Anti Microbial Resistance in *Salmonella*

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Abstract: Antibiotics are one of the major drugs to eradicate microbial infection. Many types of antibiotics have been used as therapeutics in several fields such as medical, agriculture, animal husbandry for human beings as well as animals. In past few years microbes have become resistant to some common antibiotics. We found that drug resistance is escalating at an alarming rate. Some of the infections like typhoid, pneumonia, tuberculosis, and gonorrhea are becoming difficult to treat while antibiotics are becoming less effective. Typhoid fever is one of the most common foodborne illnesses leading to many deaths annually worldwide. The emergence of multi-drug resistant *Salmonella enterica* serovar Typhi strains (*S*. Typhi) has resulted in several large outbreaks of enteric fever in many developing countries of the world leading to increased morbidity and mortality. Multi-drug resistance remains a major public health problem, particularly in developing countries of Asia and Africa. Some important measures like rational use of antibiotics, improvement in public sanitation facilities, availability of clean drinking water, promotion of safe food handling practices and public health education can play a crucial role in the prevention of multiple drug resistant typhoid fever.

Keywords: *Salmonella*, plasmids, antibiotics, multiple drug resistance.

INTRODUCTION

Salmonella is a genus consisting of serovars of facultative gram-negative bacterium. *Salmonella enterica* serovars Typhi, Paratyphi A, Paratyphi B, and Paratyphi C lead to typhoid fever in humans and are collectively known as typhoidal *Salmonella* while other serovars are grouped as non-typhoidal *Salmonella* (NTS) which are causative agents of non-typhoidal salmonellosis in animals. Typhoidal Salmonella strains that cause typhoid and paratyphoid fever are restricted to human beings whereas non-typhoidal Salmonella strains infect a broad range of animal species [1]. In current scenario typhoid fever has became a serious global health problemwith approximately 21 million cases and more than 200,000 deaths annually in developing countries of Asia and Africa as well as in some developed countries [2]. The most common cause of the infection of *S*. Typhi is consumption of contaminated food and water [3]. There is always a possibility of high risk of infection of *S*. Typhi due to unhygienic conditions and low economic status of developing countries [4, 5]. Inspite of the emergence of newer antimicrobial drugs, typhoid fever has continued to be a crucial public health problem [6]. Antibiotics such as ampicillin, ceftriaxone, co-trimoxazole and ciprofloxacin have become resistant to *Salmonella enterica*. The emergence of multiple drug resistance to the frequently used antibiotics has made the treatment of typhoid fever more complex and hence considered as one of the utmost challenges in the management of this illness [7].

HISTORY OF ANTIMICROBIAL RESISTANCE

Apart from the above causes of *S*. Typhi infection, occurrence of antimicrobial resistance in *Salmonella*Typhi has made treatment of typhoid fever more complicated. Antibiotics were used for the treatment of typhoid fever globally. Among antibiotics, chloramphenicol was the main drug of choice for the treatment of enteric fever before 1970s [8-10]. Later in 1972, the first outbreak caused by a chloramphenicol-resistant strain was reported from Mexico [11]. Afterwards, outbreaks involving chloramphenicol-resistant *Salmonella enterica*serovar Typhi were reported from several countries including India [12], South Korea [13]. Bangladesh [14] and Vietnam [15]. It was observed that self-transmissible plasmid of the HI1 incompatibility type (IncHI) was responsible for the chloramphenicol resistance. IncHI plasmids are considered to carry genes which confer resistance to many other drugs like streptomycin, sulfonamides, and tetracyclines [16, 14]. Later ampicillin and trimethoprim-sulfamethoxazole were used as first-line drugs for the treatment of typhoid fever until resistance was reported [6]. Multiple-drug resistance (MDR) to different antibiotics like ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole, was reported from several countries [17, 18] leading to large number of cases of enteric fever [19-21]. The multi-drug resistant

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Salmonella Typhistrains caused outbreaks of typhoid fever in many developing countries of Africa and South Asia like Kenya [22], Nigeria [23], India [24] and Vietnam [20]. After the development of drug resistance to the earlier used antibiotics, the use of fluoroquinolone like ciprofloxacin, ofloxacin was recommended as the substitute drugs for the treatment of enteric fever [25]. Though the cases of typhoid fever due to fluoroquinolone-resistant *Salmonella*serovar Typhi isolates were reported from several parts of the world [26, 27, 28]. Later in 2000s Cephalosporins and Azithromycin were introduced for the treatment of typhoid fever due to the development of resistance of fluoroquinolones like ciprofloxacin, ofloxacin [29]. Cephalosporins such as oral Cefixime were considered to be very effective drug against *S*. Typhi till the emergence of extended-spectrum cephalosporin-resistant strains in Asia and Africa [30]. In past few years, extended-spectrum-beta-lactamase production in a *Salmonella enterica* serovar Typhi strain from Bangladesh, Philippines [31, 32] and ACC-1 beta-lactamase producing *Salmonella enterica* serovar Typhi from India have been reported [33]. It was considered to be developed by *S*. Typhi H58 clade (genotype 4.3.1) which consists of IncHI1 plasmids carrying MDR genes and mutations causing antibiotics resistance [34]. This clade was considered to be emerged from Indian sub-continent and later spreaded to South-East Asia and Africa followed by other parts of the world [35]. Apart from plasmid mediated and adoptive MDR, chromosomal genes mediated antibiotic resistance has also been reported in *Salmonella* Typhi. These strains retain their resistance even without exposure to any antibiotics. Chromosomal mediated MDR is a very complex phenomena and many genes especially *Salmonella* genomic island I were found to be involved in it [36]. The percentage of patients undergoing clinical treatment, prolonged expensive hospital accommodation due to emergence of multiple drug resistant strains of pathogen in recent years has increased [37, 2]. In past few years MDR strains of *S.* Typhi has caused large outbreaks of typhoid fever in many developing countries of Asia and Africa [38]. Recently azithromycin resistance for both *Salmonellaenterica* serovars Typhi and Paratyphi have also been reported [39].

MECHANISMS OF DRUG RESISTANCE

Multiple-Drug Resistance

*Salmonella enterica*resists the action of antibiotics by many ways such as inactivation of the drug, transport or efflux of the antibiotics, reduced permeability of the antimicrobial drugs and modification of the drug target site. The resistance determinants located on plasmids are the major cause of resistance to the first- line drugs like ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole. Ampicillin resistance is generally mediated through lactamases whilea number of mechanisms may be related with chloramphenicol resistance. Chloramphenicol acetyltransferases (CATs) (types I to III) are considered to be responsible for chloramphenicol resistance in gram-negative bacteria but resistance due to the production of CAT type I has been reported most commonly in *Enterobacteriaceae* family [40]. Trimethoprim and sulfamethoxazole prevent the DNA synthesis as they both inhibit folate pathway.The presence of genes encoding folate pathway enzymes that do not bind these compounds is the major cause of resistance to both the antibiotics. The presence of genes such as dihydrofolate reductase (*dfr*) genes, *sul*genes like *sul1* or *sul2* in *Salmonella enterica* are responsible for mediating resistance to trimethoprim and sulfamethoxazole [41]. Similarly other antimicrobial resistance genes present in the *Salmonella* genomic island (SGI-1) of *Salmonella enterica* serovar Typhimurium confer resistance to antibiotics such as *bla*PSE-1 confer resistance to ampicillin, *floR* confer resistance to chloramphenicol and florfenicol, *aadA2* confer resistance tostreptomycin and *tetG* to tetracycline [42].

Fluoroquinolone Resistance

Fluoroquinolones are the group of antibiotics which target twoenzymes DNA gyrase and topoisomerase IV. The subunits of these enzymes are encoded by the *gyrA* and *gyrB* and the *parC* and *parE*genes respectively [43]. Mutations in these genes is considered to be the major cause of reduced susceptibility or resistance to fluoroquinolones [44, 45]. Multiple mutations in the gyrasegene or other topoisomerase genes are essential to confer complete clinical resistance to drugs like ciprofloxacin [46]. Apart from chromosomal-mediated mechanisms other mechanisms such as plasmid-mediated resistance have been reported. In the late 1990s, *qnrA* was reported as thefirst plasmid-mediated resistance mechanism to fluoroquinolones. Avariety of other plasmid-mediated mechanisms have been revealedin *Enterobacteriaceae* family [47, 48]. Theplasmid-mediated resistance mechanisms have been reported to confer decreased resistance and susceptibility to ciprofloxacin [49, 50].

Cephalosporin Resistance

Cephalosporins belong to the lactam antibiotics group. These antimicrobials target penicillin binding proteins as well as the cross-linking of the peptidoglycan, which results in disruption of bacterial cell wall synthesis [51]. Resistance to extended-spectrum or third generation cephalosporins such asceftriaxone, is generally mediated through lactamases that inactivate the drug by cleaving the lactam ring. The resistance mediated by lactamases tothird generation cephalosporins can beclassified into three groups: Plasmid determined AmpC-type lactamases, carbapenemases and extended-spectrum lactamases [52, 53, 54].

Macrolide Resistance

Macrolideare the class of antimicrobials that inhibit the protein synthesis by binding to the 50S subunit of the bacterial ribosome. Azithromycin, erythromycin, roxithromycin, and clarithromycin are the most common antibiotics that belong to Macrolides. The macrolide resistance develops due to the enzymatic modification of the target site as an enzyme encoded by the *erm* genes catalyze the methylation of the ribosome. These enzymes are responsible for methylating an adenine residue at A2058 position of the domain V of the 23rRNA of the 50S ribosomal subunit. This biochemical change hinder the binding of the drug to its target [55]. The increased azithromycin MICs have revealed the resistance in *Salmonella enterica* isolates [56]. In 2010, the first case of treatment failure with azithromycinin a patient with *Salmonella* serovar Paratyphi A isolate infection was reported[57].

Prevention and Control Measures

Contaminated water and food are the most important cause for transmission of typhoid fever. In European countries and North America the incidence of typhoid fever has decreased due to some measures taken as waste water treatment, pasteurization and improved hygienic conditions [58]. Presently, crucial measures undertaken for prevention of typhoid fever include improving sanitation and hygiene, Food and water supply safety, identification and treatment of carriers of *Salmonella* and development of effective typhoid vaccines.

Typhoid fever caused by *Salmonella enterica* serovar Typhi remains aglobal public health problemmultiple drug resistant strains continue toemerge, which is resulting in a heavy socio-economic loss in many developing countries and some developed countries of the world. Antimicrobial resistance has increased the spread of typhoid fever and also made the treatment and management of the disease more complicated. Many preventive measures have been undertaken by different countries to combat the disease. Some of the plant extracts are beneficial against drug resistant *Salmonella* Typhi isolates. Therefore, more research programmes are required on medicinal plants in order to reduce typhoid fever caused by multi-drug resistance. The frequent spread of multi-drug resistant strains of *Salmonella* around the world has minimized the action of antimicrobial drugs leading to a major problem to combat the infection. Therefore, there is a need to understand the mechanism of pathogenesis to find new drug targets and delivery systems for the MDR strains of the bacterium and to develop effective, safe and potential drugs to combat the problem against typhoid. On one hand, there is a need to develop more effective antibiotics for treatment of typhoid and on the other hand, there is a necessity to control the spread of disease by use of mass vaccination.

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