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

Jaspal Kaur *1, Priyanka Khanna 2

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

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.
Ciprofloxacin despite having minimum inhibitory concentration (MIC) values within Clinical and Laboratory Standards Institute (CLSI) susceptibility range for ciprofloxacin. 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. 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. 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, ceftiraxone 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 ceftiraxone 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. 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.

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.
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 multidrug-resistant typhoid fever. Tigecycline is a glyyclcycline (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. Carbapenems 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

