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Rapidly changing treatment options adding burden to the management of typhoid fever

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ABSTRACT

Typhoid fever continues to be a global public health problem. It *is caused by the facultative intracellular organisms Salmonella enteric serotype Typhi and Salmonella paratyphi.* Antimicrobial therapy is the mainstay for treatment of typhoid fever. Chloramphenicol, ampicillin, and cotrimoxazole had been in use for decades for treating enteric fever. But the emergence and rapid spread of drug resistance has resulted in rapid shift of treatment options from chloramphenicol to fluoroquinolones to third generation cephalosporins to azithromycin with tigecycline and carbapenems in line, thus adding burden to the health-care sector in developing countries. Rational and judicious antibiotic prescribing practices by health professionals are necessary to prevent further development of drug resistance and help in re-emergence of sensitive strains.

Keywords: Multi Drug Resistance, Typhoid, Treatment Options

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INTRODUCTION

Typhoid fever is a major public health problem worldwide especially for people living in developing areas with poor sanitation and fecal contamination of food and water.[1] In India, the disease occurs with an incidence ranging from 102 to 2,219 per 100,000 of the population.[2] One-quarter to one-third of pediatric typhoid fever cases are under five years of age.[3] No vaccine against typhoid fever is available commercially for children under two years of age.[3] So, if not treated properly, it carries a mortality rate of 30%.Antimicrobial therapy is the mainstay for treatment of typhoid fever. Antibiotics such as chloramphenicol, ampicillin, and cotrimoxazole had been in use for decades for treating enteric fever. But the emergence and spread of multidrug resistant typhoidal Salmonella is leading to rapidly changing treatment options. So, in this article we shall be reviewing the narrowing down journey of various treatment options in the management of typhoid fever which indeed is worrisome.

CHLORAMPHENICOL AS THE DRUG OF CHOICE

In 1948, a major breakthrough was achieved in the management of typhoid fever with the introduction of chloramphenicol, primarily a bacteriostatic drug inhibiting bacterial protein synthesis. The mortality rate was reduced to 1% from existing 30%. In cases of contraindications and pregnancy ampicillin was used. But being orally effective, broad spectrum and cheap, chloramphenicol was use irrationally for other infections as well, resulting in emergence and spread of resistance to chloramphenicol. However, the efficacy of chloramphenicol remained satisfactory despite sporadic reports of resistance. It was not until 1972 that chloramphenicol resistant Salmonella typhi strains became a major problem, with outbreaks being reported in Mexico (1972), India (1972), Vietnam (1973) and Korea

(1977).[4-6] These strains were also resistant to ampicillin. Chloramphenicol resistant Samonella typhi emerged due to acquisition of R plasmid encoding for an acetyl tranferase- an enzyme which inactivates chloramphenicol.

COTRIMOXAZOLE GAINED IMPORTANCE

Given the increased mortality associated with resistance to chloramphenicol and the rare chloramphenicol-induced bone marrow toxicity, co-trimoxazole became the mainstay of treatment. Co-trimoxazole remained an effective alternative drug in treating these resistant strains until 1975, when resistance to it was reported in France. By the late 1980s, strains of Salmonella typhi resistant to all three first-line drugs were in existence.[3,7,8] The Indian subcontinent and Southeast Asian countries were particularly affected by multidrug resistant Samonella typhi (MDRST) strains.[9] The epidemic zone of MDRST in Asia now appears to stretch from Pakistan in the west to China in the east.[10,11] Multi-drug resistant Salmonella typhi were first described in India in 1990. An outbreak of enteric fever called 'Dombivali Fever' was reported from Mumbai in 1990 and the causative organism was MDRST.[12] The incidence of MDRST ranged from 11% at Vellore[9], to more than 90% at Bangalore.[13] MDRST was 85% at Hyderabad[14], 38.8% at Pondicherry[15] and 58% at Manipal[16].

CHANGING OF TREATMENT OPTIONS TO FLUOROQUINOLONES

The epidemic of MDRTF led to change in treatment options in the late 1980s compelling pediatricians throughout the world to use fluoroquinolones, despite a lack of data regarding its safety for use in children.[17,18] Fortunately, follow-up studies done in children found them to be safe, effective, and less expensive with a very high sensitivity pattern.[19,20] The fluoroquinolones commonly used in children for MDRTF are ofloxacin and ciprofloxacin (15 mg/kg/day) in two doses. Both are highly active and equivalent in efficacy. As ciprofloxacin had a high cure rate with no relapse or carrier state, it was considered to be the first choice for treatment of multidrug-resistant typhoid cases. Unfortunately, lately, there have been several reports of fluoroquinolone-resistant Salmonella typhi.[21,22,23] However, there were problems with identifying these strains. Salmonella typhi resistant to nalidixic acid did not respond to ciprofloxacin despite having minimum inhibitory concentration (MIC) values within Clinical and Laboratory Standards Institute (CLSI) susceptibility range for ciprofloxacin.[24] This means that in vitro susceptibility did not always translate to in vivo efficacy and that there was risk of treatment failures in those infected with such strains.[25] To resolve this problem of discordance between in vitro and in vivo susceptibility CLSI has revised ciprofloxacin breakpoints from < 1 µg /ml in 2011 to <0.06 µg /ml in 2012. For ciprofloxacin there is clinical evidence to indicate a poor response in systemic infections caused by Salmonella spp. with reduced susceptibility to fluoroquinolones.[26] Isolates with MICs > 0.06 µg /ml should be reported as resistant. Earlier nalidixic acid resistance in the presence of ciprofloxacin susceptibility had been thought to be a reliable indicator of decreased ciprofloxacin susceptibility; however, this is now known not to be the case and it is recommended that ciprofloxacin MIC should be determined for all invasive Salmonella infections.

SHIFT TO CEPHALOSPORINS

As the efficacy of fluoroquinolones too has been questioned, mainly due to increasing reports of increasing defervescence time and poor patient response, expanded-spectrum cephalosporins, such as cefipime, cefpodoxime proxetil, ceftriaxone and cefixime, have been investigated and shown promise as therapies for the treatment of enteric fever. However, only cefixime and cefpodoxime proxetil have oral route of administration, while ceftriaxone and cefipime have parenteral route. Also, cefpodoxime proxetil has a favorable pharmacokinetic profile, which allows twice-daily administration. But recently there are reports from the Indian subcontinent of isolates that are resistant to extended spectrum cephalosporins.[27] Cefixime being orally effective became more popular resulting in its increased MIC. Extended-spectrum β-lactamase-producing Salmonella serotype Typhi and Salmonella serotype Paratyphi A have been reported.[28,29] Of even greater concern are the isolates that display concurrent resistance to quinolones and extended-spectrum cephalosporins, which may require use of an alternative antimicrobial class for management of invasive infections.

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INTRODUCTION OF AZITHROMYCIN

Azithromycin, a member of the macrolide class of antibiotics, possesses many characteristics for effective and convenient treatment of typhoid fever, including in vitro activity against many enteric pathogens, excellent penetration into most tissues, and achievement of concentrations in macrophages and neutrophils that are >100-fold higher than concentrations in serum. It has been demonstrated in clinical trials to be equivalent or superior to chloramphenicol, fluoroquinolones, and extended-spectrum cephalosporins for the management of uncomplicated typhoid fever.[30,31]

Azithromycin reduces the clinical failure rate and duration of hospital stay in comparison to fluoroquinolones and relapse rate in comparison to ceftriaxone, when used in the treatment of typhoid fever in populations with multidrug resistant typhoid fever. It also represents a potential alternative in the pediatric population for whom quinolones are contraindicated. A 5-day course of azithromycin (a dosage of 20 mg/kg per day, with a maximum dose of 1000 mg/day) is effective against uncomplicated typhoid fever in children and adolescents. Considering the potential of development of resistance to any new antibiotic introduced, azithromycin should be used guardedly to prevent the emergence of strains resistant to the drug.

TRIAL ON NEWER DRUGS

Carbapenems and tigecycline are other alternative drugs being proposed in the treatment of multidrugresistant typhoid fever. Tigecycline is a glycylcycline (tetracycline analogue). It inhibits protein synthesis and evades efflux and target-mediated resistance to classical tetracyclines. Tigecycline was found to be very potent, inhibiting 97.3% of Salmonella Typhi and all the Salmonella Paratyphi A and ceftriaxone-resistant Salmonella isolates. Nevertheless, systematic large-scale in vivo studies are needed to assess the relative merits of tigecycline versus other drugs in these infections. Carbepenems are a class of β-lactam antibiotics with broad-spectrum activity and are stable to hydrolysis by extended-spectrum β-lactamases-producing isolates. In a recent study, the MIC90 for the carbapenems, imipenem and meropenem in Salmonella Typhi and Salmonella Paratyphi A (0.064 µg/mL each) was less.[32] Recently, several studies have found that strains previously resistant to the first-line drugs (chloramphenicol, ampicillin and co-trimoxazole) are now showing decreasing resistance.[33] The withdrawal of selective pressure has probably resulted in the re-emergence of sensitivity to these first-line drugs.[33] But large-scale systematic studies are required to determine whether these drugs can again be used for the treatment of typhoid fever in developing countries.

CONCLUSION

The menace of drug resistance is posing a major therapeutic challenge in the management of typhoid fever by limiting the treatment options. The selection of antibiotics in the treatment of MDRTF in developing countries is determined by the cost, susceptibility patterns and the prevalence of antimicrobial resistance. As the treatment of multidrug resistant typhoid fever requires costly drugs, adding burden to the health-care sector in developing countries, emphasis must be placed on disease prevention, which includes vaccination of the high-risk population in endemic areas, safe food handling practices, and public health education. There is dire need for rational and judicious antibiotic prescribing practices by health professionals to curtail this growing drug resistance and to put a stop to these rapidly changing treatment options.

REFERENCES

1. Kothari A, Pruthi A, Chugh TD . The Burden of Enteric Fever. J Infect Dev Ctries 2008; 2: 253-259.
2. Chowta MN, Chowta NK . Study of clinical profile and antibiotic response in typhoid fever. Indian J Med Microbiol 2005; 23: 125-127.
3. Zaki SA, Karande S. Multidrug-resistant typhoid fever: a review. J Infect Dev Ctries 2011; 5(5):324-337.
4. Olarte J, Galindo E. Salmonella Typhi resistant to chloramphenicol, ampicillin, and other antimicrobial agents: strains isolated during an extensive typhoid fever epidemic in Mexico. Antimicrob Agents Chemother 1973; 4: 597-601.
5. Paniker CK, Vimala KN. Transferable chloramphenicol resistance in Salmonella typhi. Nature 1972; 239: 109-110.

6. Butler T, Linh NN, Arnold K, Pollack M. Chloramphenicol-resistant typhoid fever in Vietnam associated with R factor. Lancet 1973; 302: 983-985.
7. Chun D, Seol SY, Cho DT, Tak R. Drug resistance and R plasmids in Salmonella typhi isolated in Korea. Antimicrob Agents Chemother 1977; 11: 209-213.
8. Datta N, Richards H, Datta C. Salmonella typhi in vivo acquires resistance to both chloramphenicol and cotrimoxazole. Lancet 1981;1:1181-3
9. Jesudasan MV, John TJ. Multiresistant Salmonella typhi in India. Lancet 1990; 336: 252
10. Mirza SH, Beeching NJ, Hart CA. The prevalence and clinical features of multi-drug resistant Salmonella typhi infections in Baluchistan, Pakistan. Ann Trop Med Parasitol 1995; 89: 515-519
11. Zhang L. Mechanism of multiresistant Salmonella typhi. Chung Hua I HsuehTsaChih Taipei 1991; 71: 314-317, 324.
12. Deodhar L, Bhave S, Agarwal A. 'Bacteriophage typing of multi drug resistant Salmonella typhi in paediatric patients'. Bombay Hospital Journal 1993; 35: 114-15.
13. Ratish KC, Chandrashekar MR, Nagesh CN. Multidrug resistant Salmonella typhi in Bangalore. South Indian J Med Sci. 1994; 48:85-88.
14. Hemlatha R, Vijaylakshmi P, Gyaneshwari, Rao MVR, Ramani A. Multidrugresistant Salmonella typhi in Hyderabad. Ind J Med Microbiol 1999;17:39-41
15. Madhulika U, Harish BN Parija SC. Current pattern in antimicrobial susceptibility of Salmonella typhi isolates in Pondicherry. Ind J Med Res 2004; 120:111-4.
16. Ciraj AM, Seetha KS, Gopalkrishna BK, Shivananda PG. Drug resistance pattern and phage types of Salmonella typhi isolates in Manipal, South Karnataka. Indian J Med Sci 1999; 53:486-9.
17. Bavdekar SB. Antimicrobial therapy of multidrug resistant typhoid fever in children: pediatricians' opinion. J Postgrad Med 1996; 42: 65-67.
18. Gupta A. Multidrug-resistant typhoid fever in children: epidemiology and therapeutic approach. Pediatr Infect Dis J 1994; 13: 134-140.
19. Karande S, Kshirsagar NA. Ciprofloxacin use: acute arthropathy and long-term follow up. Indian Pediatr 1996; 33: 910-916.
20. Bethell DB, Hien TT, Phi LT, Day NP, Vinh H, Duong NM.Effects on growth of single short courses of fluoroquinolones. Arch Dis Child 1996; 74: 44-46.
21. Raveendran R, Wattal C, Sharma A, Oberoi JK, Prasad KJ, Datta S. High level ciprofloxacin resistance in Salmonella enterica isolated from blood. Indian J Med Microbiol 2008; 26:50-3.
22. Adachi T, Sagara H, Hirose K, Watanabe H. Fluoroquinolone- resistant Salmonella Paratyphi A. Emerg Infect Dis 2005;11:172-4.
23. Saha SK, Darmstadt GL, Baqui AH, Crook DW, Islam MN, Islam M, et al. Molecular basis of resistance displayed by highly ciprofloxacin - resistant Salmonella enteric serovar Typhi in Bangladesh. J ClinMicrobiol 2006; 44:3811-3.
24. Gupta V, Kaur J. A need to revise ciprofloxacin breakpoints in Salmonella in human beings. Internat j of Infect dis 2008; 12:e143-e144.
25. 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(1):75-81.
26. Chandel DS, Chaudhry R. Enteric fever treatment failures: A global concern. Emerg Infect Dis 2001; 7:762-3.
27. Su LH, Wu TL, Chia JH, Chu C, Kuo AJ, Chiu CH. Increasing ceftriaxone resistance in Salmonella isolates from a university hospital in Taiwan. J Antimicrob Chemother, 2005; 55:846-852.
28. Gokul BN, Menezes GA, Harish BN. ACC-1 beta-lactamase producing Salmonella enterica serovar Typhi, India. Emerg Infect Dis 2010; 16:1170-1.
29. Pokharel BM, Koirala J, Dahal RK, Mishra SK, Khadga PK,Tuladhar NR. Multidrug-resistant and extended-spectrum beta-lactamase (ESBL)-producing Salmonella enterica (serotypes Typhi and Paratyphi A) from blood isolates in Nepal: surveillance of resistance and a search for newer alternatives. Int J Infect Dis 2006; 10:434-8.
30. Capoor MR, Rawat D, Nair D, Hasan AS, Deb M, Aggarwal P, et al. In vitro activity of azithromycin, newer quinolones and cephalosporins in ciprofloxacin resistant

Salmonella causing enteric fever. J Med Microbiol 2007; 58:1490-45.

31. Effa EE, Bukirwa H. Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever). Cochrane Database of Systematic Reviews 2008, Issue 4. Art. No.: CD006083
32. Capoor MR, Nair D, Posi J, Singhal S, Deb M, Pushpa A, et al. Minimum inhibitory concentration (MIC) of carbapenems and tigecycline against Salmonella spp. J Med Microbiol 2009; 58:337–41.
33. Gupta V, Kaur J, Kaistha N. Reemerging chloramphenicol sensitivity and emerging low level ciprofloxacin resistance among Salmonella enterica serotype Typhi isolates in north India. Trop Doct 2009; 39:28-30.