CASE REPORT

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Extended Drug Resistant Typhoid Fever; A Case Report

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Abstract

Enteric fever is a potentially fatal multisystem illness caused primarily by *Salmonella typhi* and, to a lesser extent, by Para typhi A, B, and C. Decades of indiscriminate usage of Antibiotics has led to emergence of multiple resistant strains. Multi drug resistant strains against *Salmonella typhi* has made treatment options limited and costly.

According to WHO an estimated 11–20 million people get sick from typhoid all over the world. In the year 2022 an outbreak of Enteric fever emerged in April and spread all over Pakistan. This created a great concern as the causative organism were mostly Multi drug resistant. We recently have documented a case of extended drug resistant (XDR) Enteric Fever with a complicated clinical course, responding only to Carbapenem (Meropenem/Imipenem). The purpose of reporting this case was to highlight the morbidity, cost and therapeutic challenges which are associated with severe XDR *S. typhi* infection in Pakistan.

Keywords: Typhoid, COVID-19, Water Sanitation, Healthcare, Vaccine, Pakistan.

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Introduction

Typhoid fever, or enteric fever is a potentially fatal multisystem infection produced primarily by *Salmonella enterica* serotype *typhi* and to a lesser extent *S. enterica* serotypes and paratyphi A, B, and C.[1] Salmonella are motile enterobacteriaceae that can produce a variety of gastrointestinal infections.[2] It presents in a wide variety of ways ranging from an overwhelming septic illness to minor cases of diarrhea with low-grade fever.[3] It spreads through feco-oral route. Contamination of food usually occurs due to poor sanitation and sewerage water being mixed with drinking water.[1,2] Incubation period depends upon inoculum size and host factor ranging from 3-60 days with an average of 8-14 days.[6]

Case Presentation

A 24 year male, resident of Islamabad, presented to Medical OPD on 6th May, 2022 with complaints of fever, nausea and vomiting for 2 weeks. Patient was in his usual state of health until 2 weeks before admission when he developed fever which was high grade, documented up to 104 ˚F, intermittent, associated with rigors, chills, loose stools, nausea and vomiting. There was no H/O abdominal pain, cough or urinary symptoms. He denied any history of skin rash and recent travel. He was advised Cefpodoxime (3rd Generation Cephalosporin) 100 mg BD per oral for 5 days in OPD at another hospital. Loose stools settled after 3 days, however, even after 5 days of antibiotics, he remained febrile. He was also prescribed antimalarials for three days (Artemether/Lumefantrine) without any benefit.

He was a doctor by profession and resided in a hospital hostel. He has no pre morbidities and his family history was insignificant.

On Examination his vital signs were; pulse 100 beats/min, B.P = 120/80 mmHg, Temp 102 °F, Respiratory rate 20/min and oxygen saturation was 97 % on room air. On GPE, no lymphadenopathy, jaundice or pallor was present. Abdominal examination showed soft, non-tender abdomen with mild splenomegaly, shifting dullness was absent. The rest of the systemic examination was unremarkable. His investigations were

as follows (Table 1):

Table 1: Investigation follow-up for patients

Lab Investigations	Follow-up (Dates)					
	9/5/2022	6/5/2022	4/5/2022	3/5/2022	1/5/2022	29/4/22
TLC	10.6	6.5	7.1	5	6.9	7.2
Hb	11.8	13.8	12.8	12.3	14.8	16.2
Platelets	336	228	131	107	145	341
Neutrophils (%)	80	70	63	62	70	68
Lymphocytes (%)	18	25	30	31	22	22
ALT	71	58	-	-	-	-
CRP	76.6	-	-	-	-	-

His serum creatinine, urine R/E and CXR were with normal range. His MP smear and dengue serology were negative. Ultrasound was normal except a mild splenomegaly.

Patient was admitted in ward with working diagnosis of suspected Enteric Fever and was started on I/V Ceftriaxone 1 gram BD and oral Azithromycin 500 mg OD. Blood C/S report received on 2nd day of admission which showed no growth. Another sample of blood was taken and sent for culture and sensitivity. However, the patient continued to spike fever as shown in the graph below.

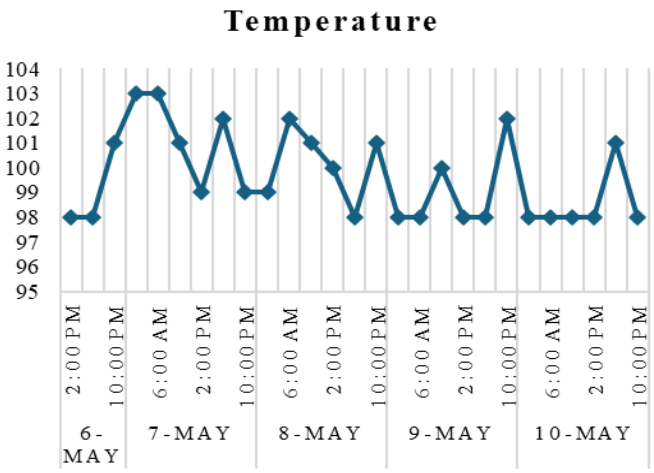

Figure 1: Pattern of patient rise in temperature (fever)

Extensively Drug Resistant (XDR) Enteric Fever was suspected on fourth day due to poor drug response. Hence patient was started on IV Meropenem at the dose of 1-gram IV TDS. IV ceftriaxone and oral Azithromycin were discontinued. On 6th day of admission, Blood C/S report was received which showed growth of *Salmonella Typhi* (XDR strain) sensitive only to Carbapenems (Meropenem/Imipenem) (Table 2).

His condition improved after Meropenem and frequency of fever spikes decreased. After 3 days he was afebrile. Meropenem was continued for a week during his hospital stay. Patient was discharged and was advised IV Meropenem for further week. Follow up showed complete recovery.

Table 2: Blood culture sensitivity test for *S. typhi*

Antibiotic	Results	Antibiotic	Results
Amoxicillin / Clavulanic Acid (Augmentin)	R	Ampicillin	R
Azythromycin (Azythrocin)	R	Chloramphenicol	R
Ciprofloxacin (Ciproxin)	R	Co-trimozole (Septran)	R
Imipenem	S	Piperacillin-Tazobactan (Tazocin)	R

*S – Sensitive, *R – Resistance

Discussion

According to WHO classification of Enteric fever non-resistant cases are those who are sensitive to first line drugs (amoxicillin / ampicillin, co trimoxazole and chloramphenicol) and 3rd generation cephalosporin with and without resistance to second line drugs.[6] Multi drug resistant are those who are resistant to first line drugs with and without resistance of second line drugs. Extended drug resistance are those who are resistant to all recommended antibiotics of typhoid.

The outbreak of Multi drug Resistant typhoid (XDR *S.*) in Pakistan have become an alarming public health

concern. National Institute of Health (NIH) Islamabad reported a total of 14,360 XDR-TF from January 2017 till June 2021 in Karachi alone, and from November 2016 to June 2021, a total of 5,741 confirmed cases of XDR-TF in all districts of Sindh province (excluding Karachi), while 69.5% cases were reported from District Hyderabad.[5]

Pakistan has been in an ongoing struggle against XDR-TF for almost 5 years now and this year also many cases have been reported. Our patient was also a suspected case of enteric fever and he did not respond to first line drugs with resistance for azithromycin. His first culture turned out to be negative, taken at the first week of illness when patient was already taking 1st generation cephalosporin. The second culture was send at the start of second week after stopping antibiotics for 48 hours confirmed *Salmonella Typhi* resistant to all first and second line drugs, with sensitivity only to carbapenem alone. He responded well to carbapenem IV and his fever settled after 3 days dose. He was advised to complete injectable treatment for 14 days to prevent recurrence and carrier state.

Our patient had XDR *S. typhi* strain that was resistant to five classes of antibiotics, i.e. chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones, and third-generation cephalosporin.[4] He was also resistant to Azithromycin which is usually reserved for resistant cases only. Since COVID 19 infection, the health care professionals are frequently prescribing Azithromycin for patients with symptoms of upper respiratory tract infections. This could be one of the factors for the emergence of resistance against azithromycin and also adds up to the cases of XDR Typhoid. This calls for adoption of a rational and evidence-based approach to prescribe Azithromycin in COVID infections.

Conclusion

Enteric fever is highly prevalent in Pakistan, and we should keep it in differential diagnosis of acute febrile syndromes. Despite of worldwide surveillance and improved diagnostic efforts, the diagnosis of Enteric fever by laboratory and clinical examination has low sensitivity so blood and stool cultures should be taken properly for accurate diagnosis.

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Authors Contribution:

[1,4,6]Substantial contributions to the conception or design of the work;

[2,3,4,5]the acquisition, analysis, or interpretation of data for the work & Final approval of the version to be published

[1,5,6] Drafting the work or revising it critically for important intellectual content.