Chapter

98

Drug-resistant Typhoid Fever — Implications for Clinical Practice

TAMILARASU KADHIRAVAN

Typhoid fever is caused by bacteremic infection with the intracellular bacterium *Salmonella enterica* subspecies *enterica* serotype Typhi. *S. typhi* evolved about 50,000 years ago and is specific to humans. Widespread improvement in sanitation led to the elimination of typhoid fever as a public health problem in the developed world. However, in developing and underdeveloped nations, typhoid fever still is one of the most common causes of acute febrile illness presenting to hospital[1] and continues to be a major public health problem. An estimated 21 million cases and 0.2 million deaths from typhoid fever occurred worldwide in the year 2000[2].

In the absence of adequate access to safe drinking water, antimicrobial chemotherapy is the only major option available under such conditions for the control of typhoid fever[3]. Apart from curing the individual of the disease, it has the potential to decrease the risk of faecal carriage and thereby preventing onward transmission of infection. Effective antimicrobial chemotherapy is available for the past 50 years at least. Extensive and unregulated use of antibiotics for the empirical treatment of fever in the community setting has resulted in a general decline in complications and mortality due to typhoid fever. However, this practice has unwittingly resulted in the emergence of antibiotic-resistant strains of *S. typhi* causing localized outbreaks and epidemics. With continued antibiotic selection pressure, these resistant strains have become endemic in many parts of the world.

Emergence and Spread of Drug-resistant *S. typhi*

Chloromycetin (chloramphenicol) was found to be effective in the treatment of typhoid fever in 1948, and soon it became the standard antibiotic for treating typhoid fever. Several years later, ampicillin and then co-trimoxazole were added to the therapeutic armamentarium. However, resistance to chloramphenicol emerged rapidly within two years after its introduction, and by 1972 chloramphenicol-resistant typhoid fever had become a major problem. Outbreaks occurred in Mexico, India, Vietnam, Thailand, Korea and Peru. But ampicillin and co-trimoxazole were still effective against these chloramphenicol-resistant strains, making them effective alternatives.

In 1990s, isolates of *S. typhi* resistant to all the three first-line drugs then in use (chloramphenicol, ampicillin, and co-trimoxazole) started emerging and sooner outbreaks of infections with these strains (designated as multidrug-resistant *S. typhi* [MDR-ST]) occurred in India, Pakistan, Bangladesh, Vietnam, the middle-east and Africa. Slowly MDR-ST became the predominant strain in many parts of Asia, including India. This change in pattern of susceptibility was reflected even in faraway places such as the United States and the United Kingdom.

Fortunately, more or less over the same period, fluoroquinolones were discovered and found clinical use in the treatment of typhoid fever. Unparalleled in clinical efficacy even today, fluoroquinolones achieved rapid defervescence of fever in less than four days time with markedly reduced rates of relapse. These features together with the widespread emergence of MDR-ST strains made ciprofloxacin the drug of choice for typhoid fever.

Ciprofloxacin-Failure – A Clinical Paradox

Towards the end of 20th century, it was observed that fever took longer time than before to clear and sometimes did not at all respond to ciprofloxacin

therapy. These isolates had reduced susceptibility to ciprofloxacin as evidenced by comparatively higher minimal inhibitory concentrations (MICs), although they were reported susceptible to ciprofloxacin by conventional disk-diffusion testing using recommended breakpoints. The MICs of ciprofloxacin for these isolates are about 10 times that of fully-susceptible strains, and these isolates are usually resistant to the first generation quinolone nalidixic acid. Subtly reduced susceptibility of this magnitude has been amply documented to result in poor clinical response to treatment with ciprofloxacin and often in treatment-failure[4-6].

Nalidixic acid-resistance serves as a surrogate marker of decreased susceptibility to ciprofloxacin[7], and the clinical response to ciprofloxacin in patients infected with nalidixic acid-resistant *S. typhi* (NARST) is far inferior to the response in those infected with nalidixic acid-sensitive *S. typhi* (NASST). Unregulated access and indiscriminate use of fluoroquinolones have obviously promoted this debacle. Isolates with reduced susceptibility to ciprofloxacin are fast becoming a major problem in South and South-East Asia. In India, currently, as high as 70 to 80% of isolates in hospital-based studies are NARST and 20 to 50% of isolates are MDR-ST[4,6,8,9].

Treatment of Drug-resistant Typhoid Fever

Fluoroquinolones (ciprofloxacin or ofloxacin 15 mg/kg/day) are the current treatment of choice for typhoid fever in patients of all age groups, including pregnant women, infected or likely to be infected with fully drug-susceptible *S. typhi* or MDR-ST.[10] Short courses of treatment for 5 to 7 days would suffice in such settings. Third-generation cephalosporins (cefixime 20 mg/kg/day for 7 to 14 days or ceftriaxone 60-75 mg/kg/day for 10 to 14 days) and azithromycin (8-10 mg/kg/day for 7 days) are suitable alternatives for the treatment of MDR-ST infections[10].

The optimal treatment for NARST infections is not known yet. Azithromycin and third-generation cephalosporins are effective for the treatment of these infections[10], though their cost is prohibitive. High-dose fluoroquinolones (20 mg/kg/day) given for at least 10 to 14 days still achieve cure in up to 75% of patients infected with NARST[3]. However, the fever clearance time is prolonged (about 7 days), and the rate of convalescent faecal carriage is high[3]. Indirect evidence suggests that the use of fluoroquinolones as first-line treatment in settings where NARST is highly prevalent may result in an excess of complications[4]. The role of newer fluoroquinolones such as levofloxacin and gatifloxacin and combination chemotherapy is currently being evaluated in clinical trials.

Clinical Implications of Drug-resistance

Some earlier studies have suggested that MDR-ST infection is associated with severe clinical disease, and blood bacterial counts have been reported to be substantially higher in patients with MDR-ST infection as compared to those infected with drug-susceptible *S. typhi*[11]. Similarly, NARST infection is associated with longer duration of clinical illness and a higher frequency of complications[4]. A large part of this observed association is attributable to the delay in initiating appropriate antibiotic treatment. It is also possible that drug-resistance and virulence of the isolate are genetically linked. It has to be remembered that none of the antibiotics used *in lieu* of fluoroquinolones achieve fever clearance as rapidly as the latter used to, and even with the latter fever clearance is prolonged in patients with NARST infection[10]. As mentioned earlier, the increased risk of convalescent faecal carriage will promote the spread of infection in the community.

Though it would be of immense use, it is not possible to identify patients infected with NARST based on clinical features, and prediction regarding the likely infecting strain is to be based solely on population-based drug-susceptibility data. Unfortunately, the latter is also largely nonexistent under most settings. Continuing fever beyond the seventh day of fluoroquinolone treatment is highly predictive of NARST infection (positive predictive value 71%)[3].

Is Ciprofloxacin Still the Drug of Choice?

Fluoroquinolones exhibit concentration-dependent killing. It has been suggested that using high-dose fluoroquinolones could be effective for the treatment of infections caused by *S. typhi* isolates with high MICs. The ratios of the 24-hr area under the serum concentration-versus-time curve (AUC/MIC) and the peak serum antimicrobial concentration to the MIC (peak/MIC) are considered the most important determinants of success of fluoroquinolone treatment[12]. These ratios have to be $\geq$ 125 and 8-10 respectively for favorable outcome. If one assumes that 90% of isolates have MICs (MIC_{90}) below 0.5 mg/L, it is estimated, one would need 3177 mg/day of ciprofloxacin to achieve an AUC/MIC ratio > 125.[3] Clinical safety of such a high dose of ciprofloxacin is unknown and is likely to be toxic. Therefore, using very high doses of ciprofloxacin to counteract the decreased susceptibility seems unfeasible. However, AUC/MIC ratios > 125 can be achieved with usual daily doses of newer fluoroquinolones such as levofloxacin and gatifloxacin[3]. Notwithstanding, it would not be long before the same fate of ciprofloxacin befalls these newer fluoroquinolones as well.

CONCLUSIONS

NARST is emerging as a major threat to public health. The optimal treatment strategy for the management of NARST infections is still unknown. Population-based drug-susceptibility data are urgently needed to inform about rational antimicrobial choices. Sustained improvement in sanitation and responsible antibiotic use in the community setting are the only measures capable of tackling the menace of drug-resistant typhoid fever in the long run.

REFERENCES

1. Murdoch DR, Woods CW, Zimmerman MD, Dull PM, Belbase RH, Keenan AJ, et al. The etiology of febrile illness in adults presenting to Patan hospital in Kathmandu, Nepal. Am J Trop Med Hyg 2004;70:670-5.
2. Crump JA, Luby SP, Mintz ED. The global burden of typhoid fever. Bull World Health Organ 2004;82:346-53.
3. Parry CM. The treatment of multidrug-resistant and nalidixic acid-resistant typhoid fever in Vietnam. Trans R Soc Trop Med Hyg 2004;98:413-22.
4. Kadhiravan T, Wig N, Kapil A, Kabra SK, Renuka K, Misra A. Clinical outcomes in typhoid fever: adverse impact of infection with nalidixic acid-resistant Salmonella typhi. BMC Infect Dis 2005;5:37.
5. Wain J, Hoa NT, Chinh NT, Vinh H, Everett MJ, Diep TS, et al. Quinolone-resistant Salmonella typhi in Vietnam: molecular basis of resistance and clinical response to treatment. Clin Infect Dis 1997;25:1404-10.
6. Rupali P, Abraham OC, Jesudason MV, John TJ, Zachariah A, Sivaram S, Mathai D. Treatment failure in typhoid fever with ciprofloxacin susceptible Salmonella enterica serotype *typhi*. Diagn Microbiol Infect Dis 2004;49:1-3.
7. Hakanen A, Kotilainen P, Jalava J, Siitonen A, Huovinen P. Detection of decreased fluoroquinolone susceptibility in Salmonellas and validation of nalidixic acid screening test. J Clin Microbiol 1999;37:3572-7.
8. Madhulika U, Harish BN, Parija SC. Current pattern in antimicrobial susceptibility of Salmonella typhi isolates in Pondicherry. Indian J Med Res 2004;120:111-4.
9. Ray P, Sharma J, Marak RS, Garg RK. Predictive efficacy of nalidixic acid resistance as a marker of fluoroquinolone resistance in Salmonella enterica var Typhi. Indian J Med Res 2006;124:105-8.
10. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. N Engl J Med 2002;347:1770-82.
11. Wain J, Diep TS, Ho VA, Walsh AM, Nguyen TT, Parry CM, White NJ. Quantitation of bacteria in blood of typhoid fever patients and relationship between counts and clinical features, transmissibility, and antibiotic resistance. J Clin Microbiol 1998;36:1683-7.
12. Crump JA, Barrett TJ, Nelson JT, Angulo FJ. Reevaluating fluoroquinolone breakpoints for Salmonella enterica serotype typhi and for non-Typhi salmonellae. Clin Infect Dis 2003;37:75-81.