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CASE SERIES

Shedding Light on Drug-resistant Enteric Fever: A Case Series

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Abstract

Enteric fever, an acute generalized bloodstream infection of the reticuloendothelial system caused by the human-restricted bacterial pathogens *Salmonella enterica* serovars Typhi (*S. typhi*) and Paratyphi A, is an important cause of morbidity and mortality in the developing world.[1] Aggressive use of antibiotics empirically has resulted in the development of multi-drug resistant organisms (MDR) – (resistant to ampicillin, co-trimoxazole, and chloramphenicol) followed by extensively drug-resistant (XDR) *S. typhi* strains (resistant to chloramphenicol, ampicillin, co-trimoxazole, fluoroquinolones, and third-generation cephalosporin).[2] In this case series, we report three blood culture-positive cases, out of which one was a culture-proven extensively resistant case that did not respond to ceftriaxone (3rd generation cephalosporin) but showed clinical response to cefepime (4th generation cephalosporin) while the other two were clinically resistant cases that showed no response to cephalosporins but responded to meropenem while the organism was sensitive to both drugs.

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Introduction

Enteric fever is a systemic febrile illness of the reticuloendothelial system with a predilection for intestinal lymphoid tissue and gallbladder caused by the pathogens *Salmonella enterica* serovars Typhi (*Salmonella typhi*) and Paratyphi A. Lack of availability of clean water, sanitation, and poor personal hygiene contribute to the prevalence of typhoid fever. Over the years, *S. typhi* has developed a resistance to previously used antibiotics, creating multi-drug resistant (MDR) strains. Multidrug-resistant typhoid fever (MDRTF) is defined as typhoid fever caused by *S. enterica* serovar Typhi strains (*S. Typhi*), which are resistant to the first-line recommended drugs, i.e., chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole while extensively drug-resistant typhoid fever (XDRTF) is defined as *S. typhi*/ Paratyphi resistant to first-line antibiotics (ampicillin, chloramphenicol, and cotrimoxazole) and also to fluoroquinolone and ceftriaxone.[3]

According to recent reports, around 21 million people contract enteric fever each year, causing 161,000 deaths. The incidence of multidrug-resistant (MDR) typhoid cases in a recently reported study in India was about 7%.[2]

Enteric fever is mainly diagnosed clinically based on history and physical examination. Blood culture is the gold standard to confirm the diagnosis by isolating

the organism and testing antimicrobial sensitivity. However, a negative culture does not exclude the diagnosis.

Case 1

A 5-year-old female child presented to us with complaints of fever, pain abdomen, loose stools, vomiting with poor oral intake for 7 days. The patient was vitally stable and on abdominal examination, hepatosplenomegaly was present. The patient was admitted and evaluated with complete blood count, C- reactive protein, liver function test, renal function test, viral markers, routine urine examination, widal test & paired blood culture, and sensitivity done by broth dilution by turbidimetric assay.

Initial reports were as follows – Hb- 9.2 g/dL, TLC – 3100 cells/mm^3, DLC – N80/L13/E1/M6, deranged liver function test -SGPT – 169 U/L, SGOT – 61 U/L, S. bilirubin – 1.22/0.6/0.62, CRP – 27.38 mg/dL, widal – O, H titres – 1:320, viral makers were non-reactive, renal function tests and urinanalysis was normal.

The child was started with inj. ceftriaxone along with supportive treatment. The child continued to have fever spikes up to 101°F for 7 days after which blood culture showed growth of Salmonella ser. Typhi which was resistant to inj. ceftriaxone. The antibiotic was changed to inj. cefepime according to sensitivity. The child became afebrile after 3 days of receiving inj. cefepime, showing dramatic improvement in appetite and general condition.

Rapid Automated Aerobic Blood Culture and Sensitivity

Selected Organism Salmonella ser. Typhi

Amoxycillin/ Clauvulanic acid S(MIC-8)
Amikacin R(MIC-4)
Cefuroxime S(MIC-4)
Ceftriaxone R(MIC-32)
Ciprofloxacin R(MIC >4)
Cefepime S(MIC <0.12)
Colistin I(MIC <0.5)
Ertapenem S(MIC <0.12)
Fosfomycin S(MIC <16)
Gentamycin S(MIC <1)
Meropenem R(MIC-8)
Trimethoprim/ Sulfamethoxazole R(MIC > 320)

CASE 2

A 2-year-old, female child was admitted with complaints of fever for 7 days, loose stool 7 to 8 episodes/day for 4 days, and vomiting for 4 days. On examination, she was conscious, febrile with a temperature of 101°F had tachycardia, and pallor. On per abdominal examination, the abdomen was soft, and non-tender while no organomegaly was present. All other systems were within normal limits.

She was admitted and investigations were sent including paired blood cultures which were as follows- Hb 7.6 mg/dL, TLC 7200 cells/mm^3, N 41%, L 58%, platelet -2.41 lac, B. urea - 22, s. creatinine 0.15, LFT-SGOT 40, SGPT 17, s. bilirubin 0.18, ALP 81, sodium 132, potassium 4.11, CRP 12.03, ESR 67. Widal was positive.

IV ceftriaxone was started along with other symptomatic treatments but the patient had continuous fever. Azithromycin was added on day 4, and IV ceftriaxone was continued but the patient had no relief in fever. On the 7th day of admission, the blood culture showed growth of Salmonella typhi sensitive to ceftriaxone.

Rapid Automated Aerobic Blood Culture and Sensitivity

Selected Organism Salmonella ser. Typhi

Amikacin R(MIC < 1)
Aztreonam S (MIC <1)
Cefuroxime S(MIC-4)
Ceftriaxone S(MIC-32)
Ciprofloxacin R(MIC -1)
Cefepime S(MIC <0.12)
Colistin I(MIC <0.5)
Fosfomycin S(MIC <16)
Gentamycin R(MIC <1)
Imipenem S(MIC <0.25)
Meropenem S(MIC <0.25)
Minocycline S(MIC-2)
Piperacillin/Tazobactam S(MIC <4)

Trimethoprim/ Sulfamethoxazole R(MIC > 320)

IV ceftriaxone was continued for 3 more days according to culture sensitivity report but the child

showed no clinical improvement after 10 days of antibiotic. Hence, antibiotics were then upgraded to IV meropenem, following which the child showed symptomatic relief. IV meropenem was continued for a total of 14 days and the patient was then discharged.

Case 3

A 10-year-old girl child presented to our OPD with complaints of high-grade fever for 12 days, vomiting, decreased oral intake for 7 days, and loose stools -2 episodes for 1 day. On examination, she was febrile with a temperature of 101°F and was tachypneic. No signs of dehydration were present.

On per abdominal examination, the abdomen was soft, mildly distended with mild hepatomegaly and mild tenderness. She was admitted and investigated.

Her blood reports were as follows - HB -8.7g/dL, TLC 4000/mm^3, N90%/L6%, and platelets 75,000. Inflammatory markers were raised. The widal test was positive with O, H titers of 1:160. IV ceftriaxone and IV fluids were started along with other supportive measures.

On day 2 of admission, she had a persistent high-grade fever. Azithromycin was added and the patient was further investigated. Her dengue serology, done in view of thrombocytopenia, was nonreactive, no malarial parasite was seen on blood smear and urinalysis was normal. USG abdomen showed mild ascites with mild hepatomegaly. Blood culture reports were obtained on the 5^{th} day of admission which showed growth of Salmonella typhi susceptible to ceftriaxone.

Rapid Automated Aerobic Blood Culture and Sensitivity

Selected Organism Salmonella ser. Typhi

Amoxicillin/Clavulanic acid S(MIC <2)
Amikacin R(MIC-2)
Cefuroxime R(MIC-4)
Ceftriaxone S(MIC <0.25)
Ciprofloxacin R(MIC >4)
Cefepime S(MIC <0.12)
Colistin I(MIC <0.5)
Fosfomycin S(MIC <16)
Gentamycin R(MIC <1)
Imipenem S (MIC <0.25)
Meropenem S(MIC <0.25)
Piperacillin/Tazobactam S(MIC <4)

Trimethoprim/ Sulfamethoxazole R (MIC <20)

Hence ceftriaxone was continued for 10 days. IV meropenem was added after 10 days in view of persisting fever and repeat investigations were sent which showed –Hb -8.74 mg/dL, TLC 6500/mm^3, N45%/L49%, platelets 2.8 lakh and CRP 0.51. Subsequently, the patient showed visible clinical improvement from day 3 of IV meropenem and was discharged after 18 days of admission as she remained clinically stable.

Discussion

Enteric fever is an acute febrile illness with the onset of symptoms 5 to 21 days after ingestion of the causative organism in contaminated food or water.[4]

The term, Enteric fever includes both typhoid fever, caused by infection with the bacteria *S. typhi,* and paratyphoid fever, caused by *Salmonella* Paratyphi A and B. Poor access to drinkable water and inadequate sanitation and hygiene increases the risk of transmission most commonly affecting children and young adults.

Enteric fever is mainly a clinical diagnosis based on history and examination. In endemic areas, a gradual onset of fever, associated with one or more abdominal symptoms, should raise suspicion of enteric fever.[4]

Blood culture is the optimum method to confirm the diagnosis by isolating the organism and testing antimicrobial sensitivity. Management includes antibiotics, adequate hydration, antipyretics for fever, and careful follow-up. Effective antimicrobial therapy according to culture sensitivity shortens the course of illness and reduces mortality from complications.

The antimicrobial choice becomes a cumbersome task due to the resistance of the organism to commonly used drugs. Culture and susceptibility results are crucial to guide treatment for individual patients and to monitor regional resistance rates, but these are often unavailable in endemic areas because of the lack of adequate laboratory facilities and trained personnel.

Chloramphenicol, amoxicillin, and trimethoprim-sulphamethoxazole were first-line choices before the 1990s. In the last two decades, several outbreaks of MDR-*S. typhi* of H58 genotype have been reported around the world. These drug-resistant organisms are a major threat to typhoid treatment as they are resistant to the first-line antimicrobials Similarly, resistance to fluoroquinolones has also increased over the same period. Consequently, third-generation cephalosporins, particularly ceftriaxone, have become preferred antimicrobials for typhoid treatment in endemic countries.

According to WHO, azithromycin is the only affordable first-line oral option for patients with XDR. However, many H58 haplotypes, especially in India, are resistant to azithromycin. Hence CDC, recommends the use of carbapenems.[3]

In November 2016, a large outbreak of ceftriaxone-resistant H58 *S. typhi*-associated typhoid fever started in Hyderabad city of Pakistan which exhibited resistance to five classes of antimicrobials and was consequently labeled as XDR S. typhi. This strain was sensitive to azithromycin and meropenem.[5] Hence, due to an increase in the number of XDR cases, the treatment choice for such infections has shifted to oral azithromycin or parenteral meropenem.[5]

Newer diagnostic methods are under development. Antigens such as HlyE and LPS, being unique to *S. typhi* exhibit high diagnostic potential in differentiating enteric fever from other febrile illness in the form of multiplex immunechromatographic strip detecting both IgA-HlyE and IgA-LPS.

In a recent study, evaluation of IgA titers against membrane components of *S. typhi* and *S. Paratyphi* using ALS samples, exhibited 78–97% specificity and 100% sensitivity in detecting the bacteria.

Nucleic Acid Biomarkers

New biomarkers, using transcriptional methods such as microarray hybridization and RNA-Seq., to evaluate gene expression profiles of host and bacterial cells during the infection have been developed. A recent study identified five host genes as a signature (STAT1, SLAMF8, PSME2, WARS, and ALDH1A1) to diagnose enteric fever with 88% specificity and 97% sensitivity.[6]

All the above-discussed diagnostic methods may not be available in all parts of our country. Srirangaraj *et al.* recommend ciprofloxacin and azithromycin susceptibility testing for *S. typhi* isolates rather than rampantly using high-grade antibiotics that result in drug resistance.[7]

Through this article, we wish to create awareness about the difficulties in treating drug-resistant cases as countries like India have similar poor water, sanitation, and hygiene (WASH) infrastructure. Hence, our country should be prepared for the potential spread of XDR typhoid. Antibiotic resistance may be controlled by various precautions such as not prescribing cephalosporins /azithromycin in suspected viral infections and avoiding sub-therapeutic dosing. Sending paired blood cultures in the appropriate volume, which is a routine practice at our institute, in all cases of suspected enteric fever is absolutely essential.

Genome sequencing and molecular testing of resistant strains are also important for any XDR cases reported in our country. PCR is a faster but less sensitive method that is being used for the diagnosis of enteric fever.[3,8]

Further, there is a lot of scope for developing better and quicker diagnostic methods for early identification and appropriate treatment approaches to avoid the emergence of drug-resistant cases of enteric fever.

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Consent for publication
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