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Antimicrobial profile of blood culture isolates of Enteric fever pathogens at tertiary care teaching hospital of Western Uttar Pradesh, India

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Abstract

Background: *Enteric fever is remains a significant public health concern globally, with its impact exacerbated by the rise of antimicrobial resistance, which is largely driven by indiscriminate and irrational antibiotic use. Continuous surveillance of local antimicrobial resistance trends is essential to guide effective treatment protocols and curb the spread of drug- resistance strains.*

Objective: *This study aimed to determine the prevalence, antibiotic sensitivity patterns, and extended-spectrum beta-lactamase (ESBL) production in culture-confirmed enteric fever cases caused by Salmonella enterica.*

Method: *A retrospective, laboratory record-based cross-sectional study was conducted at a rural tertiary care teaching hospital. Blood culture data from July 2017 to June 2019 were reviewed to identify S. enterica isolates and assess their antibiotic susceptibility patterns. Data were analyzed using Microsoft Excel 2010 and summarized using descriptive statistics (frequencies and percentages). The chi-square test was applied to determine statistical significance, with p-value < 0.05 considered significant.*

Result: *Out of 512 blood samples processed for culture and sensitivity, 35 (6.8%) yielded Salmonella species Isolates. Salmonella typhi accounted for (n = 30, 86%), followed by Salmonella paratyphi A (n = 5, 14%). S. typhi isolates showed 100% susceptibility to Imipenem, > 90% susceptibility to third-generation cephalosporins, and high susceptibility to Aztreonam (90%), Cefepime (90%), Levofloxacin (86.67%) and Ciprofloxacin (70%). S. paratyphi A strains showed complete susceptibility (100%) to Cefixime, Ceftazidime, Ceftriaxone, Amikacin, and imipenem, and 80% susceptibility to Levofloxacin, Cefotaxime, Cefepime, and Azatreonam. A low level of multidrug resistance was observed, but resistance to Nalidixic acid was notably high.*

Conclusion: *The findings highlight the importance of performing blood cultures and antibiotic susceptibility testing in all suspected enteric fever cases. The emergence of antimicrobial resistance underscores the urgent need for antimicrobial stewardship programs to regulate and rationalize antibiotic use and prevent the spread of multidrug-resistance Salmonella strains.*

Introduction

Enteric fever is a globally prevalent communicable disease involving multiple systems, caused by *Salmonella enterica*, subspecies enterica serovar typhi, and serovars paratyphi A, B & C [1].It is a serious issue of public health concern with an annual incidence rate exceeding 20 million cases and 2 lakh deaths [1].The situation has further worsened with the emergence of multidrug resistance in the enteric fever pathogens which are now reportedly resistant even to first-line antibiotics like Chloramphenicol, Ampicillin & Co-trimoxazole [2].This has resulted in irrational injudicious drug therapy leading to selection pressures attributed to a single large self-transferable plasmid [3].This in turn has resulted in an increase in the usage of Fluoroquinolones like Ciprofloxacin in clinical settings. This has resulted in a gradual rise in Minimum inhibitory concentrations of Ciprofloxacin causing therapeutic failure [3]. This problem is worsened due to the emergence of Nalidixic acid-resistant *S. typhi* (NARST) strains which are also found to be resistant to Fluoroquinolones [4, 5].

As per the existing trends, 3rd generation Cephalosporins (Ceftriaxone, Cefixime), and macrolides (Azithromycin) are the preferred therapeutic agents for Enteric fever. However, with their increasing use, resistance against these antibiotics is increasingly reported among *S. enterica* strains [6].The emerging Multidrug resistance (MDR) in these strains has resulted in treatment failures, complications, increased risk of fecal-oral transmission, and a significant rise in morbidity and mortality [7]. Regular periodic monitoring of local antimicrobial resistance trends is a prerequisite for implementing rational measures and updating the therapeutic guidelines [8].

Given the above facts, we undertook this study to assess the prevalence antimicrobial susceptibility pattern and ESBL production pattern of Enteric fever pathogens derived as blood culture isolates at a rural tertiary care centerin western Uttar Pradesh.

Method

This laboratory data-based retrospective cross-sectional was conducted in the Department of Microbiology of a rural tertiary care center of western Uttar Pradesh, India wherein the Laboratory data of blood culture-positive cases of Enteric fever maintained over 2 years from July 2017 to June 2019 was retrieved, reviewed, and analysed to determine the prevalence of culture-proven Enteric fever cases and the antibiotic susceptibility pattern of *S. enterica* isolates. This study was undertaken after seeking approval for the conduct of the study from the Institutional Ethics Committee.

Study population: Our study population comprises of patients attending the Out patients department (OPD) of the hospital with complain of fever.

Inclusion and exclusion criteria

Inclusion criteria: Samples for blood culture collected from clinically suspected cases of Enteric fever before administering antibiotics

Exclusion criteria: Patients already on antibiotics.

Sample size calculation and sampling technique

Sample size was calculated using the formula Sample size = $4pq/d^2$ where p is the prevalence, q is 100-p and d is the precision (acceptable level of error which is 0.05 at 95% confidence interval).

Sampling technique: Purposive sampling

Collection of Blood samples

10 ml venous blood from adult patients and 5 ml from pediatric patients (clinically suspected cases of Enteric fever) were collected aseptically before starting any antimicrobial and inoculated into respective blood culture bottles containing BHI Broth with SPS (Microexpress, India) respectively and transported immediately to Microbiology Laboratory [9].

The inoculated blood culture bottles were incubated aerobically at 37^0C for 24 hrs. Subcultures were made on blood agar and MacConkey agar plates every alternate day till the 7th day [9]. The pale-coloured colonies grown on MacConkey agar depicting Non-lactose fermenters (NLF) were further processed. Isolation, Identification, and characterization of *Salmonella sp.* were done using standard microbiological techniques and biochemical tests followed by Slide agglutination using antisera [10, 11]. A set of following antibiotic discs was applied on a pre-seeded Muller-Hinton agar plate with 0.5 McFarland standard inoculums by modified Kirby Bauer's disc diffusion method and was interpreted as per Clinical and Laboratory Standards Institute (CLSI) guidelines [12]. Ampicillin (10µg), Azithromycin (15µg), Ciprofloxacin (5µg),

Levofloxacin (5µg), Ceftriaxone (30 µg), Cefixime (5µg), Cefotaxime (30µg), Ceftazidime (30µg), Cefipime (30µg), Chloramphenicol (30µg), Cotrimoxazole (1.25/23.75µg), Nalidixic acid (30 µg), Tetracycline (30µg), Amikacin (30µg), Imipenem (30 µg), Aztreonam (30 µg) [Himedia Lab. Pvt Ltd, Mumbai, India]

Detection of extended-spectrum beta-lactamase

Isolates that were found to be resistant to at least two 3rd generation Cephalosporins like Cefotaxime (30µgm) Ceftazidime (30 µgm), Ceftriaxone (30 µgm), etc., were considered to be probable ESBL producers and further screened for ESBL production by Combined Disc diffusion Test as per CLSI 2016 guidelines using Antibiotic discs of Cefotaxime (30 µg) and Ceftazidime (30 µg), Cefotaxime clavulanate (30/10 µg) and Ceftazidime clavulanate (30/10 µg). More than5 mm increase in diameter of the inhibition zone of the Cefotaxime clavulanate and Ceftazidime clavulanate disc compared with the respective cefotaxime and ceftazidime disc alone was interpreted as phenotypic evidence of ESBL production [12].

Data analysis

Data collection and analysis were done using MS Office Excel 2010. Statistical analysis was done using descriptive statistics, presented as frequencies and percentages in tables and graphs. The chi square test was applied to determine the levels of significance (p-value <0.05 was considered significant).

Ethical considerations

The study was undertaken after seeking approval from institutional ethics committee, KD Medical College, Mathura (UP)-India (236/IECBMR/KDMC/2019). Confidentiality regarding the identity and personal information of the patients was maintained.

Result

A total of 512 blood samples were processed for culture sensitivity during 2 years out of which 35 clinical isolates of *Salmonella spp* (0.07%) were obtained. *Salmonella typhi* was predominant with 30 strains (86%) followed by *Salmonella paratyphi A* with 5 strains (14%).

The majority of cases of enteric fever were reported from the 21-30 years age group and least from 51-60 & >60 yrs. Age groups. In this study, Enteric fever cases exhibited male preponderance with male: female ratio being 2.2:1 for all *Salmonella* isolates with 2:1 for *S. typhi* and 4:1 for *S. paratyphi A* **(Table 1).**

Table 1: Age-wise distribution of culture-confirmed Enteric Fever cases

	Enteric fever N (%)		P- value
	Positive	**Negative**	
Sex			
Male	24	245	0.049
Female	11	232	
Age group (in yrs.)			
≤ 10	4	72	0.56
11-20	7	95	0.99
21-30	11	115	0.33
31-40	5	62	0.83
41-50	4	49	0.83
51-60	2	48	0.40
> 60	2	38	0.60

Significance calculated using chi square test with level of significance set at p< 0.05

S. typhi isolates exhibited high sensitivity towards Imipenem (100%) followed by third-generation cephalosporins [Ceftriaxone (96.67%), Ceftazidime (96.67%), Cefixime (93.33%), Cefotaxime (90%)], Monobactums like Aztreonam (90%) and fourth generation Cephalosporins like Cefepime (86.67%). The *S. typhi* isolates were least susceptible to Nalidixic acid with 76.67% of test strains being resistant followed by Tetracycline with a 50% resistance rate **(Fig 1, Table 2).**

The susceptibility pattern of *S. paratyphi A* isolates as depicted in Table 2 and Fig.2 showed the highest susceptibility towards Cefixime, Ceftazidime, Ceftriaxone, Amikacin & Imipenem(100%) followed by Levofloxacin, Cefotaxime, Cefepime and Aztreonam (80%). The highest resistance rates were seen against Nalidixic acid and Azithromycin. Amongst fluoroquinolones, Levofloxacin exhibited modest sensitivity against *S. typhi* and *S. paratyphi* (86.67% and 80%, respectively) (**Fig 2, Table 2).**

Table 2: Antibiotic susceptibility profile of Enteric fever pathogens

Antibiotics tested	*S. typhi* (30)	*S. paratyphi A* (5)	*P-value*
Ampicillin	22 (73.33)	3(60)	0.54
Azithromycin	23 (76.67)	2 (40)	0.09
Ciprofloxacin	21 (70)	3 (60)	0.65
Levofloxacin	26 (86.67)	4 (80)	0.69
Ceftriaxone	29 (96.67)	5 (100)	-
Cefixime	28 (93.33)	5 (100)	-
Cefotaxime	27 (90)	4 (80)	0.5
Ceftazidime	29 (96.67)	5 (100)	-
Cefepime	27 (90)	4 (80)	0.5
Chloramphenicol	24 (80)	4 (80)	1.0
Cotrimoxazole	21 (70)	4 (80)	0.65
Nalidixic acid	7 (23.33)	1 (20)	0.87
Tetracycline	15 (50)	3 (60)	0.68
Amikacin	26 (86.67)	5 (100)	-
Imipenem	30 (100)	5 (100)	-
Aztreonam	28 (93.33)	4 (80)	0.32

Significance calculated using chi square test with level of significance set at p< 0.05

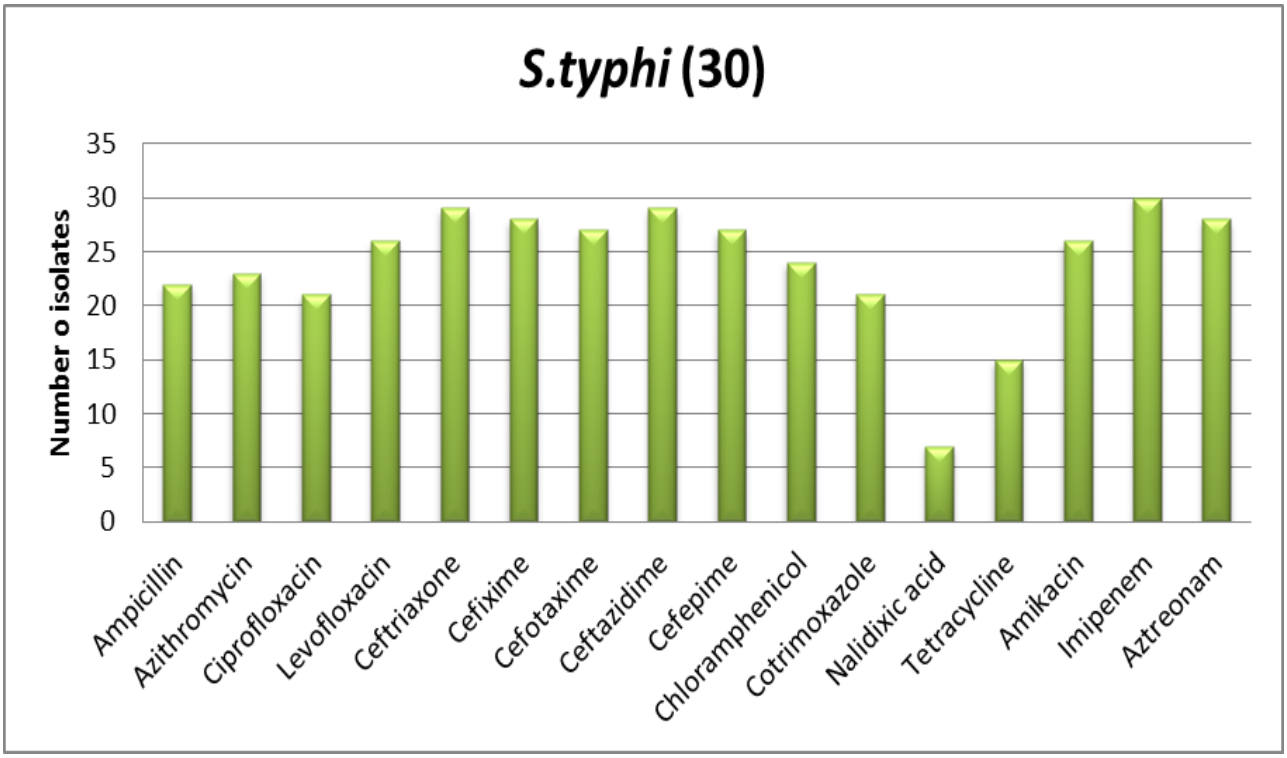

Figure.1: *Antibiotic Susceptibility Pattern of S. typhi strains*

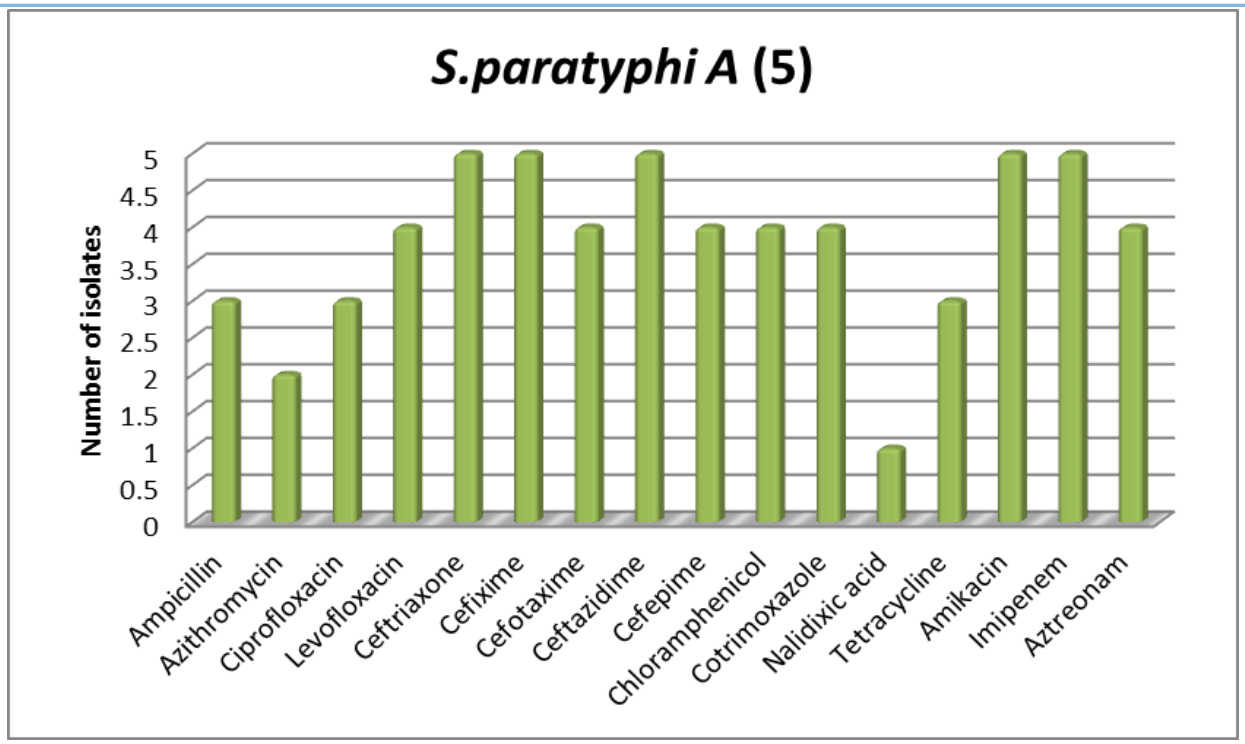

Figure 2: *Antibiotic Susceptibility pattern of S. paratyphi Astrains*

Amongst the 35 isolates, multidrug resistance towards first-line drugs was seen in 6 isolates (17 %) all being *S. typhi* strains. All these MDR strains were also resistant to Nalidixic acid (MDR-NAR). The majority of the test isolates were found to be resistant to Nalidixic acid (NARST) but predominantly susceptible to fluoroquinolones like Levofloxacin. In this study, a much higher Azithromycin resistance rate was seen for *S. paratyphi A* as compared to S. typhi with 60% of strains showing resistance. There was no significant difference in the antibiotic sensitivity pattern of *S. typhi* and *S. paratyphi* A strains (P = 0.325). Some of the important limitations of this study are that the antibiotic susceptibility pattern of *Salmonella spp.* was derived by Standard disc diffusion test with results not confirmed by MIC determination; and that it is a single-centre retrospective study with a limited sample size.

None of the isolates came out to be positive for ESBL production as screened by the combined disc diffusion test (CDST).

Discussion

Amongst the Enteric fever pathogens isolated in our study, *Salmonella typhi* was predominant followed by *Salmonella paratyphi A*, like several similar previous studies [4, 13- 16]. The majority of cases of enteric fever were reported from youngsters in the 21-30 years age group and least from the elderly as reported in a number of similar studies [8, 10, 17-19]. Like our study, several similar studies in the past have also reported male preponderance in culture-confirmed cases of enteric fever [8, 10, 14, 16, 18, 20, 21]. This is probably due to the high vulnerability of males owing to more outdoor exposure.

In our study, *S. typhi*i solates exhibited the highest sensitivity towards Imipenem followed by third-generation cephalosporins, and the least sensitivity to Nalidixic acid and Tetracycline. Similar findings were reported by many studies [16, 19, 22- 28]. Amongst fluoroquinolones Levofloxacin exhibited modest sensitivity against *S. typhi* and *S. paratyphi* (86.67% and 80% resp.) but when compared to previous studies resistance against fluoroquinolones esp. Ciprofloxacin is following an increasing trend due to the selective pressure of unrestricted rampant usage as the mainstay of typhoid therapy [3, 29-33]. None of the isolates came out to be positive for ESBL production as screened by the combined disc diffusion test (CDST). Similar findings were reported previously [10].

Amongst the 35 isolates, multidrug resistance towards first-line drugs was seen in 6 isolates (17 %) all being *S. typhi* strains. All these MDR strains were also resistant to Nalidixic acid (MDR-NAR). These observations were in line with

many similar studies [10, 16-20, 34]. In this study multidrug resistance was not found amongst *S. paratyphi* strains which is consistent with the previous reports [3, 18, 19, 35, 36].

The majority of the test isolates were found to be resistant to Nalidixic acid (NARST) but predominantly susceptible to fluoroquinolones like Levofloxacin. However, it has been suggested that such strains (NARST) should be considered Fluoroquinolone resistant; Nalidixic acid being a surrogate marker to predict FQ failure as per CLSI guidelines. As Nalidixic acid resistance amongst *Salmonella* spp. is rapidly increasing in India, which may lead to the dilemma in the use of Fluoroquinolones considered to be one of the most effective drugs in Enteric fever treatment. But the consistent use of FQ esp. Ciprofloxacin in NA-resistant cases has led to a steady rise in MIC along with further mutations at the same locus which has led to the emergence of completely resistant strains.

In this situation, the Standard disc diffusion test could no longer be relied upon and only MIC determination by any of the available methods like an E-test should be preferred for detecting Ciprofloxacin resistance, particularly in all Nalidixic acid-resistant strains [10]. As per recent therapeutic guidelines for Nalidixic acid sensitive S. typhi (NAAST) strains, a 7-day regime and for NARST a 10-14 days high dose course is recommended [3, 30]. In the MDR-NAR cases, third-generation Cephalosporins and broad-spectrum azilide-azithromycin are potential treatment options. Azithromycin can achieve rapid remission, prevent relapse, and reduce fecal carriage rates through its high intracellular concentration and long elimination half-life. Indian Academy of Paediatrics task force on the management of enteric fever had recommended Azithromycin as an oral drug for uncomplicated enteric fever where initial first-line therapy has failed [3, 37, 38]. But in this study much higher Azithromycin resistance rate was seen for *S. paratyphi A* as compared to *S. typhi* with 60% of strains showing resistance [3, 35].

A low level of multidrug resistance but a high level of Nalidixic acid resistance was reported in this study like many other studies [3, 4, 6, 29, 38-41]. This study has shown re-emergence and an appreciable increase in susceptibility of *Salmonella enterica* strains towards first-line antibiotics attributed to a sharp decline in their usage by clinicians over the last decade resulting in the withdrawal of selection pressure [4, 6, 39]. Loss of self-transmissible plasmids and the emergence of de novo susceptible strains might be the other reasons for anticipating the possibility of reconsidering these drugs as potential therapeutic agents in Enteric fever [3,18,29].

This study has shown a very high susceptibility of test strains towards third-generation cephalosporins like other studies [6, 29]. So, these drugs are often considered as drugs of choice for enteric fever esp. in fluoroquinolone-resistant cases. However, the emergence of Extended-spectrum beta-lactamase and ACC-1 AmpC beta-lactamase-producing strains causing Enteric fever is a serious public health threat resulting from selection pressure due to injudicious inappropriate rampant usage of 3rd generation cephalosporins. With the high levels of resistance being reported against Fluoroquinolones and nalidixic acid this is an alarming situation as it could seriously limit therapeutic options. Therefore appropriate judicious selection and rotation of antibiotics guided by the knowledge of their susceptibility profiles is of utmost importance [3, 6, 16, 42].

Some of the important limitations of this study are that the antibiotic susceptibility pattern of Salmonella spp. was derived by Standard disc diffusion test with results not confirmed by MIC determination; and that it is a single-centre retrospective study with a limited sample size.

Conclusion

This study indicates that first-line antibiotics could now be re-incorporated into enteric fever therapy. It is recommended to determine MIC values for fluoroquinolones before therapy to avoid treatment failures. The third generation cephalosporins should be used judiciously with caution. This study emphasizes the need for blood cultures and antibiotic susceptibility testing for every suspected case of enteric fever. Injudicious, Irrational drug therapy must be restricted through antimicrobial stewardship measures. Appropriate Surveillance strategy for regular continuous monitoring of antimicrobial susceptibility patterns with the formulation of antibiotic policy at the institutional or regional level is an important prerequisite to rationalize enteric fever treatment protocols to curb the menace of rapidly emerging drug resistance amongst such pathogens. Apart from this, improving living conditions, creating public awareness regarding general hygiene, infection control practices, and appropriate

usage of typhoid vaccines will help in controlling typhoid in a community.

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