Review Article

DOI: 10.7860/JCDR/2013/4765.2831

Microbiology Section

Increasing Antimicrobial Resistance and Narrowing Therapeutics in Typhoidal Salmonellae

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ABSTRACT

Multidrug-resistant typhoid fever (MDRTF) is a major public health problem in developing countries and is an emerging problem in the developed world. Because of the difficulties in preventing typhoid by public health measures or immunization in developing countries, great reliance is placed on antimicrobial chemotherapy. The treatment should commence as soon as the clinical diagnosis is made rather than after the results of antimicrobial susceptibility tests but the existence of MDRTF poses a serious clinical dilemma in the selection of empiric antimicrobial therapy. With the widespread emergence and spread of strains resistant to chloramphenicol, ampicillin and trimethoprim, ciprofloxacin became the drug of choice for the treatment of typhoid fever. However, of late the efficacy of fluoroquinolones too has been questioned, mainly due to increasing reports of increasing defervescence time and poor patient response. This indicates that the organism has begun to develop resistance to fluoroquinolones, and is corroborated by a steady increase in Minimum Inhibitory Concentration (MIC) of ciprofloxacin. The therapeutics of ciprofloxacin-resistant enteric fever narrows down to third- and fourth-generation cephalosporins and azithromycin. However, the emergence of extended-spectrum b-lactamases (ESBLs) in typhoidal Salmonellae poses a new challenge and would greatly limit the therapeutic options leaving only tigecycline and carbepenems as secondary antimicrobial drugs. This increasing resistance is alarming and emphasizes the need of effective preventive measures to control typhoid and to limit the unnecessary use of antibiotics.

Key Words: Antimicrobial resistance, cephalosporins, extended-spectrum b-lactamases, quinolones, typhoidal salmonellae

INTRODUCTION

Typhoid fever, which is most commonly caused by *SamonellaTyphi* and *Paratyphi A*, is a major problem for the people who live in the developing areas with poor sanitation and the faecal contamination of food and water. It has been estimated that there are at least 21 million new cases of typhoid fever each year and 250,000 deaths [1]. Almost 80% of the cases and deaths are in Asia; the rest occur mainly in Africa and Latin America [2]. In developing countries such as India, the disease occurs with an incidence which ranges from 102 to 2,219 per 100,000 of the population. If it is not treated properly, it carries a mortality rate of 30%. Hence, the drug resistance in *Salmonella* poses a major problem for the public health authorities and it is of considerable concern for both clinicians and microbiologists. In the last three decades, high rates of resistance to the common first-line antimicrobial agents have been reported among *SalmonellaTyphi,* in many regions of the world. The Indian subcontinent and the southeast Asian countries are particularly affected by Multidrug Resistant (MDR) *SamonellaTyphi* strains. A clinical resistance to fluoroquinolones has also been reported [3,4]. So, in this brief review, we will be discussing the global problem of the increasing antimicrobial resistance in the typhoidal Salmonellae, which is a phenomenon of great importance in narrowing the therapeutic options in the treatment of typhoid fever.

The Emergence of Multidrug Resistance in Salmonella Typhi

The introduction of chloramphenicol in 1948, proved to be a major breakthrough in the treatment of typhoid fever. Chloramphenicol is primarily bacteriostatic and it inhibits the bacterial protein synthesis. The treatment with chloramphenicol reduced the mortality to 1% and the duration of fever from 14-28 days to 3-5 days. In case of contraindications, as in haematological complications, ampicillin and trimethopriom/sulphamethaxazole were used as the alternate antibiotics. Ampicillin /Amoxicillin have been the treatment of choice in pregnancy and in neonates [5]. Being orally active, broad spectrum and relatively cheap, chloramphenicol was used extensively and often indiscriminately, resulting in the development of resistance. The chloramphenicol-resistant *SamonellaTyphi* emerged first in the UK, within 2 years of the successful use of chloramphenicol in typhoid. Subsequently, isolates which carried a transferable chloramphenicol resistance were described in Greece [6] and Israel [7]. Two *Salmonella Typhi* isolates from Aden and Cairo, which carried a transferable resistance to chloramphenicol, ampicillin and tetracycline, were found in 1967 [8]. Although there were sporadic reports of resistance, the effectiveness of chloramphenicol remained satisfactory until 1989, when there was a rapid emergence and spread of multidrug resistant *Salmonella Typhi* (which were resistant to chloramphenicol, ampicillin and trimethoprim-sulfamethoxazole) in several parts of India. This multidrug resistance came as a major setback in the typhoid control at a time when the disease had almost been eradicated from the west. It was found that a single strain which contained a plasmid which had multi drug-resistance had emerged among the *Salmonella Typhi* population and that it had been able to adapt to and to survive the antibiotics as they were introduced into the clinical medicine. Datta et al reported the acquisition of the R-plasmid by *Salmonella Typhi* in the bowel of man from other enteric bacteria [9]. Chloramphenicol resistant *SamonellaTyphi* have emerged due to the acquisition of the R plasmid which

encodes for an acetyl tranferase- an enzyme, which inactivates chloramphenicol. The genes which are responsible for the resistance to trimethoprim-sulfamethoxazole and ampicillin are dihydrofolate reductase type VII, and TEM-1 β-lactamase.

The Prevalence of Multi Drug Resistant (MDR) Salmonella Typhi

A chloramphenicol resistant *Salmonella Typhi* outbreak was first reported in India from Kerala [10], where a substantial outbreak took place in 1972, soon after the first epidemic was caused by a chloramphenicol-resistant strain in Mexico [11]. This was followed by outbreaks in Vietnam, Indonesia, Korea, Chile and Bangladesh [12]. A notable feature in these outbreaks was chloramphenicol resistance, in combination with a resistance to streptomycin, the sulphonamides and the tetracyclines (R-type CSSuT). A single plasmid has been known to code for the multidrug resistance. This plasmid belongs to the incompatibility group, H I1 and it is highly transmissible. The epidemic zone of MDRST in Asia, now appears to stretch from Pakistan in the west, to China in the east. Multi-drug resistant strains were first reported in Pakistan in 1987 and they have increased in prevalence to almost 90 % [13]. The prevalence of MDRST in China has increased since 1985 and by 1989, 80% of the *Salmonella Typhi* isolates in Shanghai were multiresistant. In these strains, a resistance to gentamicin and cephazolin was seen, in addition to the resistance to chloramphenicol, ampicillin, tetracycline, trimethoprim and the sulphonamides, which was encoded on a self-transferable 98 MDa plasmid [14]. In Africa and America, *Salmonella Typhi* remained sensitive to one or more of the first line agents, although large outbreaks of the infections which were caused by the strains which were resistant to chloramphenicol and some of the other antimicrobial agents, continued to occur. In the UK, multiresistant strains now represent >18% of the *Salmonella Typhi* isolates [15].

The Indian Scenario

Multi-drug resistant *Salmonella Typhi* were first described in India in 1990. An outbreak of enteric fever which was called 'Dombivali Fever' was reported from Mumbai in 1990 and the causative organism was MDRST [16]. The incidence of MDRST ranged from 11% at Vellore [17], to more than 90% at Bangalore [18]. The incidence of MDRST was 85% at Hyderabad [19], 38.8% at Pondicherry [20] and 58% at Manipal [21].

The Entry of Fluoroquinolones and the Development of Fluoroquinolone Resistance

The problem of multidrug resistance in *Salmonella Typhi* was resolved to some extent with the advent of fluoroquinolones like ciprofloxacin in the 1980s. However, of late, the efficacy of the fluoroquinolones too has been questioned, mainly due to the increasing reports of an increasing defervescence time and a poor patient response. This indicates that the organism has begun to develop resistance to the fluoroquinolones, and this has been corroborated by a steady increase in the Minimum Inhibitory Concentration (MIC) of ciprofloxacin, which has been reported from many centres in India [22, 23]. The isolates which were found to be fully susceptible to ciprofloxacin by disc testing, had a ciprofloxacin MIC of less than 0.03 μg/ml. However, a population of isolates exists, with an MIC of 0.125-1.0 μg /ml, which seems to be susceptible to ciprofloxacin by disc testing, but is associated with clinical failure. This indicates a need to revise the ciprofloxacin breakpoints for *Salmonellae* [24]. A high- level, ciprofloxacin-resistant (MIC>128 μg /ml) *Salmonella Paratyphi A* strain was isolated in Japan [25] and three strains of highly ciprofloxacin-resistant (MIC, 512 μg /ml) *Salmonella Typhi* were reported from Bangladesh [26]. The fluoroquinolones target DNA gyrase and topoisomerase IV, which are bacterial enzymes that are part of a complex that uncoils and recoils the bacterial DNA for transcription. *Salmonella Typhi* most commonly develops fluoroquinolone resistance through specific mutations in gyrA and parC, which code for the binding region of DNA gyrase and topoisomerase IV, respectively. A single point mutation, gyrA, confers a partial resistance. If a second gyrA point mutation is added, the resistance increases somewhat. However, a mutation in parC which is added to a single gyrA mutation, confers full in vitro resistance to the first-generation fluoroquinolones. The risk of a relapse after a bacterial clearance is higher in both the partially and fully resistant strains than in the fully susceptible strains. Other mechanisms which have been demonstrated are the efflux pumps which are associated with multi-antibiotic resistance (the MAR locus, outer membrane proteins), the qnr plasmid (qnr A, qnr A, AAC1F) and the up/down-regulation of the operon gene. The quinolones which are used in the therapy of enteric fever are ciprofloxacin, gatifloxacin, levofloxacin and ofloxacin. In studies which were done in India and Nepal, the first- and the second-generation quinolones showed varying results. Gatifloxacin demonstrated a better in vitro activity as compared to the other quinolones [27]. However, gatifloxacin carries a risk for dysglycaemia, which limits its use. It was concluded that all the fluoroquinolones should be tested individually, and that ciprofloxacin does not represent this group adequately. In gatifloxacin and moxifloxacin, the primary target is the gyrA gene; and for ciprofloxacin and levofloxacin, it is the parC gene. This would explain their varied patterns of susceptibilities. The disparity in the MIC levels of the quinolones is attributable to the difference in the additional fluoro- and other substitutions in their chemical structures [27].

A nalidixic acid resistance in the presence of a ciprofloxacin susceptibility, had been thought to be a reliable indicator of a decreased ciprofloxacin susceptibility; however, this is now known not to be the case, and many have suggested that a decreased ciprofloxacin susceptibility can be most reliably determined by the measurement of the ciprofloxacin minimum inhibitory concentration. The patients with the Nalidixic Acid Resistant (NAR) strains require higher doses of ciprofloxacin or ofloxacin.

The Third Generation Cephalosporins in Typhoid Fever

In response to the emergence of the flouroquinolone resistance, the efficacies of the third generation cephalosporins in the treatment of typhoid fever, have been investigated. The expanded-spectrum cephalosporins, such as cefipime, cefpodoximeproxetil, ceftriaxone and cefixime, have shown promise as therapies for the treatment of enteric fever. However, only cefixime and cefpodoximeproxetil have oral routes of administration, while ceftriaxone and cefipime have parenteral routes of administration. But, the extensive use of these agents can lead to the development of Extended-Spectrum β-Lactamases (ESBLs) production in *Salmonella Typhi,* as it happened with other gram negative bacteria [28]. In fact, there are sporadic reports of a high level resistance to ceftriaxone [29]. *Salmonella Typhi* has been found to produce a wide variety of ESBL types which include the TEM, SHV, PER and the CTXM enzymes. The emergence of ESBL in MDR *Salmonella Typhi* constitutes a new challenge and it has become a matter of concern, especially

in the underdeveloped countries. Recently, AmpC b-lactamase producing *Salmonella Typhi* has been reported [30].

The re-emergence of the susceptibility to chloramphenicol

Discontinuation of the chloramphenicol therapy has relieved the selection pressure, thus paving the way for the re-emergence of *Salmonella Typhi* isolates which are sensitive to chloramphenicol. Gautam et al reported a 90% sensitivity to chloramphenicol by MIC determination from Rohtak (Haryana, India) [31]. A study from Hyderabad reported an increase in the chloramphenicol sensitivity of *Salmonella Typhi* from 46% in 2001-2002 to 59% in 2003 and 67% in 2004 and that of *Salmonella Paratyphi A* from 60% in 2001-2003 to 80% in 2004 [32]. Only 2 of the 56 isolates of *Salmonella Typhi* were resistant to chloramphenicol at Childrens Hospital, Delhi, in 2004-2005 [33]. Another study from north India reported a 93.2% sensitivity of *Salmonella Typhi* to chloramphenicol [21]. Studies from Chandigarh, Rourkela and Calicut have reported 90%, 91.2% and 96.49% sensitivities of *Salmonella Paratyphi A* to chloramphenicol respectively [34-36]. With the increase in the sensitivity to chloramphenicol, there is a decline in the number of MDRST strains. A recent study from Karnataka (Gulbarga, India) reported only 10% strains as MDR [2]. Nevertheless, the re-introduction of chloramphenicol in the enteric fever therapeutics has a long way ahead. A high relapse rate, a high rate of a continued and a chronic carriage, and bone marrow toxicity are the other concerns with the reuse of chloramphenicol in the treatment of typhoid fever.

NEWER DUGS IN THE TYPHOID FEVER THERAPEUTICS

Azithromycin

Azithromycin, a broad-spectrum azilide, can be the drug of choice over ceftriaxone, ofloxacin and chloramphenicol, due to its negligible relapse rate and faecal carriage, and a favourable outpatient compliance. In enteric fever, its role needs to be appreciated, as it is very effective in removing the intracellular Salmonellae, its defervescence is rapid, the gastrointestinal carriage is eradicated and, in particular, it represents a potential alternative in the paediatric population for whom quinolones are contraindicated.

Tigecycline

Tigecycline is a glycylcycline (tetracycline analogue). It inhibits the protein synthesis and evades the efflux and the target-mediated resistance to the classical tetracyclines. Tigecycline was found to be very potent and it was found to inhibit 97.3% of the *Salmonella Typhi* and all the *S. Paratyphi A* and the 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 [37].

Carbapenems

The carbepenems are a class of β-lactam antibiotics with broad-spectrum activities and they are stable to the hydrolysis which is caused by the extended-spectrum β-lactamases-producing isolates. In a recent study, the MIC90s for the carbapenems, imipenem and meropenem among *Salmonella Typhi* and *Salmonella Paratyphi A* (0.064 μg/mL each) were found to be less [37].

CONCLUSIONS

Antimicrobial resistance in the typhoidal Salmonellae is a major public health problem. The optimal management of enteric fever depends on the understanding of the local patterns of the antimicrobial resistance and on the results of the antimicrobial susceptibility testing of the Salmonella which are isolated from the individual patients. Ciprofloxacin continues to be widely used, but the clinicians need to be aware that the patients who are infected with Salmonella, who have a decreased ciprofloxacin susceptibility or with the (NAR) strains, may not respond adequately. In these circumstances, the third-generation cephalosporins, such as ceftriaxone and cefixime, are the important additions to our armaments against typhoid fever. However, its cost and the route of administration make ceftriaxone less suitable for the patients' treatment in some low and middle-income countries, and the oral third-generation cephalosporin, cefixime, appears to be inferior to the other oral agents, both in terms of the fever clearance time and the treatment failure. Several small studies have reported a successful treatment of typhoid fever with aztreonam, a monobactam antibiotic [38]. This antibiotic has been shown to be more effective than chloramphenicol in clearing the organism from the blood and it is associated with fewer adverse reactions. However, a prospective clinical trial which was carried out among children in Malaysia was discontinued because of a high failure rate with aztreonam [39]. Azithromycin shows some promise for the management of uncomplicated typhoid fever and it may provide a useful alternative to ceftriaxone in thesettings where a cheaper oral regimen is needed. Though the use of azithromycin, tigecycline and carbapenem is not recommended by the Clinical Laboratory Standards Institute [40], it may become crucial, especially in the setting of ciprofloxacin-resistant and extended-spectrum β-lactamase-producing Salmonellae in enteric fever. So, the increasing complexity of managing enteric fever because of the increasing antimicrobial resistance, stresses on a need to control the disease through improvements in sanitation, a greater access to safe water and food, identification and treatment of the *Salmonella Typhi* carriers, and a more widespread use of the currently available vaccines in populations who are at a high risk of the infection. The gradual narrowing of the therapeutic options warrants the judicious use of antibiotics.

ACKNOWLEDGEMENT

Substantial work was done by me, Dr JASPAL KAUR on Salmonella Typhi and Paratyphi A (particularly on antimicrobial resistance and unusual manifestations) during my posting at Government MedicalCollege, Sec-32 Chandigarh as is evident from my various publications in the renowned national and International journals.

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FINANCIAL OR OTHER COMPETING INTERESTS:

None.

Date of Submission: **Jun 27, 2012**
Date of Peer Review: **Sep 19, 2012**
Date of Acceptance: **Dec 05, 2012**
Date of Publishing: **Mar 01, 2013**