

<b>TITLE OF CASE</b>
<b>Cotrimoxazole treats fluoroquinolone resistant <i>Salmonella</i> Typhi H58 infection</b>
<b>AUTHORS OF CASE</b>
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<b>SUMMARY</b>
<p>A 20 year old female patient presented with fever and no localizing signs. She was treated with cotrimoxazole and the subsequent blood culture was positive for <i>Salmonella</i> Typhi (<i>S. Typhi</i>), which was resistant to fluoroquinolones but susceptible to cotrimoxazole. Genotyping identified a FQ-R subclade of H58 <i>S. Typhi</i>. The fever clearance time was four days after starting the antibiotics and no relapses were noted upon two months of follow up. This inexpensive, well-known, and easily available antimicrobial could be suitably re- deployed for fluoroquinolone resistant enteric fever in South Asia.</p>
<b>BACKGROUND</b>
<p>In this case report we show that the inexpensive and easily available cotrimoxazole effectively treats resistant, ubiquitous FQ-R subclade of H58 enteric fever. We think this is an important report because, although enteric fever is common in South Asia, we could not find a single, recent report of cotrimoxazole and patient outcome after the reports of re-emergence of in-vitro susceptibility to 1<sup>st</sup> line drugs. Before the emergence of multi drug resistance <i>S. Typhi</i> and Paratyphi organisms, cotrimoxazole was very effective in the treatment of enteric fever. As the recent O'Neill report on antimicrobial resistance (AMR) notes, older antimicrobials like cotrimoxazole that have regained usefulness need to be available as options for common infectious diseases like typhoid fever as these are "low hanging fruits" which need to be utilized using proper dosage to slow down resistance, especially as there are no new drugs in the pipeline for treating common, neglected diseases like enteric fever.</p>
<b>CASE PRESENTATION</b>
<p>In August 2015, a 20-year-old female from densely populated area of Lalitpur district in Kathmandu, Nepal presented with fever and headache for six days to Patan Hospital. She had history of non-productive cough for four days. She had been experiencing decreased appetite and extreme myalgia since the fever started. There was no history of nausea, vomiting, abdominal pain, joint aches, rashes, eschar, laceration or neck stiffness. Her bowel and bladder habits were normal. She lived in a rented apartment in a family of five people. The source of drinking water was bottled water that was boiled before use. There was no history of travel to the south plains</p>

of the country or outside Nepal. No history of tuberculosis in the past or contact with infective patients. The patient wasn't a food handler. There were no additional cases in the household. On examination, her temperature was 39.3°C, pulse rate 92/min, blood pressure 100/70 mmHg and respiratory rate 18/min. She was well oriented to time, place and person. No abnormality besides the fever was detected on systemic examination.

#### INVESTIGATIONS

The initial laboratory reports showed total white blood cell count of 3,900/mm<sup>3</sup>, differential – neutrophils 60% and lymphocytes 40%, hematocrit 35% and platelets 188,000/mm<sup>3</sup>. Routine chest x-ray and urine examination were normal. Her liver function test was within normal limit. A blood culture was performed. The ultrasonography of abdomen, pelvis and lungs didn't show any collection. The chest x-ray didn't reveal any abnormalities. Her blood culture was positive for *Salmonella* Typhi (*S. Typhi*) on day seven and the isolate was susceptible to cotrimoxazole, chloramphenicol, gentamycin and azithromycin, intermediately sensitive to cephalexin but resistant to ciprofloxacin, ofloxacin and nalidixic acid. The minimum inhibitory concentration (MIC) of cotrimoxazole was 0.023 µg/ml and the zone of inhibition was 37 mm. Genotyping at nucleotide 252 on the gene *glpA* revealed the *S. Typhi* strain belonging to the FQ-R subclade of H58.

#### DIFFERENTIAL DIAGNOSIS

1. Typhus  
The signs and symptoms with typhoid are indistinguishable but she had no eschar. However doxycycline would have been started if she had not gotten better.
2. Leptospirosis  
No history of abrasions which made the diagnosis less likely.
3. Malaria  
No history of travel to the south plains of the country where malaria is prevalent.
4. Dengue  
No travel history from Kathmandu which made the diagnosis less likely.
5. Brucellosis  
The prevalence of Brucellosis in Kathmandu is low. This patient didn't have any history of consumption of raw milk and contact with infected cattle.
6. Tuberculosis  
Though an endemic region for TB, patient's history, examination and investigations were not suggestive of TB.

#### TREATMENT

As this was a case of undifferentiated febrile illness with no localized signs, in Nepal based on epidemiological findings this patient was assumed to have enteric fever. Being inexpensive, easily available and with recent anecdotal reports of success in our hospital, oral cotrimoxazole 60 mg/kg/day (Trimethoprim 10 mg/kg and sulfamethoxazole 50 mg/kg) was started twice daily empirically on the day of hospital visit for seven days. The patient was not on other antibiotics at that time and was started on cotrimoxazole, proton pump inhibitors and acetaminophen.

If the patient hadn't got better, doxycycline would be started for typhus as it presents similar to typhoid and there have been reports of outbreak of the disease after the earthquake in the country.

#### OUTCOME AND FOLLOW-UP

The fever subsided on the fourth day of starting antibiotics and her recovery was uneventful. She remained symptoms free at two months follow up visit. No public interventions were undertaken as these cases were sporadic rather than from an outbreak.

#### DISCUSSION

Enteric fever, a systemic illness caused by *Salmonella enteric* serovars Typhi and Paratyphi A, imposes high public health burden in areas of endemicity characterized by poor sanitary conditions. By the 1980s, plasmid mediated resistance had been acquired by some *S. Typhi* strains leading to the emergence of multidrug resistance (MDR) against all three first line drugs (ampicillin, chloramphenicol and cotrimoxazole).[1] The fluoroquinolones (particularly ofloxacin) now are commonly used for the treatment of enteric fever in South Asia, but recently the commonly circulating strain of H58 *S. Typhi* has shown extensive resistance against the fluoroquinolones in South Asia and even in parts of Africa. They have acquired resistance due to mutations in the *gyrA* and the *parC* gene. [2] Ceftriaxone or azithromycin are now becoming increasingly used in South Asia for effective treatment of enteric fever. However ceftriaxone and azithromycin are almost last resort antimicrobials for the treatment of enteric fever in South Asia. [3]

Recently reports from around the globe including our country have shown the re-emergence of *in vitro* susceptibility in the *Salmonella* against the aforementioned first line drugs. [4] Our previous trial comparing gatifloxacin with chloramphenicol showed excellent efficacy of chloramphenicol in the treatment of enteric fever. [5] Our ceftriaxone vs. gatifloxacin study showed low MIC for cotrimoxazole and anecdotally we noted as in this case enteric fever patients responding very well to cotrimoxazole. [6] We are now conducting a large trial which involves treatment of enteric fever with cotrimoxazole. However, we were unable to find reports of successful treatment outcomes in patients with the usage of cotrimoxazole after the reports of re-emergence of *in-vitro* susceptibility to 1<sup>st</sup> line drugs. Before the emergence of multi drug resistance *S. Typhi* and Paratyphi organisms, cotrimoxazole was very effective in the treatment of enteric fever. [7]. In our patient infected with a H58 *S. Typhi* we administered adequate dosage (60 mg/kg/day) of cotrimoxazole tablets and showed fever clearance in four days. A retrospective review of hospital records revealed eight patients of culture confirmed enteric fever (susceptible to cotrimoxazole but resistant to nalidixic acid) that showed clinical response to cotrimoxazole with fever clearance time (FCT) between 3-5 days of starting the antibiotics and no relapses. Genotyping was not performed on the organisms isolated from these patients. Although there are many *in vitro* reports of *S. Typhi* recently being sensitive to cotrimoxazole, this is the first report of a successful clinical outcome using cotrimoxazole in a patient infected with the now ubiquitous FQ-R subclade of H58 recently described to be associated with treatment failure with fluoroquinolones. [3]

Improvements in sanitary conditions have decreased the incidence of enteric fever in developed world; but it still remains a huge health burden in resource poor settings.[3] As the recent O'Neill report notes, [8] older antimicrobials like cotrimoxazole that have regained usefulness need to be available as options for common infectious diseases like typhoid fever as these drugs. There is a clear chance of re-emergence of resistance due to the circulation of MDR IncH1 plasmids in *S. Typhi* and other Gram-negative bacteria. [3] Thus to try to avoid resistance build up, one method may be to use these now effective antibiotics in cycles.

LEARNING POINTS/TAKE HOME MESSAGES
<ul style="list-style-type: none"> <li>• Older antimicrobials like cotrimoxazole that have regained usefulness need to be available as option for common infectious diseases like typhoid fever, especially as there are no new antibiotics for treatment in the pipeline.</li> <li>• Inexpensive and easily available cotrimoxazole seems to effectively treat resistant, ubiquitous subclade of H58 enteric fever.</li> <li>• Besides typhoid, typhus, leptospirosis, malaria, dengue and brucellosis need to be in the differential diagnosis of undifferentiated febrile illness in South Asia.</li> </ul>
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<b>Figure captions</b>