ZIBELINE INTERNATIONAL™ PUBLISHING

ISSN: 2785-8391 (Online)
CODEN: JHDCAZ

Journal of Healthcare in Developing Countries (JHCDC)

DOI: http://doi.org/10.26480/jhcdc.01.2022.11.14

RESEARCH ARTICLE

A STUDY OF ENTERIC FEVER AND ANTIMICROBIAL SUSCEPTIBILITY PATTERNS AT THE MANMOHAN MEMORIAL COMMUNITY HOSPITAL IN KATHMANDU, NEPAL

Dina Adhikari[a], Mahendra Aryal[b*]

[a] Department of Microbiology, Kathmandu College of Science and Technology, Tribhuvan University, 44600, Kathmandu, Nepal.
[b] Department of Chemistry, Tri-Chandra Campus, Tribhuvan University, 44600, Kathmandu, Nepal.
**Corresponding Author Email: mahendraaryalnp@yahoo.com*

ARTICLE DETAILS

Article History:

Received 11 March 2022
Accepted 15 April 2022
Available online 22 April 2022

ABSTRACT

Enteric fever is one of Nepal's most serious public health problems. An investigation was conducted to determine the prevalence of *Salmonella* species in enteric fever patients and the patterns of antibiotic susceptibility. In a study of 675 cases, only 22 *Salmonella* species were isolated. There was a low positivity rate of 3.25 % among the isolates. The prevalence of positivity was highest among those aged 15-30 years, while the incidence of the disease rose for men. The results indicated that azithromycin was 100% sensitive to *Salmonella* Typh and 94.12% sensitive to *Salmonella* Paratyphi A, and chloramphenicol was 80 and 100% sensitive to *Salmonella* Typhi and Paratyphi A, respectively. Both *Salmonella* species were 100% sensitive to ciprofloxacin, ofloxacin, ceftriaxone, and cefixime. However, all the isolates showed resistance to nalidixic acid. Out of 22 isolates, three were multidrug-resistant.

KEYWORDS

Enteric fever, Prevalence, Antimicrobial susceptibility

1. INTRODUCTION

Typhoid fever is an uncommon disease in developed countries, but it is endemic in developing ones (Ajibola et al., 2018; Browne et al., 2020). There are two strains of *Salmonella* Typhi and *Salmonella* Paratyphi responsible for this virulent disease (Browne et al., 2020). *Salmonella* species are Gram-negative, non-capsulated, and non-sporing bacteria. *Salmonella* Typhi and Paratyphi A are both strictly human serovars that can invade bloodstreams (Bharmoria et al., 2017). The symptoms of enteric fever include prolonged fever, abdominal discomfort, diarrhoea, headache, malaise, anorexia, intestinal bleeding, melena, intestinal perforations, and peritonitis (WHO, 2003). It is, however, difficult to measure the true magnitude because the symptoms are often confused with many other febrile illnesses (Parry et al., 2002). The prevalence of enteric fever is higher in younger children and young adults (Ajibola et al., 2018; Bhetwal et al., 2017). Peak incidence is seen in children aged 5-15 years of age, and it is rare in children younger than 3 years of age (Bhetwal et al., 2017; Crump et al., 2004).

Based on various documents, there is an estimated one case of paratyphoid fever for every four cases of typhoid fever (Crump et al., 2004). It is one of the most common infectious diseases in the tropical world, about 80% of cases occur in Asian countries (Browne et al., 2020; Malla et al., 2004). *Salmonella* Paratyphi A is an emerging cause of febrile illness in Nepal, India, Pakistan, China, Vietnam, and Indonesia, where up to half of the cases of enteric fever are caused by this organism rather than *Salmonella* Typhi (Acharya et al., 2012; Kapil et al., 1997; Wood et al., 2006). In Nepal, enteric fever is also widely regarded as "Bisham Joauro'', which means fever with poison. It is well-known that the fever is endemic in Nepal, with its peak incidence occurring in May and August (Bhetwal et al., 2017). Microbiologically, the urban water supply in Nepal is very poor and may lead to lethal outbreaks of enteric fever (Bhatta et al., 2007).

Successful treatment of enteric fever depends upon the bacteria causing it to be susceptible to affordable antibiotics (Maskey et al., 2008). In an enteric fever, antimicrobial agents are especially useful to prevent the complications related to extreme infection and death of the sufferers (Bhetwal et al., 2017). Nalidixic acid is a naphthyridine, which is regarded as one of the earliest synthesized quinolone antibiotics. Resistance to nalidixic acid is therefore used as an indicator of decreased susceptibility to fluoroquinolones (Abbasi et al., 2011). In 1991, Watson and Pettibone first reported multidrug-resistant (MDR) *Salmonella* Typhi in Nepal (Watson and Pettibone, 1991). Among febrile patients in Nepal, antibiotics are the most preferred treatment. The use of antibiotics, as noted by reduces the susceptibility of *Salmonella* to treatment and has serious consequences for the powerful treatment of enteric fever (Parry et al., 2002). In recent years, third generation cephalosporins have been used more frequently to overcome the failures of fluoroquinolones, thus increasing the cost of treatment. A mixture of nalidixic acid- and multidrug resistance (NAR/MDR) is particularly problematic since it hinders the therapy for typhoid fever patients.

At the community level, the prevention measures should include educating people about the importance of handwashing, sanitary, disposal of human faeces, and the cleanliness of food preparation (Bharmoria et al., 2017). Providing safe drinking water to consume, disposing of sewage properly, pasteurizing milk, enforcing satisfactory control methods in industries, preparation of food or drink for human consumption, instructing in personal hygiene and keeping typhoid patients from handling foods are also important (Lewis et al., 2005). The main objectives of this study were to; (a) find out the prevalence of enteric fever among febrile patients visiting Manmohan Memorial Community Hospital (MMCH), (b) compare the prevalence and distribution of *Salmonella*

Quick Response Code	Access this article online	
	Website: www.jhcdc.com.my	DOI: 10.26480/jhcdc.01.2022.11.14

Cite The Article: Dina Adhikari, Mahendra Aryal (2022). A Study of Enteric Fever and Antimicrobial Susceptibility Patterns at The Manmohan Memorial Community Hospital in Kathmandu, Nepal. *Journal of Healthcare in Developing Countries, 1(2): 11-14.*

species in the blood culture, (c) evaluate the antimicrobial susceptibility of isolates, and (d) examine the multidrug-resistant (MDR) pattern of isolates.

2. Materials and Methods

2.1 Ethical Approval

Permission to conduct this study was obtained from the Institutional Review Committee of Manmohan Memorial Community Hospital (MMCH) prior to the start of the study. Written consent was taken from every patient or their guardians, before enrolment into the study. The patients who refused to participate were excluded from the study.

2.2 Study Site

Manmohan Memorial Community Hospital (MMCH) was established in 2006 under the umbrella of Nepal Health Care Co-operative Ltd. (NEHCO Nepal), one of the largest non-government health cooperatives in Nepal. The hospital has been focused on serving poor people with all clinical, surgical, and diagnostic services. The hospital has a hundred beds and has highly skilled professional health care staff. This organization offers outreach medical camps to people of deprived and underprivileged backgrounds. Therefore, MMCH was chosen to study the prevalence of enteric fever.

2.3 Sample Collection and Processing

This prospective cross-sectional study was carried out from July to September 2012. A total of 675 blood samples were collected from patients suspected of having enteric fever for blood culture. This study excluded blood samples from patients who had already taken antibiotics. From the patients suspected of enteric fever, 5 ml of blood from adults, and 0.5-2 ml of blood from children were collected aseptically by way of professional clinical technicians. The accumulated blood was transferred into the sterile brain heart infusion (BHI) broth.

2.4 Isolation and Identification of Microorganisms

Culture bottles were incubated at 37 °C for 7 days. To make a positive culture diagnosis, they were examined day by day for visual evidence of microbial growth, consisting of turbidity above the red cell layer, colonies growing on the top of the red cells (cotton balls), gas bubbles, haemolysis, and clots. The sub-culture was done on Mac-Conkey agar and blood agar plates at 37 °C for 24 hours. Mac-Conkey agar was tested for the growth of non-lactose fermenters. Standard microbiological techniques were used to identify bacterial pathogens from positive culture plates, including colony morphology, gram stain, and biochemical reaction (Isenberg, 2004).

2.5 Serotyping Tests

The serotyping of *Salmonella* species was conducted using a kit. On a clean glass slide, a drop of normal saline was placed, and a suspension of the organism was introduced from nutrient agar. Clumping of the suspension was observed on the slide. Positive results were indicated by the rapid agglutination of the organisms. Additionally, suspension without antisera was kept as a control to detect auto-agglutination (Isenberg, 2004).

2.6 Antimicrobial Susceptibility Testing

A standard disc method was used to test for susceptibility to antimicrobial agents of all isolates on Muller Hinton agar. A comprehensive screening of antimicrobial susceptibilities to ampicillin (10 μg), azithromycin (15 μg), cefixime ofloxacin (5 μg), ceftriaxone ofloxacin (5 μg), ciprofloxacin (5 μg), chloramphenicol (30 μg), cotrimoxazole (25 μg), nalidixic acid (30 μg), and ofloxacin (5 μg) was performed. The antibiotic susceptibility results were determined using interpretative zone diameters (CLSI, 2006). Quality control was also carried out in specimen collection and blood culture using *Escherichia coli* (EUCAST, 2011). As soon as the test was completed, the Petri plates and test tubes were autoclaved to destroy living organisms.

2.7 Statistical Methods

Data regarding the bacterial isolates, their susceptibility to various antibiotics, and other information were analysed using the Statistical Package for Social Sciences (SPSS) version 20.0 (IBM, Armonk, NY, USA). By using conditional logistic regression, matched univariate analysis was used to study the association between enteric fever and each exposure. The results were presented in percentage-based distribution.

3. Results and Discussion

3.1 Prevalence of *Salmonella* Species in The Blood Culture

A total of 675 samples have been included in the analysis. Of these, only 22 samples have been found to be positive. As can be seen in figure 1, the growth positive rate for *Salmonella* species was 3.25 %. A group researchers reported a positive rate of 2.3%, which is lower than the present findings (Prajapati et al., 2008). There have been reports of slightly higher growth positive rates for *Salmonella* species (5.1 and 6.9%) (Khanal et al., 2007; Sharma et al., 2006). Possibly, this low prevalence rate is the result of seasonal variations and short study periods. There is a shortage of manpower, funding, and facilities in many developing countries, making it difficult to diagnose enteric fever (Ivanoff et al., 1994).

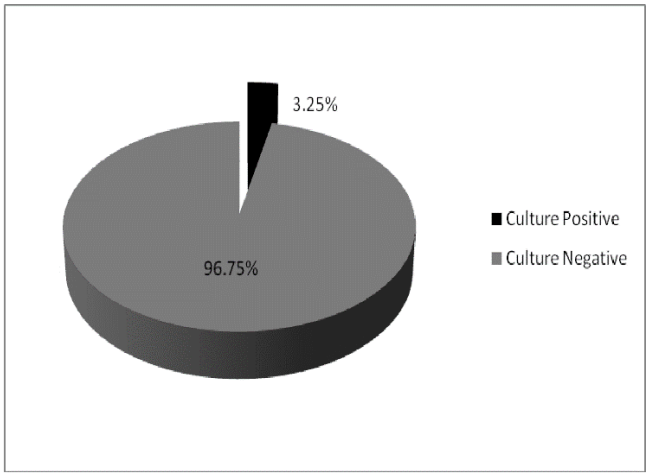

Figure 1: Prevalence of Salmonella Species in The Blood Culture

3.3 Distribution of Salmonella Species Isolated From Blood Culture

Figure 2 summarizes the distribution of *Salmonella* species isolated from blood cultures. There were more cases of paratyphoid fever associated with *Salmonella* Paratyphi A. Both *Salmonella* Paratyphi A and Typhi species in culture were estimated to be positive at 77.27% and 22.73%, respectively. A similar result has also been found (Bhetwal et al., 2017). According to the percentage of *Salmonella* Paratyphi A isolates in blood cultures has increased from 23% to 34% in 1993-1998 and 1999-2003 (Maskey et al., 2008). Vollaard et al., (2004) suggested that a higher risk of transmission may take within the household for typhoid fever, whereas paratyphoid fever regards as more frequently transmitted outside the household. WHO stated that the transmission of paratyphoid fever from *Salmonella* species may be affected by exposure to unsafe water and by the consumption of food from street vendors in developing countries (WHO, 2003).

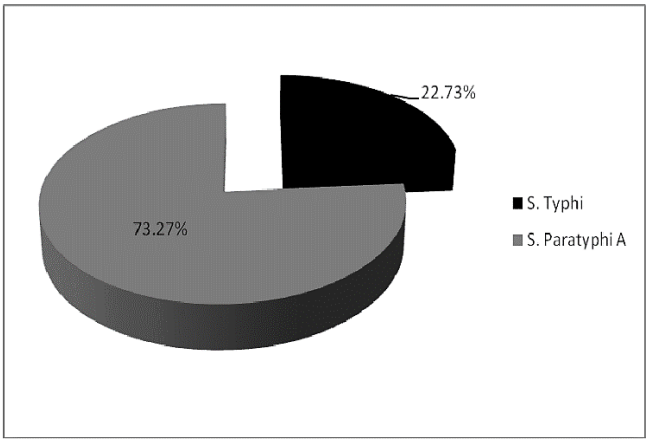

Figure 2: Distribution of Salmonella Species Isolated From Blood Culture

3.4 Distribution of Age and Bacteriological Culture

The age-wise distribution of bacteriological outcomes is given in Table 1. The results indicated that the incidence of *Salmonella enterica* at MMCH was very low. In comparison with *Salmonella* Typhi, *Salmonella* Paratyphi A was more prevalent. There were most patients between the ages of 15 and 30 who were suspected of having enteric fever, with 402 (59.56%). Furthermore, 77.27% of cultures were positive in the same age group. There was no significant association between the presence of enteric fever and the age group of the patients ($p > 0.05$). A similar study was also published (KC et al., 2007). Compared to our study, a study by Gautam et al., (2012) documented the highest number of positive cultures among age groups between 10-19 years.

Table 1: Age-Wise Distribution of Bacteriological Culture Results.

Age	Culture Positive	Culture Negative	Total
0-5	0	7 (1.07%)	7 (1.07%)
5-15	1 (4.55%)	29 (4.44%)	30 (4.44%)
15-30	17 (77.27%)	385 (58.96%)	402 (59.56%)
30-45	4 (18.18%)	122 (18.68%)	126 (18.67%)
45-60	0	84 (12.86%)	84 (12.44%)
>60	0	26 (3.98%)	26 (3.85%)
Total	22 (100%)	653 (100%)	675 (100%)

3.4 Distribution of Gender and Bacteriological Culture Result

Table 2 shows the distribution of enteric fever by gender. A total of 371 males (54.96%) and 304 females (45.03%) were suspected to have suffered from enteric fever. The results of blood cultures found that 15 (7.04%) males and 7 (2.3%) females were positive. There were no significant associations between gender and enteric fever cases ($p > 0.05$). The prevalence of enteric fever among males was higher in this study. This gender-wise difference in enteric fever and growth positive rates may be due to the relatively higher proportion of male patients involved in this study than female patients (Browne et al., 2020).

Table 2: Gender Wise Distribution of Enteric Fever Cases.

Gender	Culture positive	Culture negative	Total
Male	15 (7.04%)	356 (95.96%)	371 (54.96%)
Female	7 (2.3%)	297 (97.69%)	304 (45.03%)
Total	22 (3.25%)	653 (96.75%)	675 (100%)

3.5 Antimicrobial Susceptibilities of Salmonella Typhi and Paratyphi

The susceptibilities of *Salmonella* species to antimicrobials are listed in Table 3. The *Salmonella* Typhi strain showed 20% resistance to ampicillin, cotrimoxazole, and chloramphenicol, whereas *Salmonella* Paratyphi was resistant to 88.24, 11.76, and 5.88% of these antibiotics, respectively. *Salmonella* Typhi and Paratyphi were both 100% susceptible to azithromycin and chloramphenicol. It was observed that *Salmonella* Typhi was 80% sensitive to ampicillin, cotrimoxazole, and chloramphenicol, and *Salmonella* Paratyphi was 94.12, 88.24, and 11.76% sensitive to azithromycin, cotrimoxazole, and ampicillin, respectively. Our results on chloramphenicol sensitivity were similar to those (Acharya et al., 2012). It was reported that 100% sensitivity to chloramphenicol and cotrimoxazole (Joshi et al., 2011). Singh et al., (2011) found that amoxicillin (80.95%), chloramphenicol (80.95%), and cotrimoxazole (66.66%) were the most sensitive antibiotics, which was consistent with our findings.

Table 3: Antimicrobial Susceptibilities of *Salmonella* Species

Antibiotics	*Salmonella enterica serovar Typhi*				*Salmonella enterica serovar Paratyphi*			
	Sensitive		Resistance		Sensitive		Resistance	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Ampicillin	4	80	1	20	2	11.76	15	88.24
Cotrimoxazole	4	80	1	20	15	88.24	2	11.76
Azithromycin	5	100	0	0	16	94.12	1	5.88
Chloramphenicol	4	80	1	20	17	100	0	0
Ciprofloxacin	5	100	0	0	17	100	0	0
Ofloxacin	5	100	0	0	17	100	0	0
Ceftriaxone	5	100	0	0	17	100	0	0
Cefixime	5	100	0	0	17	100	0	0
Nalidixic acid	0	0	5	100	0	0	17	100

The results showed that both *Salmonella* isolates (22) were 100% resistant to the antibiotic nalidixic acid. In all isolated positive cases, the antibiotic susceptibility pattern was 100% sensitive against fluoroquinolones (ciprofloxacin and ofloxacin), and third generation cephalosporins (cefixime and ceftriaxone). *Salmonella* isolates were significantly sensitive to fluoroquinolones in this study, especially ofloxacin. Some researchers documented that 80.49 % of 41 *Salmonella* isolates were resistant to nalidixic acid (Acharya et al., 2009). A group researcher also found that *Salmonella* isolates were fully susceptible to 5 mg ciprofloxacin, but not to 30 mg nalidixic acid (Asna et al., 2003). It has been suggested that resistance to nalidixic acid may be an indication of decreased susceptibility to ciprofloxacin (Asna et al., 2003; Kapil and Das, 2002). Nair and Sudarsan, found that 90.22% of *Salmonella* Typhi strain isolates were resistant to nalidixic acid, indicating that ciprofloxacin was not effective (Nair and Sudarsan, 2004). The multidrug resistance pattern of *Salmonella* species is shown in Table 4. *Salmonella* isolates showed three different types of drug resistance patterns (13.6%). Two of them were *Salmonella* Paratyphi A and one was *Salmonella* Typhi. The same results were also noted by (Pokharel et al., 2006). In others study, researchers investigated 63.4 and 72% multidrug resistance (MDR) cases in nearby hospitals and laboratories in Kathmandu, Nepal (Gautam et al., 2012; Paudyal et al., 2011).

Table 4: Multidrug Resistance Pattern of *Salmonella* Species.

Antibiotic resistance pattern	Total No. (N)	No. of resistance (n)	% Resistance
Salmonella Typhi			
Amp, Chl, Cot, and NA	5	1	29.41
Salmonella Paratyphi			
Amp, Azt, Cot, and NA	17	1	5.88
Amp, Cot, and NA	17	1	5.88

4. Conclusion

Enteric fever is an invasive disease caused by *Salmonella* species that can be fatal. The results of this study indicated that *Salmonella* Paratyphi A was more prevalent than *Salmonella* Typhi. It was observed that enteric fever was more common in groups of 15-30 years old. It was determined that all isolates exhibited a variety of antimicrobial susceptibilities. Enteric fever can be treated most successfully with third generation cephalosporins like ceftriaxone and cefixime. There were three cases of multidrug resistance (MDR) detected in *Salmonella* isolates. It is important to consider the results of antibiotic susceptibility testing before prescribing antibiotics for the treatment of various isolates, since they may differ in antibiotic susceptibility. It can be concluded that the government should be responsible for providing safe and pure drinking water to the community, as well as educating the public about health and sanitation in order to prevent the spread of the enteric fever.

Acknowledgement

We would like to thank the microbiology department at Manmohan Memorial Community Hospital, along with the enrollees, for their assistance and cooperation in this study.

Authors' Contributions

DA carried out the data collection, laboratory work, and analyzed the data. DA and MA interpreted the data and drafted the manuscript. All authors read and approved the final manuscript.

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