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Original Article

Reemergence of Chloramphenicol Sensitivity among *Salmonella enterica* serovars Typhi and Paratyphi : a six year experience in a tertiary care hospital in Nepal.

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Abstract

Emerging drug resistance among *Salmonella* Typhi and Paratyphi has become challenging in the treatment of enteric fever. The objective of this study was to determine the antibiotic susceptibility pattern of *Salmonella* serotypes isolated from patients with enteric fever admitted to Manipal Teaching Hospital, Pokhara,Nepal. A total of 30 *Salmonella enterica* serovar Typhi, Paratyphi A, and Paratyphi B isolated from cases of typhoid and paratyphoid fever admitted to Manipal Teaching Hospital over a period from January 2012 to March 2018 were investigated. All strains were identified by standard microbiological methods and tested for *in vitro* antibiotic susceptibility testing,using Kirby-Bauer disc diffusion method following the criteria designed by the Clinical and Laboratory Standards Institute (CLSI 2013). *S* Typhi was the most predominant amongst all the isolates (18 of 30 i.e. 60%), followed by *S* Paratyphi A (33.3%, 10 out of 30) and *S* Paratyphi B (6.6%; 2 out of 30). Overall, 91.3% of the isolates were susceptible to chloramphenicol. The percentage sensitivities towards ceftriaxone, ciprofloxacin, cotrimoxazole and ampicillin were 82.6%, 75.8%, 63% and 37% respectively. All the isolates were sensitive to imipenem and amikacin. These findings suggested that there were changing patterns of antibiotic resistance in enteric fever with reemergence of chloramphenicol sensitive *Salmonellae*. This necessitates continuous surveillance of cases and re-evaluation of chloramphenicol therapy in *Salmonella* infections in Nepal.

Keywords: *Enteric fever; Salmonella; Chloramphenicol; Re-emergence of chloramphenicol sensitivity.*

Introduction

Enteric fever caused by *Salmonella enterica serotypes* Typhi and Paratyphi is a growing concern worldwide. (Parry, 2010) World Health Organization (WHO) estimated more than 33 million cases of enteric fever globally every year. (Crump *et al*., 2004) Enteric fever is still one of the serious public health problems in many geographic areas and is endemic in most developing countries. (Prashant, 2010) This disease is endemic in Asia, Africa, Latin America, the Caribbean islands, and Oceania; majority of cases being reported from Bangladesh, China, India, Indonesia, Laos, Nepal, Pakistan, or Vietnam. (Chau *et al.,* 2007)

In Nepal, enteric fever has popularly been known, since ancient times, in the name of "bisham joauro" meaning fever with poison. In

Nepal, this disease is prevalent in mountains, valleys and southern belts as an endemic disease with its peak incidence during May to August and is one of the leading causes of fever of unknown origin encountered in most of the hospitals. (Rauniar *et al*., 2000; Sharma *et al.,* 2003)

Chloramphenicol had been the "gold standard" of therapy for enteric fever since its introduction in 1948. However, *Salmonella enterica serovars* Typhi and Paratyphi A acquired resistance to chloramphenicol and other antimicrobial agents during the period from 1978-1990 in many countries, causing a major setback in the management of enteric fever cases. (Parry *et al*., 2002) Thus, ciprofloxacin continues to be the mainstay in the treatment of enteric fever in many places as it is orally effective and economical. (Ishaleku *et al*., 2015) With increasing use of ciprofloxacin instead of chloramphenicol, resistance to ciprofloxacin showed an upsurge. (Mandal *et al*., 2004)

Thus, there is a growing concern over enteric fever treatment in Nepal because of rapid development of fluoroquinolone resistance among *Salmonella* isolates. (Karki *et al.,* 2013; Khanal *et al.,* 2007)

However, discontinuation of chloramphenicol therapy relieved the selection pressure paving the way for re-emergence of *Salmonella* strains sensitive to chloramphenicol. From 2006 onwards, resistance of *Salmonella* serotypes to chloramphenicol showed a decline, which was attributable to non-usage of the drug for a long duration of time (Arora *et al.,* 2010) or due to emergence of de novo susceptible strains.

The trend of multidrug resistance *Salmonellae* showing susceptibility towards conventional first line drugs provided an opportunity to reevaluate the first line traditional drugs as possible therapeutic alternatives.

Thus, the aim of this retrospective study was to analyze drug sensitivity pattern of blood culture isolates in cases of enteric fever at Manipal Teaching Hospital over a period of more than 6 years and to look for any reemergence of sensitivity towards chloramphenicol.

Materials and Methods

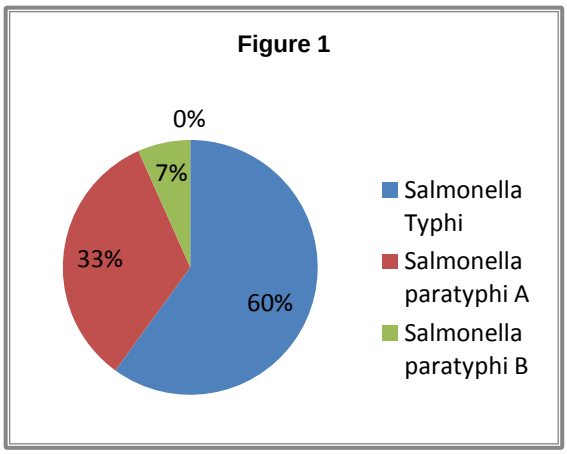
This was a retrospective study carried out at the Manipal Teaching Hospital, Pokhara over a period of more than six years (January 2012 - March 2018). A total of 30 *Salmonella enterica* serovar Typhi, Paratyphi A and Paratyphi B isolates from as many blood culture positive cases of enteric fever were analyzed.

All strains were identified by conventional biochemical tests and confirmed by serotyping (Khanal *et al.,* 1994) using *Salmonella* agglutinating sera (Seiken Laboratories, Tokyo, Japan). Antibiotic sensitivity testing was carried out by the standard Kirby Bauer disc diffusion method, (Bauer *et al.,* 1966) using the following antibiotics (conc. /disc): chloramphenicol (30µg), ampicillin (10 µg), ciprofloxacin (5 µg), ceftriaxone (30 µg), cotrimoxazole (25µg), imipenem (10 µg) and amikacin (30 µg).

Results

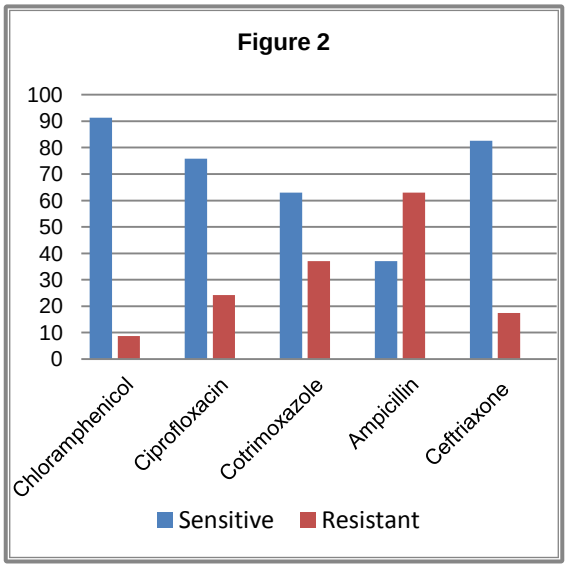
Thirty isolates were obtained over the period from Jan 2012 to March 2018. *Salmonella enterica serovar* Typhi was isolated from 18 patients, *Salmonella enterica serovar* Paratyphi A from 10 patients and Paratyphi B from 2 patients; *Salmonella enterica serovar* Typhi being the most common, accounting for 60% (18/30) of all the isolates.

Figure 1. Antibiotic sensitivity pattern of the isolates



All patients were in the age group of 2-59 years, commonest age group being 10-25 years. Sensitivity pattern of the isolates has been depicted vide figure 2.

Figure 2. Percentage isolates of sensitive and resistant Salmonella serotypes



It was interesting to note that 91.3% of the isolates were susceptible to chloramphenicol. The percentage sensitivities to ceftriaxone, ciprofloxacin, cotrimoxazole and ampicillin were 82.6%, 75.8%, 63% and 37% respectively. All the isolates were sensitive to imipenem and amikacin.

Discussion:

Enteric fever is a major public health problem in many developing countries. This disease remains as one of the commonest cause of fever in most parts of the developing world including Nepal. (Parry *et al.,* 2010; Maskey *et al*., 2006).

Chloramphenicol was the mainstay of treatment for enteric fever until 1989 following which MDR strains (resistant to ampicillin, chloramphenicol, cotrimoxazole) were reported worldwide in the year 1990 with the emergence of plasmid R type ACCoSuTTm H1 incompatibility group. (Capoor *et al.,* 2010; Pokharel, et *al.,* 2006) Since then ciprofloxacin was introduced as the first line therapy providing good alternative for the multidrug resistant (MDR) enteric fever pathogens. (Daga, *et al*., 1994) Thereafter, there were several encouraging reports on the therapeutic efficacy of ciprofloxacin with the clinical evidence of subsidence of fever after a mean of 3 days ciprofloxacin treatment. (Sood *et al.,* 1999).

Subsequently, nalidixic acid resistant *Salmonella typhi* with decreased susceptibility to ciprofloxacin emerged causing therapeutic failure worldwide and it became endemic in many parts of world with the consequence that high level ciprofloxacin resistance enteric fever evolved in many Asian countries. (Capoor *et al.,* 2010) This was exemplified by the observations of cases in whom fever subsided only after 5-6 days of ciprofloxacin therapy. (Sood *et al.,* 1999) In addition community based studies conducted in India reported that 21.9% of cases took longer than 8 days to become afebrile and 9 percent cases did not respond to ciprofloxacin even after 15 days of therapy despite *in vitro* sensitivity. (Crump *et al*., 2004) Over and above, studies conducted earlier in India and Nepal documented that first and second generation quinolones had varying results over the *in vitro* activity against *S. typhi* and *S paratyphi*. (Pokharel *et al.,* 2006; Joshi S *et al.,* 2007)

In context to the above, we looked for the overall sensitivity of our isolates towards both newer and older generation of antityphoidal agents. It was observed that, percentage sensitivity towards chloramphenicol amongst the isolates was as high as 91.3%. This observation was similar to those reported earlier by Prajapati *et al* from Nepal. (Prajapati *et al*., 2010) In yet another study in Nepal, Bhatia and colleagues found that 100 percent of *Salmonella enterica serovar* Paratyphi A and 96% of *Salmonella enterica serovar* Typhi were sensitive to chloramphenicol (Bhatia *et al.,* 2007). In a study from Nigeria, Ishaleku *et al* observed that 85.9% of their *S. typhi* and 86.4% *S. paratyphi* were susceptible to chloramphenicol (Ishaleku *et al.,* 2015).

Such reemergence of chloramphenicol sensitivity in the recent years, could be due to the omission of chloramphenicol from the treatment regime of enteric fever, which could have led to the withdrawal of selective pressure. Thus resistant bacteria no longer had the advantage of survival in such settings. Reemergence of chloramphenicol sensitive *Salmonellae* may suggest the necessity for continuous surveillance of enteric fever cases in different geographical areas across the country, as well as globally, to keep abreast

with the emerging pattern of drug sensitivity among enteric fever pathogens.

Considering the changing drug sensitivity pattern (sensitive to resistance and vice-versa) it is advisable to have continued surveillance of resistance pattern of isolates which would help deciding rational use of antibiotics in the management of enteric fever in near future. In view of the reemergence of chloramphenicol sensitivity among *S typhi* and *S paratyphi* isolates in many parts of the world, this drug may be reconsidered as the antibiotic of choice in the treatment of enteric fever.

Conclusion

Our findings suggested reemergence of chloramphenicol sensitivity among the blood culture isolates of *Salmonellae* in Nepal. This highlights the necessity for continuous monitoring of cases and rolling back to chloramphenicol as the antibiotic of choice in the treatment of enteric fever.

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