Editorial: The Value of Monitoring Local Antimicrobial Resistance Patterns in Enteric Fever

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Enteric (typhoid and paratyphoid) fever is a significant cause of febrile illness in South Asia where a large proportion of the population lacks access to clean water and adequate sanitation.[1] Enteric fever affects more than 14 million people globally each year, predominantly children and young adults, including an estimated 7 million living in South Asia.[2] Antimicrobials transform this febrile illness, with mortality between 10 and 30%, to a treatable condition where symptoms resolve within 1 week and a mortality of less than 1%.[1] This paradigm is challenged whenever there is an emergence of resistance to the antimicrobials being used for treatment. Periodic surveillance of antibiotic resistance patterns and revising the treatment protocol based on the findings help in preventing the morbidity and mortality related to the disease.

In this issue of the journal, Joshi et al evaluated the clinical profile and antibiotic susceptibility pattern of enteric fever in a cohort of 70 children admitted to a tertiary hospital in Northern India.[3] Fortunately, almost all children grew organisms that were sensitive to the most commonly currently used first-line drugs (cefixime, ceftriaxone, and azithromycin), and none of the cultured isolates were multidrug resistant. The sensitivity to quinolones and second-generation cephalosporins was abysmally low.

Over the years, there has been a gradual change in the sensitivity pattern of Salmonella Typhi and Paratyphi. Oral chloramphenicol, ampicillin/amoxicillin, and trimethoprim–sulfamethoxazole were commonly used and found to be effective before the 1990s. In the late 80s, multidrug resistance with plasmid-mediated resistance to all these three options appeared.[1] Thereafter, fluoroquinolones became a common choice to treat enteric fever but soon high-level resistance became widespread in South Asia and some areas of sub-Saharan Africa.[1] Since then, parenteral ceftriaxone and oral cefixime have been the drug of choice, particularly in children. Azithromycin is another drug that has been commonly used for treating enteric fever in recent years.

Since 2016, an extensively drug-resistant typhoid strain appeared in Pakistan.[4] These organisms are resistant to chloramphenicol, ampicillin/amoxicillin, trimethoprim–sulfamethoxazole, ciprofloxacin, and ceftriaxone/cefixime. These isolates have remained susceptible to oral azithromycin and parenteral meropenem. Sporadic isolates with resistance to ceftriaxone have also been reported from locations outside Pakistan, and it is important to monitor the pattern of resistance, and treatment choices should take account of local resistance patterns. The study by Joshi et al highlights the need for surveillance and monitoring of antimicrobial resistance.

In the study under discussion, some patients were stepped down to oral cefixime, while others were put on oral azithromycin.[3] If an isolate is susceptible to more than one antibiotic, how does one choose which antibiotic to use? Is one antimicrobial better than another? Three published Cochrane Systematic Reviews have studied antimicrobial efficacy in enteric fever from the perspective of the fluoroquinolones, azithromycin, and cephalosporins (ceftriaxone and cefixime).[5–7] In these reviews, the authors found limited evidence to make firm conclusions over the advantage of one antimicrobial over another. The other issue is that of dual antibiotics. In the study by Joshi et al, a few patients were treated with a combination of antimicrobials. Is there a rationale in combining antibiotics? Studies have indicated that S. Typhi infection is a mixture of an intracellular and an extracellular infection, suggesting that antimicrobials used to

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treat enteric fever should target both intracellular and extracellular bacteria. Azithromycin reaches very high intracellular concentrations but low extracellular concentrations.[8] Several randomized controlled trials with azithromycin have demonstrated a slow microbiological clearance, indicated by positive blood culture during treatment. It is possible that this occurs because the low extracellular plasma levels do not clear the extracellular bacteria. Cefixime is predominantly active in the extracellular compartment, although in vitro evidence indicates some intracellular activity.[9] The relative lack of intracellular cefixime activity may be the reason for the variable treatment results in typhoid. It is possible that a combination of both azithromycin, active mainly intracellularly, and cefixime, active mainly extracellularly, will be a better option for the treatment of enteric fever. This combination should still be efficacious if the infecting pathogen was resistant to one of the drugs. It is also possible that the combination may also prevent the emergence of resistance. However, more trials and data are required before any definite recommendations can be made in this regard.

To conclude, management of suspected enteric fever is a challenge clinicians face throughout endemic areas. Knowledge of the local resistance patterns for S. Typhi and S. Paratyphi is critical for making empiric treatment choices. Future studies should explore the value of antimicrobial combinations.

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