



# Emergence of Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) Typhoid Fever in Aligarh, Uttar Pradesh: A Case Series

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## ABSTRACT

Salmonella Typhi is a Gram-negative rod which causes enteric fever in humans. The introduction of antibiotics to treat typhoid has considerably improved its outcome, but rising multidrug-resistant (MDR) and extensively drug-resistant (XDR) cases due to injudicious use of antibiotics is a matter of grave concern. This case series presents four cases of XDR typhoid fever from a tertiary care centre in northern India. The patients presented in Pediatrics OPD between June 2022 to August 2022, and were admitted and managed in the Pediatrics ward, Jawaharlal Nehru Medical College, AMU, Aligarh. There were two males and two females with a mean age of  $10.5 \pm 1.73$  years. All the patients presented with fever of more than 10 days duration (median duration of symptom before admission  $13 \pm 5.74$  days, IQR 10.5-20.5) and had been on oral cefixime for enteric fever. But, these patients did not show clinical resolution of fever and other symptoms such as fatigue, weakness etc. After the addition of Azithromycin, patients showed clinical improvement and were subsequently discharged over a period of 6-7 days. We are witnessing rapid emergence of XDR typhi strains across the world particularly in resource limited countries like ours. Azithromycin can be used as safer alternative in both MDR and XDR salmonella bacteremia. Additionally, blood culture should be sent of all suspected patients before start of antibiotics.

**Key words:** Typhoid fever, XDR typhoid fever, MDR typhoid fever, Drug resistant typhoid fever

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## INTRODUCTION

Enteric fever (more commonly known as typhoid fever) remains endemic in many developing countries including India. Enteric fever is caused by a gram-negative bacterium named *Salmonella typhi*. Other serotypes, *Salmonella paratyphi* (A, B, C), also cause similar illness but with less clinically significant disease. Paratyphoid infections constitute about 20% of all cases of enteric fever worldwide. As enteric fever is a disease transmitted by the feco-oral route, its greatest burden is in resource limited countries where access to safe water and sanitation remains elusive. Worldwide, approximately 12–27 million cases of typhoid fever occur annually causing 161,000 deaths (1-2).

Typhi isolates are defined as MDR if they are resistant to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole, and as XDR if they are MDR, non-susceptible to fluoroquinolones, and resistant to third-generation cephalosporins. The world witnessed its first case of Extensively Drug Resistant Typhoid Fever (XDR-TF) in the year 2016 when Pakistan's second most populated province Sindh reported a large number of blood-culture confirmed Typhoid Fever (TF) cases that were nonresponsive to conventional antibiotic therapy (3). Since then, a total of 14,360 XDR typhoid fever cases have been reported in Karachi and another 5,741 confirmed cases of XDR typhoid fever have been reported from Sindh province (4).

Since the emergence of the drug resistant cases in Pakistan, emerging trend of MDR and XDR typhoid fever has been reported across the world. A meta-analysis reported a rising trend of resistance in Iran (5). In India, the incidence of multidrug-resistant (MDR) typhoid cases has been reported to be 7% (6). Resistance to fluoroquinolone group of antibiotics is becoming extremely prevalent in India (7-8). Ceftriaxone resistant strains have also been identified sporadically in India (9). Manas Pustake et al (2022) in their recent article note: 'even though very few ceftriaxone-resistant cases have been reported in India to date, in clinical practice, we have encountered numerous ceftriaxone unresponsive cases. Such cases go unreported due to insufficient workup, patients' financial

constraints, and a lack of proper enforcement of national surveillance policies (10).

Here we present a case series of Typhoid fever cases which seems to support their observation.

## METHODS

We included patients with fever of more than 10 days duration who were Widal positive and culture positive for *S. typhi*. The patients presented in Pediatrics OPD between June 2022 to August 2022, and were admitted and managed in the Pediatrics ward, Jawaharlal Nehru Medical College, AMU, Aligarh.. Detailed general and systemic examinations were performed and routine investigations along with Bactec for culture sensitivity of blood sample were sent. Hematological parameters such as reticulocytopenia, anemia, thrombocytopenia and leukocytopenia were taken as significant hematological involvement.

During the study period around 85 more patients of Typhoid were admitted, they were either culture negative or drug sensitive.

### Antibiotic Susceptibility Test

Blood culture sample was first processed through BacT/ALERT microbial identification system for detecting the presence of microorganism. Subsequently the sample was evaluated with VITEK system to identify the organism and its antibiotic susceptibility. The isolates were tested against a panel of the following antibiotics- amoxicillin, ampicillin, chloramphenicol, ciprofloxacin, ceftazidime, cefuroxime, ceftriaxone, imipenem, meropenem, cefoperazone, sulbactam, trimethoprim-sulphamethoxazole, Tigecycline, colistin and piperacillin/tazobactam.

### Statistical Analysis

Descriptive statistics were used to summarise the results. For description of quantitative variables, mean and standard deviation or median and Interquartile range (IQR) were used. For Categorical variables, counts and percentages were used.

### Ethics

Informed consent was obtained from all the participants and their guardians for the publication of information in this article



## **Description of Cases**

### **Case 1**

A 12-year-old fully vaccinated male child presented with complaints of fever on and off and generalized weakness for 3 weeks. He was previously treated as probable enteric fever on OPD basis and had received oral cefixime in enteric dose for 1 week. Physical examination revealed fever, tachycardia, lethargy and mild right hypochondrial tenderness. Rest of the examination was normal. Investigations were sent and patient was started on parenteral ceftriaxone. Routine blood investigations, CXR, RDT/MPS, Dengue serology returned normal results. After 48 hours of parenteral ceftriaxone, fever intensity remained the same. Empiric 2<sup>nd</sup> line antibiotic azithromycin was added to the treatment. Patient starts improving and bactec reports comes to be positive for Salmonella which was resistant to ceftriaxone and other 3<sup>rd</sup> generation cephalosporins (Table 2).

### **Case 2**

This 11-year-old female presented with fever and loose stools on and off for 10 days. She has been experiencing nausea and tiredness for the last 5 days. General and systemic examination was normal at the time of presentation. Patient was admitted for workup and parenteral ceftriaxone was started. Blood sample for culture-sensitivity was sent along with other pertinent investigations. Lymphocytic predominance was noted on complete blood count and WIDAL test was positive. Other investigations i.e. RDT/MPS, LFT, dengue serology and CXR-PAV were normal. On the third day of admission Azithromycin was added to the treatment empirically as the fever peaks were persisting. Blood culture-sensitivity report revealed resistance to all first- and second-line drugs including ceftriaxone. The patient improved after addition of oral Azithromycin and was discharged on the 7<sup>th</sup> day.

### **Case 3**

An 11-year-old boy presented in the OPD with fever for the last 23 days and has been experiencing weakness and fatigue for the last 2 weeks. He has been treated before at three different health facilities but was not relieved. On examination the patient was febrile and rest of the examination was normal. Patient was admitted, parenteral ceftriaxone and oral azithromycin was given empirically. Routine blood investigations, CXR, RDT/MPS, and Dengue serology were found to be normal. WIDAL returned positive result. Culture report yielded positive result for *S. typhi* which was resistant to 1<sup>st</sup> and 2<sup>nd</sup> line drugs (Table 2). Patient improved gradually on treatment and was discharged on the 7<sup>th</sup> day.

### **Case 4**

The fourth case was an 8-year-old fully vaccinated and nutritionally appropriate female child, who was brought to pediatric emergency with complaints of fever for 2 weeks, generalized weakness, nausea, vomiting and excessive sleepiness. She was diagnosed as typhoid fever on the basis of Widal report at a private hospital and received oral cefixime. At the time of presentation to pediatric emergency, fever, tachypnea and tachycardia were present. On CNS examination she was stuporous and planter response was extensor. Rest of the systemic examination was within normal limit. Investigations were sent, patient was started on IV fluid, intravenous ceftriaxone and later azithromycin was added due to unresponsiveness to monotherapy. Later, blood culture-sensitivity report returned positive result for Salmonella ser. Typhi. The organism was resistant to the conventional 1<sup>st</sup> line and 2<sup>nd</sup> line typhoid drugs including FQs (Table 2).

Table 1 A summary of cases of drug resistant enteric fever

	Case 1	Case 2	Case 3	Case 4	Summary
Age (year)/sex	12/M	11/F	11/M	8/F	
Time of presentation (days of illness)	14	10	23 days	12 days	Median 13 days
Fever duration(days)	14	10	23 days	12 days	Median 13 days
GI and hepatobiliary	+	+	-	+	75%
CVS	+	-	-	+	50%
CNS	+	+	+	+	100%
Respiratory system	-	-	-	-	0%
Hematologic ( $\geq 2$ cell line affected)	+	+	+	+	100%
Duration of hospital stay	6 days	7days	7days	7days	Median 7 days
Outcome	Improved	Improved	Improved	Improved	
Follow up at 1 week	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic	
Follow up at 4 weeks	Asymptomatic	Asymptomatic	Asymptomatic	Asymptomatic	

## RESULTS

The demographic and clinical characteristics of the 4 patients in our case series is presented in table 1. There were two males and two females with a mean age of  $10.5 \pm 1.73$  years. All the patients presented with fever of more than 10 days duration (median duration of symptom before admission  $13 \pm 5.74$  days, IQR 10.5-20.5) and had been on traditional antibiotic treatment for enteric fever. But, these patients did not show clinical resolution of fever and other symptoms such as fatigue, weakness etc. The patients were readmitted for further workup and Azithromycin in enteric dose was added empirically to their treatment during the course of admission. All the patients returned positive WIDAL test and blood culture yielded presence of Salmonella typhi. The Antibiotic sensitivity

profile of the isolates is presented in table 2. All the isolates were found resistant Ampicillin and 3 of 4 (75%) isolates were resistant to Trimethoprim/sulfamethoxazole. Complete resistance to even Ceftriaxone and Ciprofloxacin was detected. After the addition of Azithromycin, patients showed clinical improvement and were subsequently discharged over a period of 6-7 days. The dosage of Azithromycin for drug resistant Typhoid preferably in single dose is 20 mg/kg/day (maximum dose 1gm/dose) divided over two doses but may be divided over 2 doses for 5-7 days. The patients were followed up weekly for 1 month of duration and none of the patients developed relapse.

Table 2 culture report and antibiotic sensitivity profile

Antibiotic	Case 1	Case 2	Case 3	Case 4	Total Resistance%	Total % sensitivity
Ampicillin	R	R	R	R	100%	0
Amoxicillin/Clavulanic acid		R	S	S	33%	66%
Piperacillin/Tazobactam	R	R	I	R	75%	25%
Cefuroxime	R	R	R	R	100%	0
Cefuroxime axetil	R	R	R	R	100%	0
Cefotaxime	R	R	R	-	100%	0
Ceftriaxone	R	R	R	R	100%	0
Cefoparzone/ Sulbactam	R	R	-	I	66%	33%
Cefepime	SDD	SDD	-	S	0%	100%
Imipenem	-	R	S	R	66%	33%
Meropenem	S	S	S	R	25%	75%
Amikacin	R	S	R	R	75%	25%
Gentamicin	R	S	R	S	50%	50%
Ciprofloxacin	R	R	R	R	100%	0
Tigecycline	-	S	S	R	33%	66%
Colistin	-	-	I	I	0%	100%
Trimethoprim/ sulfamethoxazole	R	R	S	R	75%	25%

**Abbreviations: I= Intermediate, R= Resistant, S=sensitive, SDD= Susceptible dose dependent, I&SDD taken as sensitive strain**

## DISCUSSION

With the introduction of antibiotics, the prevalence of typhoid fever has declined, but alarmingly, the causative agent has gradually developed resistance to multiple drugs over the years. Figure 1 shows proportion of *Salmonella typhi* isolates becoming resistant to antimicrobials in Asia over the last four decades. The rising resistance to the traditionally first line antibiotic treatment led to the use of fluoroquinolones (e.g., ciprofloxacin) group as the first-line treatment (11). However, since the early 2000s, increasing fluoroquinolone non-susceptibility (intermediate or full resistance to ciprofloxacin), particularly in South Asia, has led to the use of third-generation cephalosporins (e.g., ceftriaxone) as the first-line treatment. In

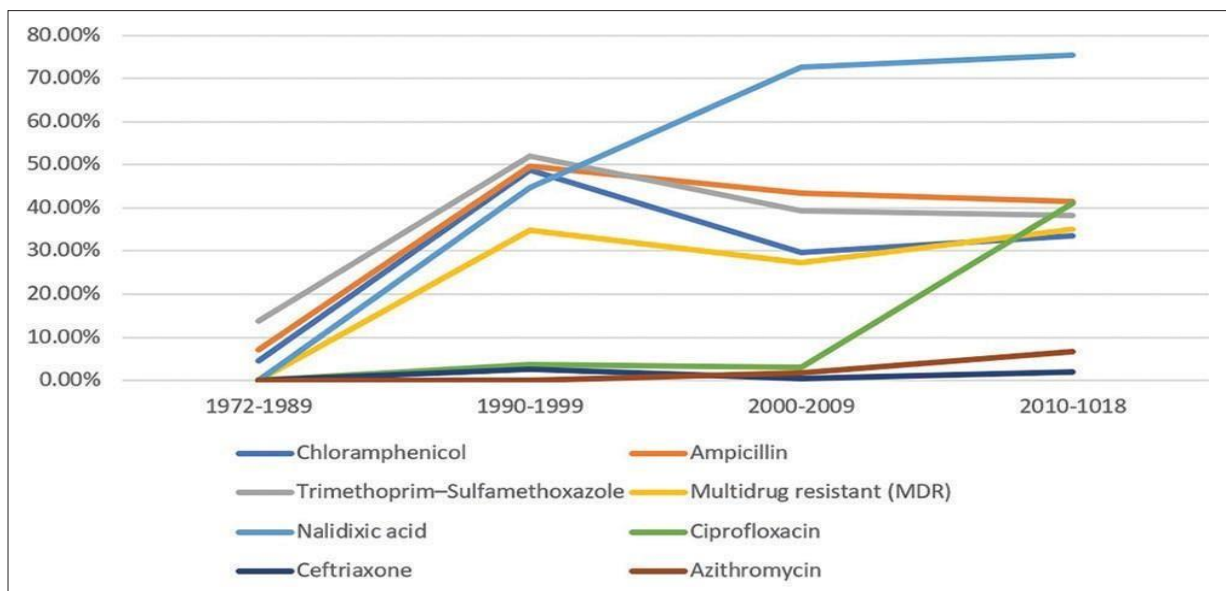
this case series we included patients who were not responsive to the recommended first and second line antibiotics for enteric fever and subsequently (on antibiotic susceptibility report) resistance to fluoroquinolones and third generation cephalosporins was observed. With the emergence of fluoroquinolone non-susceptible strains that are also resistant to third-generation cephalosporins, such as ceftriaxone treatment of typhoid fever becomes difficult. The XDR Typhi strain is only susceptible to azithromycin, carbapenems and tigecycline (3). In this case series we have observed clinical improvement in patients after the addition of Azithromycin (in a dose 20mg/kg/day in two divided doses for 7 days) to the treatment.

Azithromycin dosing for typhoid fever is higher than the dosage for more routine indications (12). We suggest that empirically Azithromycin should be used to treat patients with suspected uncomplicated typhoid fever while culture-sensitivity report is awaited or in resource limited settings where culture-sensitivity could not be done. Patients with suspected severe or complicated typhoid fever (which includes encephalopathy, intestinal perforation, peritonitis, intestinal hemorrhage, or bacteremia with sepsis or shock) may be treated with a carbapenem on the basis of sensitivity pattern (12). Treatment regimens can further be

adjusted when culture and sensitivity results are available.

Pakistan became the first country to introduce new typhoid vaccine into its routine immunization programme after rapid spread of drug resistant cases in huge numbers across the country (13). With the current trend of rising resistance globally and shrinkage of options for antibiotic therapy, other countries may consider introducing typhoid vaccine in their routine immunization programs.

Figure 1: Salmonella typhi isolates developing resistant to antimicrobials in Asia over the last four



decades (Marchello *et al.*, 2000)

## CONCLUSION

We are witnessing rapid emergence of XDR typhi strains across the world particularly in resource limited countries like ours. Azithromycin can be used as safer alternative in both MDR and XDR enteric fever. Additionally, sending blood culture prior to starting of antibiotics might be a potential best step for both rational management of the patient as well as prevention of emergence of drug resistant Salmonella infection. With the current trend of rising resistance, there's a potential for outbreaks and hence the need for surveillance, infection control measures, and public health

education. Also, there's a need for continuous research into the epidemiology, pathogenesis, and clinical management of MDR and XDR enteric fever, and the development of new diagnostic tools as well as regular update regarding treatment strategies.

## LIMITATION

Azithromycin was not part of the antibiotic susceptibility VITEK cassette, it was added empirically to the treatment and the suggestions have been made based on the clinical improvement.

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