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**ORIGINAL ARTICLE**

# Antibiotic Sensitivity Pattern in Blood Culture Positive Typhoid Fever

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## ABSTRACT

**Objective:** The aim of this study is to determine the antibiotic sensitivity pattern in blood culture positive typhoid fever.

**Study Design:**Retrospective study

**Place and Duration:**Children Medical Center (CMC) / Dr Habib un Nabi Children Hospital Mingora Swat and Pediatrics department of Hamdard University Hospital, Karachi for the duration between June 2020 and December 2020.

**Methods:** There were total one hundred and twenty patients of both genders were presented. Patients were aged between 5-15 years of age. Patients detailed demographics age, sex and body mass index were recorded after taking informed written consent. All the patients had fever. Blood sample of all the patients were taken for salmonella species. The Kirby Bauer Disc Diffusion method was used to test for antibiotic susceptibility, and the results were interpreted in accordance with National Committee for Clinical Laboratory Standards (NCCLS) guidelines. SPSS 20.0 version was used to analyze complete data.

**Results:**There were 84 (70%) males and 36 (30%) females. Mean age of the patients was 11.5±3.48 years. Among 120 cases of salmonella, 89 (74.2%) were Salmonellatyphi and Salmonella paratyphi was found in 31 (25.8%) patients. Sensitivity of antibiotics chloramphericol, cotrimoxazole, and azithromycin was 100% greater than that of ciprofloxacin and ofloxacin. (6.7%, vs 5.8%) But resistance of both antibiotics was high. Nalidixic Acid showed 108 (90%) resistance to salmonella typhi.

**Conclusion:** We observed a very high degree of diversity in the antimicrobial sensitivity pattern, with extremely high levels of sensitivity to antibiotics that have been utilized in the past, such as chloramphenicol and cotrimoxazole. It was discovered that the quinolones, which were widely utilized in the last two decades, have a very poor sensitivity.

**Keywords:**Typhoid fever, Sensitivity, Antibiotics, Resistance

## INTRODUCTION

Enteritis is a potentially fatal bloodstream infection caused by the pathogens Salmonella typhi (S. typhi), Salmonella paratyphi (S. paratyphi), and Salmonella paratyphi A (S. paratyphi) [1]. Enteric fever is largely spread by the fecal–oral route and can cause a wide range of symptoms, including malaise, fever, chills, nausea, abdominal discomfort, a transitory rash, and hepatosplenomegaly [2–4]. [2–4]. Viruses that spread through the fecal-oral pathway are to blame. However, despite advancements in sanitation and personal hygiene, and the availability of efficient treatment for enteric fever in undeveloped countries, notably in sub-Saharan Africa. Poor countries report between 11.9 million and 20.6 million cases of typhoid and paratyphoid fever each year, according to the WHO [3, with death tolls ranging from 129,000 to 223,000]. In addition, the majority of these cases and deaths occur in South Asia, where the incidence peaks during the rainy season from June to August [4], with seasonal variations.

Enteric fever is most prevalent in densely populated places, such as large cities and the low-lying southern Terai, as it was in Nepal [5–7]. In these densely populated places, a lack of access to safe drinking water and proper sanitation facilities worsens the quality of life, increasing the frequency with which infectious diseases like typhoid and paratyphoid fever emerge. Since Salmonella is the most often found pathogen in blood cultures in Nepal, this suggests that enteric fever strikes the country's residents more frequently than other pathogens [6]. Clinical trials have indicated that antimicrobials such as chloramphenicol, ampicillin, co-trimoxazole, and fluoroquinolones are the most effective drugs for treating enteric fever [7]. It is estimated that 10-30% of patients will die without antibiotics, but this number lowers down to 1–4% with the correct course of antibiotics [2]. Drug resistance in pathogenic strains of Salmonella, also referred to as multidrug resistance (MDR), has arisen as a result of the widespread and unjustified prescribing and usage of these drugs [6].

Treatment failures are attributed to MDR strains, as are fewer medication regimens available and a rise in infection severity and death [8]. Fluoroquinolones, such as ciprofloxacin, were first used to treat Salmonella infections in the late 1980s when standard first-line antibiotics (chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) were ineffective due to antibiotic resistance. No matter how much progress is made, a worldwide epidemic of fluoroquinolone-resistant pathogens threatens to break out [10].

Both people and animals are susceptible to quinolone resistance due to mutations in the quinolone resistance-determining region (QRDR) of DNA gyrase and topoisomerase IV, which have been found. The gyrA, gyrB, parC, and parE genes encode the topoisomerase IV subunits, while the gyrB gene encodes the gyrase subunits. Due to the fact that antimicrobial medicines have a primary focus on the gyrA gene, the pathogen can benefit from mutations in these determinants [11,12]. There have also been findings on the role of plasmid-mediated resistant determinants (PMQR) like qnr genes and aac (60)-Ib-cr4 in quinolone resistance.

Chloramphenicol was compared to other anti-typhoid medications (cefixime, ofloxacin, azithromycin, and ceftriaxone) for their susceptibility to Salmonella (including S. typhi and S. paratyphi A) isolates by the Kirby Bauer Disc Diffusion method to determine their MIC breakpoints.

## MATERIAL AND METHODS

This retrospective study was conducted at Children Medical Center (CMC) / Dr Habib unNabi Children Hospital Mingora Swat and Pediatrics department of HamdardUniversity Hospital, Karachi for the duration between June 2020 and December 2020. A total of 120 participants participated in the trial. Following the receipt of informed written consent, the demographic information of the enrolled cases was calculated. Patients who did not provide written consent were precluded from participation in this study.

Patients ranged in age from five to seventy years old. In the laboratory, all salmonella strains were identified by their serotypes. All blood cultures were incubated at 370 degrees Celsius for a minimum of 7 days. According to the Bauer-Kirby method, Salmonella strains were tested for their susceptibility to eight anti-microbial medications using the disc diffusion method and Mueller Hinton agar. In accordance with the diameter of the zone of inhibition, the strains were divided into three categories: sensitive, moderate, and resistant. To conduct the analysis in this study, the intermediate sensitive strains were used as resistant strains. The full data set was analysed using the SPSS 20.0 edition.

## RESULTS

There were 84 (70%) males and 36 (30%) females. Mean age of the patients was 28.14±9.55 years. Among 120 cases of salmonella, 89 (74.2%) were S typhi and salmonella paratyphi was found in 31 (25.8%) patients.(table 1)

Table 1: Characteristics of enrolled cases

| Variables | Frequency | %age |
|---|---|---|
| Mean age (years) | 11.5±3.48 | |
| Gender | | |
| Male | 84 | 70 |
| Female | 36 | 30 |
| Type of Salmonella | | |
| S typhi | 89 | 74.2 |
| P typhi | 31 | 25.8 |

Sensitivity of antibiotics chloramphernicol, cotrimoxazole, and azithromycin was 100% greater than that of ciprofloxacin and ofloxacin. (6.7%, vs 5.8%) But resistance of both antibiotics was high. Nalidixic Acid showed 108 (90%) resistance to salmonella typhi.(table 2)

Table 2: Frequency of sensitivity among enrolled cases

| Variables | Sensitivity | Resistance |
|---|---|---|
| Antibiotics | | |
| chloramphernicol | 120 (100%) | 0 |
| cotrimoxazole | 120 (100%) | 0 |
| azithromycin | 120 (100%) | 0 |
| ciprofloxacin | 8 (6.7%) | 112 (93.3%) |
| ofloxacin | 7 (5.8%) | 113 (94.2%) |
| Nalidixic Acid | 12 (10%) | 108 (90%) |

## DISCUSSION

As a result of the threat they pose to human health, antibiotic-resistant bacterial infections are a major source of medical anxiety. The high mortality and morbidity rates associated with typhoid fever can be attributed in part to medication resistance. It was common practise for decades to utilise fluoroquinolones and third-generation cephalosporins as the first-line antibiotics for enteric fever. Unfortunately, because of their broad antibacterial activity, low cost, and ease of accessibility, they have been frequently employed in human medicine without receiving adequate investigation before usage. Several cases of clinical failure have been documented around the world as a result of NARST, a drug-resistant staphylococcus aureus with a MIC 50 of 0.125–1 mg/ml that is becoming an endemic illness in portions of South Asia, particularly India. [15,16]

A total of 120 salmonella species were given in this study. There were 84 males (70 percent) and 36 females (30 percent) in the group. The mean age of the patients was 28.149.55 years. The patients were from all over the world. Salmonella typhi was detected in 89 (74.2 percent) of the 120 instances of salmonella, and salmonella paratyphi was found in 31 (25.8 percent) of the patients. Previous studies came up with results that were similar to ours. [17,18] Our investigation of the development of resistance to chloramphenicol and cotrimoxazole, the antibiotics that were used in the early days of typhoid treatment, uncovered some unexpected findings. A 100 percent sensitivity to early-day antibiotics, notably Chloramphenicol and Cotrimoxazole, was seen, which is consistent with the findings of previous studies. [19] According to our research, Salmonella typhi has demonstrated a remarkable reversal in its antibiotic resistance trend. In this study, Salmonella strains that were nearly 100 percent sensitive to fluoroquinolones a decade or two ago were found to have a very low degree of sensitivity to these antibiotics, with 6.7 percent sensitivity to Ciprofloxacin and Ofloxacin and 5.8 percent sensitivity to Ciprofloxacin and Ofloxacin, respectively.

This suggests that NARST strains, which may exhibit antibiotic susceptibility to fluoroquinolones in vitro, are resistant to fluoroquinolones in vivo[20], which results in a decrease in the actual sensitivity of these fluoroquinolones. The study also discovered that third generation Cephalosporin sensitivity has decreased, with Cefotaxime exhibiting the largest decline at 82 percent. The antibiotic azithromycin, on the other hand, exhibits perfect sensitivity. According to their findings, Yashavanth and Vidyalakshmi

(2010) and Bhatia et al (2007) reported 100 percent sensitivity to ofloxacin in S. typhi and S. paratyphi A isolates, whereas Dutta et al (2014) reported ofloxacin resistance in 56 percent of S. paratyphi A isolates and 18.2 percent of S. typhi isolates. [21-23] As a result, the high level of resistance to ofloxacin, which was formerly the treatment of choice for enteric fever, is a severe source of concern, and health authorities should take the appropriate steps to reduce the widespread use of fluoroquinolone antibiotics in general.

It was discovered throughout our analysis that the prevalence of fluoroquinolone resistant salmonella species was exceptionally high, and this was true for both Ciprofloxacin and Ofloxacin in our sample. With the NARST strain having a resistance rate of 90 percent in our study, it can be concluded that these strains would have an even higher percentage of resistance in vivo, because even those strains that are sensitive to fluoroquinolones in vitro would be resistant in vivo if they are resistant to Nalidixic acid in vitro. Historically used antibiotics, such as chloramphenicol and cotrimoxazole, as well as antibiotics that have only lately been utilised, such as azithromycin, have all demonstrated 100 percent sensitivity.

## CONCLUSION

When it comes to antimicrobial sensitivity patterns, we found an extraordinarily high degree of variation, with extremely high levels of sensitivity to antibiotics that have previously been used, such as chloramphenicol and cotrimoxazole. During the last two decades, it has been discovered that quinolones, which have been widely used, have a very low sensitivity.

## REFERENCES


1 Crump, J.A.; Mintz, E.D. Global trends in typhoid and paratyphoid Fever. Clin. Infect. Dis. 2010, 50, 241–246.

2 Qian, H.; Cheng, S.; Liu, G.; Tan, Z.; Dong, C.; Bao, J.; Hong, J.; Jin, D.; Bao, C.; Gu, B. Discovery of seven novel mutations of gyrB, parC and parE in Salmonella Typhi and Paratyphi strains from Jiangsu Province of China. Sci. Rep. 2020, 10, 7359.

3 Salerno-Goncalves, R.; Kayastha, D.; Fasano, A.; Levine, M.M.; Sztein, M.B. Crosstalk between leukocytes triggers differential immune responses against Salmonella entericaserovarsTyphi and Paratyphi. PLoSNegl. Trop. Dis. 2019, 13, e0007650.

4 Karkey, A.; Arjyal, A.; Anders, K.L.; Boni, M.F.; Dongol, S.; Koirala, S.; My, P.V.; Nga, T.V.; Clements, A.C.; Holt, K.E.; et al. The burden and characteristics of enteric fever at a healthcare facility in a densely populated area of Kathmandu. PLoS ONE 2010, 5, e13988.

5 Environment and Public Health Organization Typhoid: The Neglected Urgent in Nepal. 2019. Available online: http://enpho. org/featured/typhoid-the-neglected-urgent-in-nepal/ (accessed on 27 August 2020).

6 Petersiel, N.; Shrestha, S.; Tamrakar, R.; Koju, R.; Madhup, S.; Shrestha, A.; Bedi, T.; Zmora, N.; Paran, Y.; Schwartz, E.; et al. The epidemiology of typhoid fever in the Dhulikhel area, Nepal: A prospective cohort study. PLoS ONE 2018, 13, e0204479.

7 Ugboko, H.; De, N. Mechanisms of Antibiotic resistance in Salmonella Typhi. Int. J. Curr. Microbiol. App. Sci. 2014, 3, 461–476.

8 Kunwar, D.; Bhatta, S.; Chaudhary, R.; Rijal, K.R. Antibiotic susceptibility pattern of nalidixic acid resistant Salmonella isolates in shreeBirendra hospital chhauni. TUJM 2017, 4, 11–14.

9 Rowe, B.; Ward, L.R.; Threlfall, E.J. Multidrug-resistant Salmonella Typhi: A worldwide epidemic. Clin. Infect. Dis. 1997, 24 (Suppl. 1), S106–S109.

10 Ventola, C.L. The antibiotic resistance crisis Part 2: Management strategies and new agents. Pharm. Ther. 2015, 40, 344–352.

11 Hooper, D.C. Bacterial topoisomerases, anti-topoisomerases, and anti-topoisomerase resistance. Clin. Infect. Dis. 1998, 27 (Suppl. 1), S54–S63.

12 Nordmann, P.; Poirel, L. Emergence of plasmid-mediated resistance to quinolones in Enterobacteriaceae. J. Antimicrob. Chemother. 2005, 56, 463–469.

13 Cui, X.; Wang, J.; Yang, C.; Liang, B.; Ma, Q.; Yi, S.; Li, H.; Liu, H.; Li, P.; Wu, Z.; et al. Prevalence and antimicrobial resistance of Shigellaflexneri serotype 2 variants in China. Front. Microbiol. 2015, 6, 435.

14 Park, C.H.; Robicsek, A.; Jacoby, G.A.; Sahm, D.; Hooper, D.C. Prevalence in the United States of aac(60 )-Ib-cr encoding a ciprofloxacin-modifying enzyme. Antimicrob. Agents Chemother. 2006, 50, 3953–3955.

15 Threlfall EJ, Ward LR, Skinner JA, Smith HR, Lacey S.. Ciprofloxacin-resistant Salmonella typhi and treatment failure. Lancet 1999;353:1590–1

16 Capoor MR, Nair D, Aggarwal P, Mathys V, Dehem M, Bifani PJ. Salmonella entericaserovartyphi: molecular analysis of strains with decreased susceptibility and resistant to ciprofloxacin in India from 2001-2003. Braz J Infect Dis. 2007;11:423-5

17 Maharjan, A.; Dhungel, B.; Bastola, A.; Thapa Shrestha, U.; Adhikari, N.; Banjara, M.R.; Lekhak, B.; Ghimire, P.; Rijal, K.R. Antimicrobial Susceptibility Pattern of Salmonella spp. Isolated from Enteric Fever Patients in Nepal. Infect. Dis. Rep. 2021, 13, 388–400

18 Joshi RD, Khadka S, Joshi DM, Shrestha B, Dangal G, Acharya KP, Shrestha S, Dongol Y. Antimicrobial Sensitivity Trend in Blood Culture Positive Enteric Fever. J Nepal Health Res Counc. 2018 Jul 3;16(2):228-232. PMID: 29983442.

19 Pandit V, Kumar A, Kulkarni MM, Pattanshetty SM, Charmine C, Kamath S. Study of clinical profile and antibiotic sensitivity in paratyphoid fever cases admitted at teaching hospital in South India. J Family Med Prim Care. 2012;1:118-21.

20 Karkey A, Thwaites GE, Baker S. The evolution of antimicrobial resistance in Salmonella Typhi. CurrOpinGastroenterol. 2018;34(1):25–30

21 Dutta S, Das S, Mitra U, et al. Antimicrobial resistance, virulence profiles and molecular subtypes of Salmonella entericaserovarsTyphi and Paratyphi A blood isolates from Kolkata, India during 2009-2013. PLoS One. 2014;9(8):e101347

22 Bhatia JK, Mathur AD, Arora MM. Re-emergence of chloramphenicol sensitivity in enteric fever. Med J Armed Forces India. 2007;63(3):212–214.

23 Yashavanth R, Vidyalakshmi K. The re-emergence of chloramphenicol sensitivity among enteric fever pathogens in Mangalore. J ClinDiagn Res. 2010;4(5):3106–3108