No.1. Wayne PA: 2006

[10] Daga MK, Sarini K, Sarkar R. A study of culture positive multidrug resistance enteric fever : Changing pattern and emerging resistance to ciprofloxacin. J Assoc Physicians India 1994; 42:599 - 600.

[11] Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid Fever. NEJM 2002; 347:1770-82.

[12] Maheshwari VD, Agarwal SK. Present status of drug resistance in cases of enteric fever in Rajasthan. J Assoc Physicians India1996; 44:618-9.

[13] 13.Misra RN, Bawa KS, Magu SK, Bhandari S, Nagendra A, Menon PK. Outbreak of multidrug resistant *Salmonella typhi* enteric fever in Mumbai. Medical Journal Armed Forces India 2005; 61: 148-50.

[14] Bhatia JK , Mathur AD, Arora MM. Reemergence of Chloramphenicol Sensitivity in Enteric Fever. MJAFI 2007; 63: 212-14

[15] Zaidi AKM, Rumina H, et al. Correspondence- Typhoid fever. NEJM 2003; 348:1184-5.

[16] Rahman M, Ahmad A, Shoma S. Decline in epidemic of multidrug resistant Salmonella typhi is not associated with increased incidence of antibotic susceptible strain in Bangladesh. Epidemiol Infect 2002; 129 : 29-34.