CASE REPORT

Cotrimoxazole treats fluoroquinolone-resistant *Salmonella typhi* H58 infectionManan Karki,¹ Sarbagya Pandit,¹ Stephen Baker,² Buddha Basnyat¹¹Oxford University Clinical Research Unit, Patan Hospital, Kathmandu, Nepal²Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam

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SUMMARY

A woman aged 20 years presented with fever and no localising signs. She was treated with cotrimoxazole and the subsequent blood culture was positive for *Salmonella typhi* (*S. typhi*), which was resistant to fluoroquinolones but susceptible to cotrimoxazole. Genotyping identified an FQ-R subclone of H58 *S. typhi*. Fever clearance time was 4 days after starting the antibiotics, and no relapses were noted on 2 months of follow-up. This inexpensive, well-known and easily available antimicrobial could be suitably redeployed for fluoroquinolone-resistant enteric fever in South Asia.

BACKGROUND

In this case report, we show that the inexpensive and easily available cotrimoxazole effectively treats resistant, ubiquitous FQ-R subclone of H58 enteric fever. We think that 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 first-line drugs. Before the emergence of multidrug-resistant *S. typhi* and Paratyphi organisms, cotrimoxazole was very effective in the treatment of enteric fever.

As the recent O'Neill report on antimicrobial resistance 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 used with proper dosage to slow down resistance, especially as there are no new drugs in the pipeline for treating common, neglected diseases like enteric fever.

CASE PRESENTATION

In August 2015, a woman aged 20 years from densely populated area of Lalitpur district in Kathmandu, Nepal, presented with fever and headache for 6 days to Patan Hospital. She had a history of non-productive cough for 4 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 of the country or outside Nepal. No history of tuberculosis in the past or contact with infective patients. The patient was not 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 mm Hg 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 cell count of 3900/mm³, differential—neutrophils 60% and lymphocytes 40%, haematocrit 35% and platelets 188 000/mm³. Routine chest X-ray and urine examination were normal. Her liver function test was within normal limit. A blood culture was performed. Ultrasonography of the abdomen, pelvis and lungs did not show any collection. Chest X-ray did not reveal any abnormalities. Her blood culture was positive for *S. typhi* on day 7 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 subclone 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 improved.
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 did not have any history of consumption of raw milk and contact with infected cattle.
6. Tuberculosis (TB): Though an endemic region for TB, the patient's history, examination and investigations were not suggestive of TB.

TREATMENT

As this was a case of undifferentiated febrile illness with no localised 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 two times per day empirically on the day of

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hospital visit for 7 days. The patient was not on other antibiotics at that time and was started on cotrimoxazole, proton pump inhibitors and acetaminophen.

If the patient had not improved, doxycycline would have been started for typhus as it presents similar to typhoid and there have been reports of outbreak of the disease after the recent 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 2 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 characterised 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 the effective treatment of enteric fever. However, ceftriaxone and azithromycin are almost the last resort antimicrobials for the treatment of enteric fever in South Asia.³

Recently, reports from around the world 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 study on the efficacy of ceftriaxone versus gatifloxacin 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 first-line drugs. Before the emergence of MDR *S. typhi* and Paratyphi organisms, cotrimoxazole was very effective in the treatment of enteric fever.⁷ In our patient infected with an H58 *S. typhi*, we administered adequate dosage (60 mg/kg/day) of cotrimoxazole tablets and showed that fever had subsided in 4 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 and 5 days of starting the antibiotics and no relapses. Genotyping was not performed on the organisms isolated from these patients. Although there are many recent in vitro reports of *S. typhi* 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 the developed world; but it still remains a huge health burden in resource-poor settings.³ As the recent O'Neill⁸ report notes, 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.¹ Thus to try to avoid resistance build up, one method may be to use these now effective antibiotics in cycles.

Learning points

- ▶ Older antimicrobials like cotrimoxazole that have regained usefulness need to be available as an option for common infectious diseases like typhoid fever, especially as there are no new antibiotics for treatment in the pipeline.
- ▶ Inexpensive and easily available cotrimoxazole seems to effectively treat resistant, ubiquitous subclade of H58 enteric fever.
- ▶ Besides typhoid, typhus, leptospirosis, malaria, dengue and brucellosis need to be in the differential diagnosis of undifferentiated febrile illness in South Asia.

Contributors MK and SP took care of the patient. SB helped with the isolation of the organism and subsequent diagnosis. BB conceived the idea and supervised the patient care. All helped with the write up and approval of the final manuscript.

Competing interests None declared.

Patient consent Obtained.

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