

An Altered Drug Resistance Pattern in *Salmonella Typhi*

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Abstract Enteric fever is an endemic disease in the tropics and subtropical region. It is caused by the bacterium *Salmonella typhi*. It is a systemic disease and occurs by ingestion of infected food or water usually from a feco-oral source. It is primarily found in developing countries where sanitary conditions are poor [1,2]. Despite the emergence of newer antibacterial drugs, enteric fever has continued to be a major health problem. *S. typhi* bacterium has gained resistance to antibiotics like ampicillin, ceftriaxone and cotrimoxazole, besides developing resistance to previously efficacious drugs like ciprofloxacin [3]. The emergence of multidrug resistance to the commonly used antibiotics has further complicated the treatment and management of enteric fever and this is recognized as one of the greatest challenges in the management of the disease [4,5]. Resistance to various antibiotics has been previously reported in *Salmonella typhi*. However, to the best of our knowledge, a strain that is resistant to 3rd generation cephalosporins, as well as commonly used fluoroquinolones but sensitive to chloramphenicol has not been identified yet. In this case report, we provide evidence of such a strain and its successful resolution through the use of chloramphenicol.

Keywords: enteric fever, chloramphenicol, anti-microbial resistance, anti-bacterial drugs

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1. Case Report

An 18 year old boy presented with high grade continuous fever (100° to 103° F), chills and rigors of four days duration. Also present were nausea, vomiting and burning micturition. At admission, patient was febrile (oral temperature 104° F) but conscious and had a pulse rate of 98/minute and a supine blood pressure of 130/80 mmHg. The abdomen was soft and examination revealed normal bowel sounds. Liver enlargement was seen 2 cm below the right costal margin and the spleen was also palpable 3 cm below the left costal margin. Both, the liver

and spleen, were soft and non-tender on touch. There was no palpable lymph node enlargement.

Haematological investigations revealed a normal blood count, erythrocyte sedimentation rate and routine biochemistry. Malarial antigen test was non-reactive. Widal test was negative but the Typhidot test (for *S. typhi* IgM/IgG) was positive. Patient's urine examination revealed 12-14 granulocytes per high power field and traces of albumin. Blood and urine samples were sent for microbial testing. Based on the clinical findings, patient was provisionally diagnosed with enteric fever and started on ceftriaxone, 2 g, and ofloxacin, 200 mg, intravenous, twice daily.

Table 1. Susceptibility Information

Selected Organism : <i>Salmonella ser. Typhi</i>					
Antimicrobial	MIC	Interpretation	Antimicrobial	MIC	Interpretation
ESBL			Meropenem	<=0.25	S
Ampicillin/Sulbactam	>32	R	Amikacin	<=2	R*
Gatifloxacin	<0.25	S	Gentamicin	<=1	R*
Cefazolin	>64	R	Tobramycin	<=1	R*
Ceftriaxone	>64	R	Ciprofloxacin	>4	R*
Cefepime	>64	R	Moxifloxacin	0.25	S
Aztreonam	<=1	S	Trimethoprim/ Sulfamethoxazole	>32	R
Ertapenem	<=.5	S	Chloromycetin	4	S
Imipenem	<=1	S			

* AES Modified

R = Resistant

S = Sensitive; Parameter Set = Copy of CLSI + Natural Resistance

Ultra-sonography of the abdomen showed a borderline splenomegaly without any enlargement of the periportal lymph nodes. Initial blood culture was negative for pathogens and despite being on antibiotics, the patient continued to be febrile with complaints of abdominal pain. Subsequent microbial tests on blood samples every 8 hours revealed *S. typhi* sensitive to meropenem, gatifloxacin and chloramphenicol and resistant to cephalosporins, ciprofloxacin and ofloxacin (see Table 1). Following this, the patient's antibiotic therapy was revised because no clinical improvement had been observed after three days of ofloxacin and ceftriaxone therapy. Ofloxacin and ceftriaxone was stopped, and patient was started on meropenem 1 gm iv infusion in 100 ml normal saline 8 hourly. However, this had to be discontinued the next day when patient displayed an adverse drug reaction with rash over his limbs and eruptions at the injection site. Subsequently, patient was put on oral chloramphenicol, 500 mg, four times a day. After five days of this therapy, patient improved symptomatically and was afebrile and was discharged.

He was advised to continue with Cap Chloramphenicol 500mg three times a day for three more days at home. He remained afebrile and fever did not relapse.

MIC values have been evaluated using the VITEK 2 System of BioMerieux, based broth microdilution method.

2. Antibiotic Sensitivity Method

MIC (Minimum inhibitory concentration) method by Vitek 2 system – fully Automated system by Biomeriux company MIC interpretation guideline; by CLSI M100-S19(2009). AES parameter ; By CLSI natural resistance. Therapeutic interpretation guideline; Natural resistance.

3. Discussion

Since the emergence of multidrug resistant typhoid in the 1970s and 80s, the broad-spectrum fluoroquinolones, especially ciprofloxacin and ofloxacin, have been the treatment of choice for suspected typhoid fever, especially in South Asia and Southeast Asia where the disease is endemic. [6,7] However, this indiscriminate use has led to reports of *S. typhi* strains that are resistant to fluoroquinolones [8].

The use of appropriate antibiotic is of paramount importance in the successful treatment of enteric fever with minimal complications. It has been discussed in a recent review [9] that satisfactory cure rates can be achieved in drug sensitive cases using chloramphenicol as a first-line agent. Thus, with emergence of *S. typhi* strains like the one we isolated, that are resistant to contemporary therapy with fluoroquinolones as well as 2nd and 3rd generation cephalosporins, but maybe sensitive to older and cheaper antibiotics; it might be clinically and economically beneficial to treat these patients with antibiotics, like chloramphenicol, as first-line therapy. This is specially significant in the developing countries of South East Asia, Africa and Latin America, due to the fact that cost of therapy is significantly reduced if drugs like chloramphenicol are used instead of costlier drugs like 3rd generation cephalosporins or the carbapenems. Our case report is evidence of this approach for successfully treating enteric fever.

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