

## Troubling news from Asia about treating enteric fever: a coming storm



In *The Lancet Infectious Diseases*, Amit Arjyal and colleagues<sup>1</sup> report the results from their randomised clinical trial comparing gatifloxacin with ceftriaxone for patients with uncomplicated enteric fever in Nepal. Their two main findings are sobering. First, they suggest that fluoroquinolones should no longer be recommended as front-line empirical treatment for individuals with enteric fever in Nepal. Second, a large proportion of individuals in Nepal who are syndromically characterised as having uncomplicated enteric fever probably have an alternative diagnosis.

Briefly, the investigators did a trial through two hospitals in Kathmandu valley, Nepal, enrolling 239 individuals with suspected enteric fever and randomly assigning them to either gatifloxacin (n=120) or ceftriaxone (n=119). 116 patients had microbiologically confirmed disease—either *Salmonella enterica* serovar Typhi (the cause of typhoid fever) or *S enterica* serovar Paratyphi A (a prevalent cause of paratyphoid fever in Nepal). Analysis of the modified intention-to-treat population showed that treatment failure did not differ between patients treated with gatifloxacin (18 [15%]) versus ceftriaxone (19 [16%]; hazard ratio [HR] 1.04 [95% CI 0.55–1.98]; p=0.91). However, when the cohorts were separated into patients with microbiologically confirmed enteric fever versus those who were blood-culture negative, substantial differences emerged. In the blood culture-confirmed population, 16 (26%) of 62 patients who received gatifloxacin failed treatment, versus four (7%) of 54 who received ceftriaxone (HR 0.24 [95% CI 0.08–0.73]; p=0.01). However, in the culture-negative subgroup, only two (3%) of 58 patients who received gatifloxacin failed treatment, versus 15 (23%) of 65 who received ceftriaxone. What do these results mean?

First, some context: multidrug-resistant strains of *S Typhi* are now globally prevalent.<sup>2</sup> In this reality, three classes of drugs have become the cornerstones of treatment for enteric fever: fluoroquinolones, third-generation cephalosporins, and macrolides. Despite a stepwise progression in both the degree and spread of fluoroquinolone resistance for *S Typhi*, until 2010–11 patients still seemed to clinically respond to

the fourth-generation gatifloxacin.<sup>3,4</sup> However, the results from Arjyal and colleagues<sup>1</sup> suggest that even advanced fluoroquinolones might now be ineffective. Indeed, their trial was terminated early because of the high clinical failure rate of gatifloxacin in patients with culture-confirmed enteric fever caused by *S Typhi*. The fact that fluoroquinolone-resistant strains of *S Typhi* might actually have a selective advantage over wild-type strains also strongly suggests that such highly-resistant strains might rapidly globally spread.<sup>5</sup>

The results from Arjyal and colleagues' study also suggest that simply switching to another class of drug, such as third-generation cephalosporins, would not be a wholly correct solution, at least in Nepal, because individuals who were culture-negative for enteric fever in this study and received ceftriaxone actually fared significantly worse than those receiving gatifloxacin. One reason for these findings is that a large percentage of individuals in this study who were syndromically categorised as having enteric fever probably had instead an infection caused by other pathogens that were not affected by ceftriaxone (but were susceptible to fluoroquinolones). Indeed, in other studies,<sup>6,7</sup> this same group of investigators has shown that a large proportion (5%–20%) of non-specific febrile illness in Nepal is murine typhus.

Thus, the study by Arjyal and colleagues is important for several reasons. First, it strongly suggests that time is running out for effective antimicrobial drugs for enteric fever, and that the widespread inappropriate use of antimicrobial agents must be curtailed. With the loss of fluoroquinolones, treatment will be reduced to a few advanced antimicrobials that need to be given intravenously, oral agents such as cefixime (that has been associated with a high occurrence of clinical relapse in initial field studies),<sup>8</sup> and azithromycin (the so-called back-to-the-wall option). Soberingly, salmonella strains that have acquired resistance to extended spectrum beta-lactamases and carbapenemases will probably soon spread globally, further curtailing these already scarce options. Then, when azithromycin-resistant strains emerge (and they will), options will simply no longer exist. Second, the findings underline that diagnostically,



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confusion prevails when patients receive clinical care in resource-limited areas with non-specific but serious febrile illnesses. Sensitive, accurate, inexpensive, and point-of-care diagnostic assays are needed that can distinguish enteric fever from other common non-specific febrile illnesses that need individualised treatment, including invasive non-typhoidal salmonellosis, rickettsiosis, leptospirosis, malaria, and arboviral and other viral infections.<sup>9</sup> Unfortunately, many decades might pass until the most impoverished members of our global community live in the conditions that mitigate their risk of acquiring such diseases. In the meantime, crucial methods that enhance our ability to care for these patients are either absent or have been lost. Now is the time to initiate coordinated control programmes against typhoid before the storm hits—we have been warned.

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I declare no competing interests.

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