

Case of Extensively Drug-Resistant (XDR) Typhoid with Resistance to Azithromycin

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ABSTRACT:

An 18-year-old boy from Haripur, Pakistan was diagnosed with extensively drug-resistant (XDR) typhoid fever after presenting with acute febrile illness. Blood culture confirmed the isolates of *Salmonella Typhi*. Antimicrobial susceptibility testing revealed that the isolates were extensively drug-resistant (XDR) to all the first line antibiotics in addition to azithromycin. Only a few antibiotics such as meropenem, colistin and tigecycline were found effective against the bacterium. Empirical therapy with a first line antibiotic failed to treat the infection. After the antimicrobial susceptibility report, the patient was managed successfully with a costly course of meropenem. Azithromycin and carbapenem are the two antibiotics that are recommended to treat XDR typhoid fever. Therefore, resistance to azithromycin is a worrying sign, limiting the treatment options against XDR typhoid, and increasing the cost of therapy as well as the complications.

Keywords: Azithromycin, Extensive Drug-Resistance (XDR), *Salmonella Typhi*, Typhoid fever

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INTRODUCTION:

Typhoid fever, is a bacterial infection caused by *Salmonella Typhi*.¹ In 2021, there were estimated 9.3 million cases of enteric fever and 107.5 thousand deaths worldwide.² The highest number of cases and deaths were reported from South Asian countries.² In Pakistan, the incidence rate was 493.5 per 100,000 cases in 2018, which has drastically increased after emergence of new extensively drug-resistance (XDR) typhoid outbreaks in subsequent years.³

Salmonella Typhi is a Gram-negative bacillus that is transmitted through ingestion of contaminated food or water. Upon reaching the small intestine, bacteria penetrate the mucosal epithelium causing acute infection and enters the bloodstream through lymphatic drainage from mesenteric nodes.⁴ Symptoms usually begin 7-14 days after exposure. The clinical presentation of typhoid fever varies from a mild febrile illness with headache, abdominal discomfort, dry cough or constipation to life threatening complications such as intestinal perforation, bleeding, hepatitis, meningitis,

nephritis, osteomyelitis, septic shock etc which usually develop in third or fourth week of infection. Typhoid fever causes variable leucocyte and platelet count. Liver transaminases may be raised. The definite diagnosis of typhoid fever is made through isolation of organism mostly through blood culture.¹ However, bacterium can be identified in stool, urine or bone marrow culture depending on duration of illness.

Due to emergence of resistant isolates of *Salmonella typhi*, the choice of antibiotics is changing rapidly, especially fluoroquinolones and third generation cephalosporins are no longer effective against XDR isolates. XDR isolates are resistant to all antibiotics except few such as azithromycin, meropenem or tigecycline in most cases.⁵ However, cases of typhoid fever with XDR isolates resistant to azithromycin⁶ and carbapenem⁷ have been reported. Hence, the choice of antibiotic to treat XDR typhoid has been narrowed to few antibiotics, which are costly and sometimes inaccessible in developing countries like Pakistan. Transmission of typhoid fever can be prevented by clean food and water supply, proper sanitation and vaccination especially in endemic areas. Health education is crucial to aware public about good hygiene and to induce mass behavioural change.

This case report is presented to alert the health community and decision makers about increasing burden of XDR typhoid cases with extended resistance to more antibiotics. There is need to address the underlying causes that are rendering life-saving antibiotics ineffective against this prevalent bacterial infection.

Case Presentation:

18-year-old boy studying in a high school of district Haripur,

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Pakistan presented to a local hospital in August 2024 with high grade fever, headache, lethargy and abdominal discomfort. There was no history of any chronic disease. However, he reported recurrent upper respiratory tract infections over the last 5 years, for which he received multiple courses of antibiotics such as amoxicillin, azithromycin, fluoroquinolones etc. He also received 3 days course of unknown parental antibiotic during a severe episode of acute pharyngitis. He had completed vaccination schedule for children. His younger sister was admitted twice in hospital for typhoid fever.

The boy was admitted to the medical ward. On physical examination, the patient was ill-looking and dehydrated with temperature of 105 °F, relative bradycardia (86 per min) and mild tenderness in right hypochondrium. Investigations including blood culture and drug sensitivity testing were ordered. Leukocyte count was 10800 cells/ μ L with relative lymphocytosis (46%). Alanine transaminase (ALT) was two times above the upper limit of normal. C-reactive protein (CRP) was raised. Empirical therapy was started with intravenous ceftriaxone 2-gram once daily. In addition, intravenous fluid and antipyretic were infused to relieve the symptoms. Frequent cold sponging was done to lower the body temperature close to normal. Blood culture revealed the isolates of *Salmonella Typhi*. Drug sensitivity report showed that the isolates were resistant to ampicillin, cotrimoxazole, chloramphenicol, third-generation cephalosporins, fluoroquinolones and azithromycin, with sensitivity to meropenem, tigecycline and colistin, as shown in Table-I. Treatment was modified to intravenous meropenem 1-gram every 8 hours. The fever subsided within 48 hours after the initiation of meropenem injection. The antibiotic course was continued for 10 days.

The patient was improved and discharged with advice on personal hygiene, clean food and boiled drinking water, proper sanitation and typhoid vaccination. Follow-up with infectious disease specialist was recommended for future deliberations.

Blood Culture	Isolates of <i>Salmonella Typhi</i>
Antimicrobial	Drug Sensitivity Result
Drug	(R=Resistant, S=Sensitive)
Ampicillin	R
Cotrimoxazole	R
Chloramphenicol	R
Ceftriaxone	R
Ciprofloxacin	R
Azithromycin	R
Meropenem	S
Colistin	S
Tigecycline	S

DISCUSSION:

The first case of extensively drug-resistant (XDR) typhoid fever emerged in Sindh province of Pakistan in 2016, where the outbreak of cases refractory to treatment by first line antibiotics occurred.⁸ Compared to multi-drug resistant (MDR) typhoid resistant to ampicillin, cotrimoxazole and chloramphenicol, XDR isolates have extended resistance to fluoroquinolones and third generation cephalosporins.⁵ The recommended options to treat XDR typhoid have been contracted to carbapenem and azithromycin. However, there are case reports depicting resistance to azithromycin⁶ and carbapenem⁷ as well.

Several factors have contributed to development of XDR strains. Misuse of antibiotics is a major factor in countries like Pakistan where the availability of over-the-counter medicines, overuse of antibiotics for minor febrile illnesses and incomplete treatment course are complicating the problem. Poor sanitation and faecal contamination of water supply allows the spread of resistant strains. In addition, low literacy rate, lack of typhoid vaccination and foreign travel to endemic areas are contributing factors as well.⁹ Genetic basis for resistance to antibiotics involve chromosomal mutations and acquiring plasmids having resistance genes.¹⁰

This case report is worrisome where the XDR isolates of *Salmonella Typhi* were found resistant to azithromycin in addition to all first line antibiotics. The finding reinforces the earlier case reports by Octavia S, *et al*⁶ and Nizamuddin S, *et al*⁷, about increasing resistance to antibiotics that were useful against XDR typhoid. History of the case suggests the liberal use of antibiotics to treat episodes of acute upper respiratory tract infections that might have been caused by viruses. The bacteria developed mutations to resist the action of antibiotics, gradually leading to isolates which were able to survive against potent antibiotics such as azithromycin.

Knowingly, a pro-active and exclusive strategy is needed to address the problem on emergency basis. Government needs to ensure clean drinking water and proper sanitation to prevent contamination of water supply with faecal matter. There should be implementation of food safety regulations to ensure healthy food at hotels and local shops. Antibiotics should be issued only with a doctor's prescription and the duration of treatment should be completed. Integration of conjugate typhoid vaccine in national vaccination program is strongly advocated. Health education should promote public awareness about personal hygiene.

The case report emphasizes the need to report and study more resistant cases refractory to treatment by antibiotics that were previously effective against XDR typhoid. This will create public campaign to address fore-mentioned problems responsible for antibiotic resistance.

CONCLUSION:

We found that the cases of XDR typhoid resistant to potent antibiotics are increasing, limiting treatment options that will add to cost of therapy, complications and mortality. Measures to improve public awareness, personal hygiene, sanitation and vaccination can control the situation.

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Authors Contribution:

Naeem Ullah: Conceptualization of study design, Literature research, Drafting of Discussion and Conclusion, Proof reading, Final Approval

Aneeqa: Collection of Patient's data, Drafting of Case Report, Proof Reading, Final Approval

Rafia Khurshid: Literature review, Drafting of Table, Proof Reading, Final Approval

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