CASE REPORT

Pan drug-resistant Salmonella serovar Typhi septicaemia in a child: A case report

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Abstract

Typhoid fever, caused by *Salmonella enterica* serovar Typhi, is a common cause of febrile illness, especially in lower-middle-income countries. The only known reservoirs of this infection are humans, and it is prevalent in areas with limited availability of clean drinking water and sanitary conditions. Lately, extensively drug-resistant *Salmonella ser.* Typhi (XDR S. Typhi) has emerged as one of Pakistan's most challenging public health concerns. Here, we report a case of relapsed typhoid fever in a child, in whom the isolate was found to be resistant to meropenem and azithromycin.

Keywords: *Salmonella*, Antibiotics, typhoid fever, Septicaemia.

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Introduction

Bacterial infections, such as typhoid fever, have greatly reduced in their prevalence in developed countries because of better sanitary conditions, effective antimicrobial therapy, subsequent infection prevention and control, and case surveillance. However the disease remains a significant public health issue for the resource-limited, developing endemic areas of the world.[1] Humans are the only known reservoirs of typhoid fever which is a severe, systemic febrile disease characterised by transmission via the faeco-oral route, that is from the consumption of contaminated food and water.[2] For the past two decades, multi-drug-resistant (MDR) typhoid strains have been endemic in Pakistan.[3] In 2016, an epidemic of extensively drug-resistant (XDR) typhoid cases was reported from Sindh, Pakistan which has now spread all over the country and there has also been a global increase in ceftriaxone-resistant Salmonella.[4] Antimicrobial resistance has resulted in an escalation in morbidity and mortality, in addition to the costs associated with treating typhoid fever. These extensively drug-resistant strains of Salmonella are susceptible to azithromycin and carbapenems which are the only treatment of choice for these isolates thus increasing the cost exceptionally.[4]

Here, we report a case of Salmonella serotype. Typhi bacteraemia in a child that was found to be resistant to carbapenems and azithromycin.

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Case Report

A 6-year old female child, known case of Down syndrome, ventricular septal defect and pulmonary hypertension, presented in August 2022 in Shifa International Hospital, Islamabad with the complaints of fever associated with rigors and chills, abdominal pain and nausea for one week. On examination, her temperature was 101º F, blood pressure was 95/70 mmHg and heart rate was 130/min. The rest of her systemic examination was unremarkable. Further history revealed that she had previously been treated for typhoid fever with IV meropenem and syrup azithromycin for 14 days but fever relapsed after 10 days of stopping the antibiotics. She had not been previously immunized as the mother did not know about free available Salmonella immunization. Her initial blood culture was positive for Salmonella ser. Typhi susceptible to meropenem and azithromycin. She was admitted and her blood culture was sent again. Blood for malarial parasite was negative and blood complete picture was within normal range. Because resistant Salmonella species were suspected, therapy was initiated with intravenous injection meropenem 350 mg 8-hourly.

Her subsequent blood culture was received in the Microbiology department of Shaukat Khanum Memorial Cancer Hospital and was incubated in Bact/Alert Virtuo (Biomeriaux, France). It flagged positive after 18 hours and the Gram stain showed Gram-negative rods. After incubation of 24 hours, all three types of culture plates of Sheep blood agar, chocolate agar and MacConkey agar showed growth of a single type of Gram-negative rods. On MacConkey agar, these Gram-negative rods grew as non-lactose fermenters and were found to be oxidase-negative. The organism was identified as Salmonella ser. Typhi by API 20E system. It was later confirmed with matrix assisted laser desorption ionization-time of flight mass 2 spectrometry (MALDI-TOF MS). The initial drug susceptibility was performed by Kirby-Bauer disc diffusion method on Mueller Hinton agar that showed resistance to Ampicillin (10 μg), chloramphenicol (30 μg), ceftriaxone (30 μg),

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Microbiology Report

SPECIMEN: Blood

TEST: Culture and Sensitivity

SMEAR REPORT: Gram Negative Rods Seen

CULTURE REPORT:

Salmonella typhi isolated after 6 DAYS

Sensitive to : Colistin.

Resistant to : Ampicillin. Ceftriaxone. Cefixime. Chloramphenicol. Ciprofloxacin. Co-trimoxazole. Imipenem. Azithromycin. Meropenem.

NOTE: MIC of Colistin: 1.0ug/mL(S :< =2, R: >=4)

PATHOLOGIST'S NOTE: Colistin as monotherapy should be avoided. It may be combined with meropenem, cotrimoxazole, amikacin, tigecycline or rifampicin for better action. Onetime loading dose is suggested. Give maximum renal-adjusted dose. It is less effective for pneumonia.

Ceftazidime/ avibactam, Tigecycline, Amikacin and Gentamicin look sensitive in vitro but their efficacy in vivo has not yet been established. Infectious disease consultation is advised.

Highly resistant isolate.Please avoid spread to community or other patients.

Figure: blood culture and sensitivity report.

cefixime (5 μg), trimethoprim-sulphamethoxazole (25ug), ciprofloxacin (5 μg), meropenem (10 μg), imipenem (10ug) and azithromycin (15 μg). In order to confirm the unusual sensitivity results, broth microdilution was performed using the Vitek-2 system (BioMerieux, France) and resistance to carbapenems was confirmed (Figure). Owing to its resistant nature, the isolate was also checked for other antibiotics as well [Tigecycline 15 μg (zone size: 18mm), Ceftazidime-avibactam 50ug (zone size: 21mm), and Colistin (MIC: 1 ug/ml by disc elution technique)].

Upon receiving the blood culture results, therapy was initiated with prolonged infusion of intravenous meropenem 700 mg 8-hourly along with intravenous colistin 12-hourly. On the sixth day of therapy, the patient's fever subsided and her repeat blood culture turned out negative after 10 days. She completed 14 days of colistin therapy. On follow up after six months, she has been free of relapse.

Discussion

To the best of our knowledge, this is the first case report of extensively drug-resistant *Salmonella* resistant to meropenem. There have been few case reports that have showed a delayed treatment response with meropenem despite having in-vitro susceptibility. The isolates of all these cases did not respond adequately to meropenem.[1,5-7] Godbole et al. have proposed that limited intracellular penetration of meropenem may be responsible for the treatment failure along with the phenomenon of tolerance and persistence.[5] These kinds of behaviour in the bacterial population may lead to the delayed response, relapse or even the treatment failure. However, this was not the case with our patient as the isolate was found to be resistant to meropenem in vitro as well.

It should be noted that there are few studies that provide a guide to optimum combination or sequential antibiotic approaches to manage extensively drug-resistant Salmonella. Combination therapies have been used for relapsing typhoid fever that is difficult to treat. Kleine et al. have used a combination of meropenem and fosfomycin for the treatment of Salmonella ser. Typhi bacteraemia which was resistant to azithromycin and was failing to clear from blood on repeated blood cultures.[6] MA Caravedo et al. treated their case of relapsed typhoid fever with the combination of IV meropenem and azithromycin which was initially treated with meropenem monotherapy.[2]

This case demonstrates that simultaneous resistance to azithromycin and carbapenems is a serious concern that poses a treatment challenge, as many current medicines appear to be ineffective. Notably, in spite of some resistance to meropenem, its combined use with colistin can lead to a strong regimen capable of rapidly overcoming Salmonella serotype Typhi infections. All the elements of antibiotic stewardship including early and correct diagnosis and therapy according to culture results are required to prevent development of such antibiotic resistance.

Conclusion

A newly emerging carbapenem-resistant strain identified in this case report poses a significant threat and creates a worrisome situation. Emergence of such highly resistant organisms highlights the importance of antimicrobial stewardship and the need for research on new and safe antibiotics.

Patient's consent: Informed consent had been taken from the mother of the child before writing the case report.

Disclaimer: Contents of this case report have not been published or presented before in any journal or conference.

Conflict of interest: The authors declare that they have no conflict of interest.

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