XDR *Salmonella* Infection with Multisystem Involvement: Case Report and Literature Review

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ABSTRACT

Background: Enteric fever, also known as typhoid fever, results from infections by *Salmonella typhi* (*S. typhi*). The bacteria are classified as extensively drug-resistant (XDR) when they are resistant to fluoroquinolones, chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, and third-generation cephalosporins[1].XDR *Salmonella* infections are an emerging health threat globally. Empiric antibiotic choices in patients from or visiting endemic areas differ and may affect morbidity and mortality.

Case presentation: We report a 20-year-old female patient presenting with multidrug-resistant *Salmonella* bacteremia with systemic involvement including the lungs, liver, bone marrow, and gastrointestinal tract (GI).

Conclusions: Our case report is unique in that few cases have been reported worldwide of multidrug resistant Salmonella infection, that is complicated by liver, and bone marrow involvement. The highlights the importance of having high index of suspicion for resistant organisms in cases of Salmonella infection. Further studies are required to establish treatment protocols for multidrug resistant Salmonella infection.

Key words: Salmonella, Resistance, antimicrobials, infectious diseases

BACKGROUND

Typhoid fever is a water-borne infection, caused by Salmonella enterica, and represents a significant public health concern especially in developing countries, due to paucity of standardized treatment protocols[2]. The emergence of multidrug resistant Salmonella infection has generated new interests in antimicrobial resistance mechanisms , and the Centers for Disease Control (CDC) describe multidrug-resistant (MDR) Salmonella strain a "Serious Threat Level pathogen"[3] .We present a case of young female with no prior medical history who presented to a tertiary center in multidrug resistant Salmonella infection with extensive systemic involvement including the liver, GI tract and bone marrow who responded to a combination therapy of Carbapenem and azithromycin. Our case aims to shed light on the importance of establishing unified management guidelines for multidrug resistant salmonella strains as it can lead to more severe and serious health outcomes, compared to antibiotic-sensitive strains[4] .

CASE PRESENTATION

An ill-looking 20-year-old Pakistani female with no prior medical illness presented to the emergency department (ED) with a history of high-grade fever and associated vomiting and diarrhea.

She reported that 10 days prior to arrival at our center, she was seen in a clinic in Pakistan. There, she had presented with history of fever, abdominal pain, diarrhea, vomiting and loss of appetite. These symptoms began 2 days after eating chicken from a restaurant in Pakistan.. Her symptoms resolved following a 3-day course of oral ciprofloxacin prescribed by that clinic. Two days later, she travelled to Saudi Arabia. She felt feverish again the day she arrived, and presented to our ED the following day..

The patient described the symptoms of the second bout of illness as fever with a temperature of 39C associated with multiple episodes of vomiting all recently-ingested food, two episodes of watery diarrhea and loss of appetite.. She denied having any abdominal pain, changes in mental status, or urinary complaints. She also denied having any skin rashes, joint symptoms or abdominal distension.

The ED team initially diagnosed this as a case of acute gastroenteritis and managed it with intravenous hydration and thereafter discharged her.. However, when her blood cultures showed gram-negative bacilli, she was called back to the hospital and admitted.

At this point, physical examination revealed a young female, who was febrile at 39 C, with normal vital signs. Physical examination was unremarkable, but complete blood count (CBC) results showed leukopenia (WBC: 2.3 * 10^9/l) and thrombocytopenia (platelets115 * 10^9/l) and, Hemoglobin was s 12.2 x 10^9/l. CRP was elevated at 214 mg/l, and LFT showed transaminitis (ALT 137 umol/L and AST 195 unit/l and bilirubin 7.7 umol/l)

Investigations and Treatment

The patient was started empirically on piperacillin-tazobactam (4.5g IV, every 6 hours).However, , symptoms did not improve.. Therefore, piperacillin-tazobactam was stopped, and standard-dose meropenem therapy was started on the second day of admission, given her history of travel to an area with high rates of resistant *Salmonella* species. Our list of differential diagnoses at that point included:

- Infection with a multidrug-resistant pathogen
- Deep-seated collections (given lack of response to antibiotics)
- Malaria (given history of travel to an endemic area, bone marrow (BM) involvement, and persistent fever)

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Table 1. Clinical case progression over the course of admission with the antibiotic regime used

Clinical parameters	On admission	Day 2	Day 6	Day 7	Day 8	Day 10	Day 14	Day 16
Fever Temp	39C	39C	39C	39.1C	38.7C	No fever	No fever	No fever
Hemo-globin	12.2*10^9/l	11*10^9/l	10.3 *10^9/l	10.1*10^9/l	9.6*10^9/l	10.7*10^9/l	11.6*10^9/l	11.6*10^9/l
WBC count	2300*10^9/l	1700*10^9/l	2300*10^9/l	2900*10^9/l	3000*10^9/l	4800*10^9/l	5300*10^9/l	5300*10^9/l
Platelet count	115*10^9/l	94*10^9/l	59*10^9/l	53*10^9/l	87*10^9/l	130*10^9/l	211*10^9/l	318*10^9/l
Liver function tests	ALT 137 umol/l AST 195 umol/l	ALT 163 umol/l AST 294 umol/l	ALT 319 umol/l AST 403 umol/l	ALT 296 umol/l AST 344 umol/l	ALT 233 umol/l AST 313 umol/l	ALT 187 umol/l AST 280 umol/l	ALT 138 umol/l AST 100 umol/l	ALT 25 umol/l AST 26 umol/l
Antibiotics *(started on indicated day)*	pipercillin-pazobactam	meropenem		meropenem/ azithromycin	meropenem/ azithromycin	meropenem/ azithromycin	meropenem	None

- Enteric fever (given GI involvement and history of travel)
- Noninfectious causes were plausible, but unlikely, given known bacteremia

Initial stool culture showed no growth. Blood culture results revealed XDR Salmonella spp.(Table 2) .
Relevant laboratory results, significant findings are shown below(Table 1):

Table 2. Antibiotic susceptibility and correspondent mean inhibitory concentrations

BLOOD CULTURE (PERIPHERAL)

Culture Result: @cultureresult

Organism 1: Salmonella sp.

Antimicrobical Susceptibility:

Antibiotic	1.Salmonella sp.	
Imipenem	S	MIC(<=0.25)
Ceftriaxone	R	MIC(>=64)
Ciprofloxacin	R	MIC(>=4)
Trimethoprim/Sulfamethoxazole	R	MIC(>=320)
Ampicillin	R	MIC(>=32)

MIC values are in ug/mL

Due to COVID-related supply chain issues, the reagent necessary for final serotyping of *Salmonella* was not available, and so serotyping could not be done. The patient continued to suffer high-grade fever, vomiting and reduced appetite. Ultrasound of the abdomen (Figure 1 revealed mild pericholecystic fluid with thickening of the gallbladder wall.

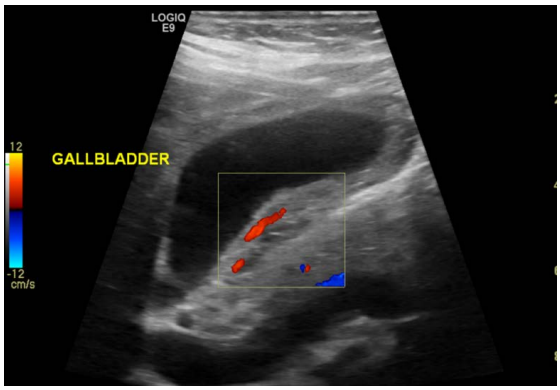

Figure 1. Grey-scale and Doppler ultrasound showed significant gallbladder wall thickening with cystic spaces and internal vascularity

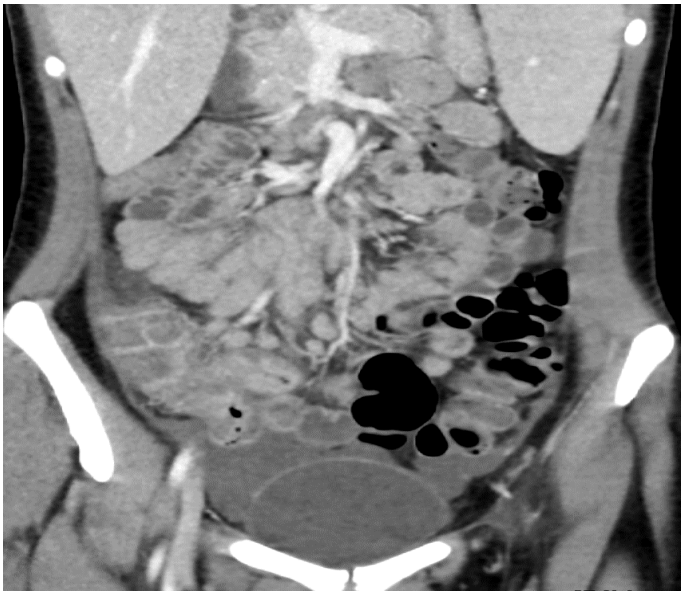

Figure 2. Contrast CT images showing diffuse thickening of terminal ileum and cecum with prominent mesenteric/ileocolic lymph nodes; the appendix

Ordered to rule out deep-seated collections, CT of the abdomen and pelvis with contrast showed edematous thickening of the terminal ileum, cecum and ascending colon with multiple prominent ileocolic lymph nodes associated with mild splenomegaly, moderate ascites and diffuse gallbladder wall thickening/pericholecystic fluid (Figure 2). After 5 days of admission, the patient reported a new dry cough without sputum production or dyspnea. In light of persistent fever and concerns for lung involvement, azithromycin 500mg OD IV was added to the antibiotic regimen on the 7th day of admission. The patient demonstrated clinical and biochemical improvement after 3 days of azithromycin, which she continued to receive for 4 more days for a total of 7 days. Meropenem was continued for a total of 14 days.

On the first clinic follow up appointment 2 weeks after discharge, the patient reported no fever, vomiting or diarrhea. She had no abdominal pain and her appetite was**.** Stool and blood cultures showed no growth, and the previously noted hepatitis and pancytopenia also resolved without any further interventions

DISCUSSION

Enteric fever is a bacterial infection with multisystem involvement, caused by *Salmonella enterica* serovar *typhi* and *Salmonella* enterica

serovar paratyphi A, B, and C.[5] Despite the development of typhoid vaccines over a century ago, the current estimated global burden of typhoid fever is thought to be between 11 and 21 million cases, with around 128,000 to 161,000 annual deaths, according to the World Health Organization (WHO).[6]

The classic symptoms of enteric fever - abdominal pain, fever, and chills - usually arise 5-21 days after exposure to the causative inoculum, generally in contaminated water or food.[7 8]. Additionally, recent data suggest that constipation is likely to occur with the same frequency as diarrhea, or that diarrhea may even be more common.[9] Also, dry cough has interestingly been found to be a common association with enteric fever, and was found to be present in around 20-45% of patients. The underlying mechanism of cough in the setting of enteric fever has not been investigated as yet. Bacteremic seeding was also described in the literature, including involvement of the hepatobiliary, cardiovascular, respiratory, genitourinary, CNS, and musculoskeletal systems[10].

Interestingly, our patient presented with pancytopenia which is a unusual manifestation of *Salmonella* bacteremia. Multiple mechanisms have been hypothesized as the underlying cause for pancytopenia, including bone marrow suppression due to systemic infection, or hemophagocytic syndrome.[11] This patient had a normal coagulation profile, and her pancytopenia resolved after appropriate therapy for XDR *Salmonella* bacteremia. Thus, no additional work up was requested as her presentation was consistent with Bone marrow involvement secondary to a systemic infection.

Since November 2017, there has been an emergence of enteric fever caused by XDR S. typhi [12]. This strain is resistant to recommended first-line antibiotics and cephalosporins, but susceptible to second-line treatments including azithromycin and carbapenems [13]. In the past, Typhoid fever secondary to XDR *Salmonella* species –associated with subpar sanitation practices – used to be prevalent mainly in low and medium-income countries. However, increased international travel and increasing antimicrobial resistance have led to more reported cases in higher-income countries.[14]

There is limited data on the efficacy of combination therapy of azithromycin and carbapenems for the treatment of XDR *Salmonella* infections, compared to each antibiotic alone. The available data are from four case reports, which all point towards the clinical inefficacy of meropenem alone, either because of disease relapse or the need for additional anti-microbial agents to achieve adequate clinical response. [15,16,17,18]. A retrospective study conducted in Pakistan in 2020 included 81 XDR salmonella patients, assessed the response of XDR *S. typhi* to combination therapy with azithromycin and meropenem. Fever clearance time for XDR Salmonella patients treated with either azithromycin or meropenem was similar to that of patients treated with a combination of meropenem and azithromycin[19] However, we know of no large, controlled trials that assessed the synergistic effect of the combination therapy of meropenem and azithromycin for the treatment of XDR *Salmonella* infections. Our patient had a suboptimal response to meropenem monotherapy and continued to have high grade fever despite 7 days of meropenem therapy. Significant clinical improvement was noted after the addition of azithromycin to the antibiotic regimen. The bacteremia was completely resolved on follow up, supporting the idea that azithromycin helps the infection with XDR *Salmonella* species. Given azithromycin's long half-life and its ability to accumulate intracellularly, its potential effectiveness for the treatment of intracellular infections like enteric fever is promising. [20,21] However, larger studies are needed to establish the value of combined carbapenems and azithromycin therapy for the treatment of XDR *Salmonella* infections.

CONCLUSION

In conclusion, this case signifies the importance of always considering multidrug resistant strains, particularly when dealing with cases who have a history of travel to regions of endemicity. It also highlights the significance of pre-travel advice and following safe water and food practices and hand hygiene measures.

Owing to the uniqueness of XDR *Salmonella strains*, no treatment guidelines have been generated yet. Hence, evidence-based treatment protocols need to be established in order to attempt to limit the global spread of XDR strains of Salmonella and prevent further mutations.

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Potential Conflicts of Interest: None

Competing Interest: None

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