

Fluoroquinolone resistant *Salmonella* species

Abstract

Fluoroquinolones are widely used most effective medication, systemic antibacterial that have long been used against respiratory and Urinary Tract Infections. Fluoroquinolones are effective against both aerobic and anaerobic gram positive and negative bacteria, most especially *Salmonella* species. Resistance comes as a curse with antibiotics that occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals or other agents designed to cure or prevent infections. The main problem connected with the therapeutic use of fluoroquinolones is the establishment of more virulent and resistant *Salmonella* species due to the development of either altered DNA-binding proteins or efflux pump mechanisms for antibiotics. It is currently a serious public health threat that affects people all around the world. When a *Salmonella* species develops resistance to fluoroquinolones, the fluoroquinolones are no longer effective in treating *Salmonella* infections. This review provides an overview of *Salmonella* infection, and discusses the fluoroquinolones, Mechanisms of antibiotics resistance in *Salmonella*, Pathogenesis of *Salmonella* species and clinical manifestations.

Keywords: Fluoroquinolones, Salmonella, antibiotics resistance, infection, enteric fever

INTRODUCTION

Fluoroquinolones are a class of broad-spectrum, systemic antibacterial that have long been used to treat respiratory and urinary tract infections. Fluoroquinolones are effective against both aerobic and anaerobic gram positive and negative bacteria. The fluoroquinolone anti-microbials incorporate ciprofloxacin, ofloxacin, perfloxacin, spartfloxacin antibiotic medications, gemifloxacin, levofloxacin and Moxifloxacin [5, 2]. They act by inhibiting the bacterial enzyme DNA gyrase, which is accountable for bacterial DNA division, winding, and alternative path during multiplication [2].

Salmonella is a member of the Enterobacteriaceae family of bacteria [18]. Salmonella is divided into two types based on their clinical appearance: typhoidal and non-typhoidal Salmonella (NTS). Typhoidal Salmonella, which contains the serovars Typhi and Paratyphi A, B, and C of *Salmonella enterica* subspecies *enterica* (hereinafter Salmonella), causes enteric fever [9, 5]. *Salmonella* resistance to antimicrobial agents is reported to be influenced by a variety of factors, interaction of a few mechanical components of epidemiological research including chromosomal defects, alterations, plasmid acquisition, and drug resistance gene exchange via integron or transposon activities [8]. In various sections of the globe, *Salmonella* strains that are multidrug resistant (MDR) are common is the cause of some endemic and epidemic typhoid fever infections in the community [1, 14]. Multi Drug Resistant strain *Salmonella* is of concern not only because of its resistance to accessible fluoroquinolones, but also because it presents a risk of disease outbreaks that may be difficult to stop [1, 14, 19]. Such an outbreak will certainly be annihilating, particularly in developing countries where health facilities are often insufficient [5]. Multiple drug resistance is characterized as resistance to the first-line antibiotics ampicillin, chloramphenicol, and trimethoprim/sulfamethoxazole in *Salmonella*. The high prevalence of MDR in typhoidal *Salmonella* and iNTS [5]. Invasive *Salmonella* infections or patients at risk of developing an invasive infection are now treated with the fluoroquinolone (FQ) ciprofloxacin and the third-generation cephalosporin ceftriaxone [5, 2]. As an alternative, the macrolide antibiotic azithromycin may be used. *Salmonella* resistance to these prescribed antibiotics is, however, becoming much more common [5, 2].

Fluoroquinolones

Fluoroquinolones are a broad-spectrum antibacterial agent that inhibits both Gram-positive and Gram-negative bacteria. Gram-positive bacteria include penicillinase-producing and non-

penicillinase-producing Staphylococci, Streptococcus pneumoniae and Streptococcus viridans, Enterococcus faecalis, Listeria monocytogenes, and Nocardia species. Neisseria meningitidis and gonorrhoeae, Haemophilus influenzae, Pseudomonas aeruginosa, Vibrio species, and the majority of Enterobacteriaceae species, especially Salmonella species [2]. Fluoroquinolone antibiotics includes Ciprofloxacin, ofloxacin, perfloxacin, sparfloxacin, gemifloxacin, levofloxacin, and Moxifloxacin, Nalidixic acid, Cinoxacin, Norfloxacin, Lomefloxacin, Enoxacin, Gatifloxacin, Trovafloxacin [2].

Fluoroquinolones Mechanism of action

Fluoroquinolones function by blocking bacterial DNA replication and transcription, both of which are required for the cell's proper operation [2]. During DNA replication and transcription, enzymes called DNA gyrase or DNA topoisomerase uncoil double-stranded DNA into a single-stranded structure. By hydrolyzing adenosine triphosphate, DNA gyrase prevents gyrase separation from DNA. This complex consists of two A subunits (gyrA) and two B subunits (gyrB). DNA gyrase creates negative super-helical twists in bacterial DNA (figure 1) [2]. Quinolones and fluoroquinolones connect to the A subunit of this enzyme and hinder bacteria from reproducing or generating proteins. A DNA-binding groove exists between the A and B subunits, and fluoroquinolones can cause the DNA gyrase molecule to conform by adhering to this groove. Fluoroquinolones bind to DNA and DNA gyrase as a result of this interaction. The primary location of fluoroquinolone activity in many bacteria, including E. coli [2], is DNA gyrase. In vitro, fluoroquinolones have also been found to inhibit topoisomerase IV, which has a structure similar to DNA gyrase [2]. Topoisomerase IV, which consists of two ParC subunits (parC) and two ParE subunits, is the fluoroquinolones' second target site (parE). The genes parC (ParC) and parE (ParE) code for proteins that are homologous to DNA gyrase's A and B

subunits, respectively. In bacteria, topoisomerase IV helps with the segregation of replicating chromosomes or plasmids by decatenating and relaxing DNA [2]. Inhibition of topoisomerase IV improves the bactericidal action of fluoroquinolones [2].

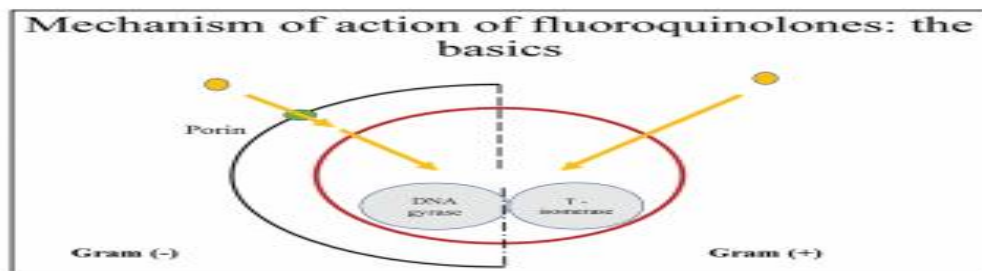


Figure 1: Fluoroquinolone mechanism of action.

Fluoroquinolone Resistance Mechanisms

The most common pathways of resistance to fluoroquinolones are mutations in the target enzymes DNA gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria. The second strategy for decreasing fluoroquinolone accumulation is an efflux system. Increased expression of a chromosomal gene causes an increase in fluoroquinolone efflux Figure2 [2].

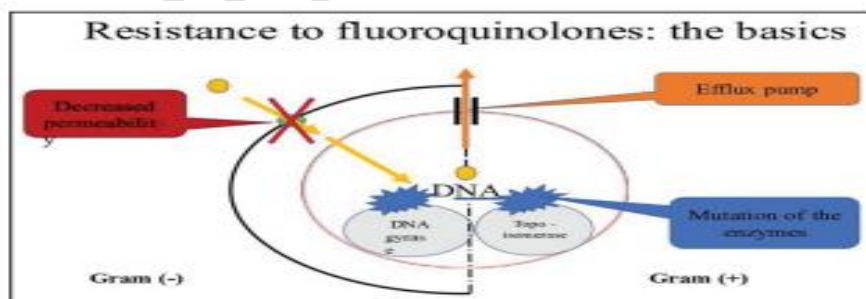


Figure 2: Resistance to fluoroquinolone.

Antibiotic Resistance Mechanisms in Salmonella

Bacteria can avoid the activities of antibiotics utilizing different mechanisms. Antibiotic resistance mirrors the assault and counterattack of complex microbial flora to an antimicrobial agent to set up and survive in ecological niches [6]. Antibiotic resistance mechanisms include (i) antimicrobial agent modification or degradation, (ii) efflux pumps pumping the antimicrobial agent out of the cell, (iii) antibiotic target modification or substitution, and (iv) decrease in cell layer permeability. As a result, microorganisms evolve resistance mechanisms by mutating target protein gene areas or acquiring mobile genetic components, such as plasmids, integrons, and transposons that carry resistance genes [12]. Antimicrobial drugs come in a variety of classes, and the most excellently antimicrobials against which *Salmonella* has developed resistance are aminoglycosides, -lactams, chloramphenicol, quinolones, tetracyclines, sulfonamides, and trimethoprim [12].

Plasmid mediated resistance

Plasmids are extra chromosomal pieces of self-reproducing roundabout double stranded DNA that can dwell in the host cell. They cover a range of genes which are favorable to the host cell. Resistance to aminoglycosides, chloramphenicol, penicillins, cephalosporins, erythromycin, tetracycline, and sulphonamides has also been connected to plasmid-related genes [17]. They are clinically significant in the event that they contain virulence or resistance genes. Plasmids are vital in the study of disease transmission and spread of resistance to antibiotics. Plasmids can be on a horizontal moved starting with one bacterial host then onto the next even between bacterial species [3].

Reduced membrane permeability

Reduced membrane permeability emerges because when drug has been unable to pass through bacteria membrane. As new genetic knowledge changes the idea of proteins in the layer, the membrane penetrability changes. These changes modify the membrane transportation system pores, making it impossible for an antimicrobial agent to cross the layer at this stage. *Salmonella typhi* developed resistance to tetracycline, quinolones, and some aminoglycosides as a result of this process. Sulfonamide resistance can also be followed by a reduction in permeability [17].

Adjustments to the goal position

When the pathogen's target enzyme or cellular structure is altered, the drug no longer interacts with it. This is known as alteration of target site tolerance. *Salmonella typhi* and other sulfonamide-resistant bacteria have a function similar to *Salmonella*. These bacteria have produced an enzyme with a high affinity for PABA (p-aminobenzoic acid) but a low affinity for sulfonamide. The enzyme performs admirably enough to keep the bacterium alive even in the presence of sulfonamides [12].

Efflux pump or rapid extrusion

Rapid extrusion, also known as efflux, is an antibiotic resistance mechanism that involves the drug being pumped after it has reached the cell, it must leave. Transcription factors are translocases in the plasma membrane that extract drugs and export them out of the cell, and they are present in a few pathogens.

These transport proteins are often referred to as multi drug resistance because they can pump a wide range of drugs, including quinolones (MDR) pumps. A plasmid-encoded transport

mechanism that effectively exports the drug out of the cell mediates sulfonamide resistance. [6, 12].

Resistance mediated by the chromosome

Mutations in the gene that codes for the drug's target or the transport mechanism that regulates the drug's take-up in the layer that regulates the drug's take-up resistance mediated by chromosomes [6]. Mutations in the chromosomal target gene dihydrofolatereductase, the enzyme that translates dihydrofolate to tetrahydrofolate, were expected to be the main cause of trimethoprim resistance. Moreover, a chromosomal mutation in the gene coding for the target enzyme dihydropteroatesynthetase has been discovered to mediate sulfonamide resistance, decreasing the drug's binding affinity [6].

Pathogenesis of *Salmonella* species

Salmonella strains are harmful because they may infiltrate, multiply, and live in human host cells, potentially causing death. *Salmonella* has a distinct property when it infects non-phagocytic human host cells [16]. In order to gain entry to the host cell,

it actually starts phagocytosis on its own. When bacteria enter the digestive tract by contaminated water or food, they can ordinarily penetrate the intestinal epithelial cells. *Salmonella* pathogenicity islands (SPIs) are multi-channel proteins that allow *Salmonella* to infuse its effectors into the cytoplasm via the intestinal epithelial cell layer [16].

After being absorbed by the host cell, *Salmonella* are encased in a vacuole, which is a layer compartment comprised of the host cell membrane. Under normal circumstances, the presence of a bacterial foreign body might trigger an immunological response in the host cell, resulting in

lysosome fusion and intracellular bacterium death, as well as the release of a digestive enzyme. *Salmonella*, on the other hand, is a bacterial strain. It alters the compartment structure by infusing additional effector proteins into the vacuole via the type III discharge mechanism. The reconstructed vacuole prevents lysosomes from fusing, allowing the bacteria to survive and reproduce inside the host cells. Bacteria can go via the reticuloendothelial system because they can live inside macrophages (RES) [11]. *Salmonella* is responsible for a diverse selection of human beings infections, including gastroenteritis, enteric fever, and bacteremia [11].

Infections Due to *Salmonella*

Colonization and attachment of intestinal columnar epithelial cells and specific micro fold cells on surface of Peyer's patches are one of *Salmonella* species' ability to cause human infection [19]. *Salmonellosis* symptoms involve diarrhoea, stomach pain, nausea, and vomiting that very last 1 to 7 days. In healthy adults, the infection is highly self-limiting, with a 1% mortality rate [19]. If the patient is not treated promptly with the necessary antibiotics, the infection can progress to septicemia and death.

The drugs of choice are fluoroquinolones, macrolides, and third-generation cephalosporins [10, 15]. Immunocompromised individuals, children, infants, and the aged people are on their way to demanding antimicrobial treatment. Antimicrobial resistance strain infections may compromise therapeutic efficacy, result in increased morbidity and mortality [19]. Rarely, chronic disorders such as reactive arthritis, Reiter's disease, and ankylosing spondylitis may occur in a few individuals [13].

Salmonellosis infective doses in adult humans have been documented It will be in the range of 10^4 to 10^6 cells or higher, but in profoundly susceptible individuals, it can be as low as 10^1 to 10^2

cells. Because of differences in inoculation doses, pathogenicity systems, virulence factors, age, and the host's immune response, symptoms can vary [19]. In addition to gastroenteritis, *Salmonella* can cause meningitis, osteomyelitis, pneumonia, colecystitis, peritonitis, pyelonephritis, endocarditis, pericarditis, vasculitis, aseptic arthritis, and Reiter's syndrome [19].

Salmonellosis

Salmonellosis is an infection caused by members of the genus *Salmonella* [7]. It is a significant cause of diarrheal sickness in human, answerable for approximately 1.4 million diseases and 600 deaths yearly in the United States [7]. Quite a bit of what is thought about the study of disease transmission of salmonellosis came from outbreak examinations. These examinations have confirmed that most human diseases result from the ingestion of food of animal origin that are contaminated with *Salmonella* species [7].

Enteric fever

The disease is brought about by *S. Typhi* and it happens most regularly in children and young adult (3-19) years. Enteric fever signs include a prolonged high fever with a low heart rate, severe headache, spleen enlargement, nausea, and apathy or mental confusion [18].

In reticulo endothelial cells, the species replicate. In untreated late typhoid, invasion of the intestine triggers inflammation and perforation, and also epistaxis, intestinal hemorrhages, toxemia, and renal failure. On fair skin, a rash on the trunk may develop. The all-out white cell check in uncomplicated typhoid is typical or low, with a relative lymphocytosis. With intestinal perforation, an unexpected increase in white cell count may occur. *S. Typhi* infection can also

cause osteomyelitis and typhoid arthritis, especially in people who have sickle cell disease or thalassemia [4].

Enterocolitis

Several *Salmonella* serovars are capable of causing this *S. typhimurium* and *S. enteritidis* are the most common causes in developing countries. Ingestion of *Salmonella* in food that has been infected from human or animal intestinal sources, either directly or indirectly, causes infection. Diarrhoea, vomiting, fever and abdominal pain happen 12-36 hours after eating contaminated food. In acute infection, blood and mucous are available in fecal examples. Infant and the elderly, person in poor health, those with ulcerative colitis, malignancy and immunosuppressed persons are at more serious danger of developing genuine disease [4].

Bacteraemia

Salmonella nontyphi (NTS), especially *S. typhimurium* and *S. enteritidis* are common cause of *bacteraemia* and *septicaemia* in young children in developing countries. NTS bacteremia is also normal in HIV co-infected people in Africa and elsewhere. The elderly in poor health, those with cancer, sickle cell disease, and chronic *schistosomiasis* are also at risk [4].

Treatment of typhoid fever

General management

Supportive treatments, such as oral or intravenous hydration, antipyretics, proper nutrition, and blood transfusions if needed, are vital in the treatment of typhoid fever. Oral antibiotics, dependable care, and close medical follow-up for problems or failure to respond to medication can be treated at home in more than 90% of patients [19]. Patients with persistent vomiting,

severe diarrhea, or abdominal distension, on the other hand, may need to be admitted to the hospital and given antibiotics intravenously [19].

Antimicrobial therapy

The selection of first-line antibiotics in underdeveloped nations is based on efficacy, availability, and cost. This section goes through the treatment instructions for typhoid fever in people of all ages. It should be emphasized, however, that pediatric therapeutic techniques, such as antibiotic choice, dosage regimen, and treatment duration, may differ from those used in adults [18, 19].

For the treatment of typhoid fever in adults, fluoroquinolones are largely regarded as the best option [19]. Chloramphenicol, ampicillin, amoxicillin, and trimethoprim-sulfamethoxazole were previously first-line antibiotics that were reasonably inexpensive, well tolerated, and more quickly and reliably effective. The vast majority of isolates remain susceptible. Fluoroquinolones have better tissue penetration than other medications, kill *S. typhi* in its intracellular stationary stage in monocytes/macrophages, and had higher active drug levels in the gall bladder. They generate a quick therapeutic response, with fever and symptoms clearing in three to five days and very low post-treatment carriage rates [18, 19]. Fluoroquinolones are equally efficient in the treatment of typhoid fever in children, according to evidence from diverse Asian countries [18, 19].

Prevention of typhoid fever

Typhoid fever is spread mostly through drinking contaminated water or eating food infected with *Salmonella typhi*. Access to potable water and the promotion of proper food handling procedures are the cornerstones of prevention. To improve public awareness and promote behavior change, health education plays an important role [18, 19].

Safe water

Typhoid fever is a waterborne disease, and the most effective way to avoid it is to ensure that you have access to clean water. Water must be of good quality and sufficient to provide enough drinking water for the entire community as well as for all other home activities such as cooking and washing [18, 19].

The following control methods are particularly important during outbreaks: Control and treatment of water supply systems from catchment to user must be increased in metropolitan areas. The populace should have access to safe drinking water via a piped system or tanker trucks.

Wells in rural regions must be tested for diseases and treated as needed. At home, purification and storage of water must be given special attention, regardless of how safe the source is. Boiling water for one minute or adding a chlorine-releasing chemical can make it safe to drink. Narrow-mouthed pots with coverings for storing water can help prevent secondary typhoid fever transmission. When water is held in metallic containers, chlorine is rendered ineffective [18]. Fuel for boiling water and storage containers may be required in particular settings, such as impoverished rural communities in developing countries or refugee camps [18].

Food safety

Another key vector for typhoid fever transmission is contaminated food. During epidemics, the following fundamental hygiene measures must be implemented or reinforced: washing hands with soap before making or eating food, avoiding raw food, shellfish, and ice, and consuming only cooked and still hot food or reheating it [18, 19].

Food safety checks at restaurants and activities of street food sellers must be reinforced during outbreaks. Chronic carriers of typhoid who do not follow proper food hygiene standards can transfer the disease to others. Any actions involving the preparation or serving of food should be

avoided by these carriers. They should not return to work until three negative stool cultures have been obtained, separated by at least one month [18, 19].

Sanitation

Sanitation helps to reduce the risk of any diarrhoeal infections, including *Salmonella typhi*, being transmitted. Appropriate facilities for the disposal of human waste must be offered to the entire community. Pit latrines can be easily constructed in an emergency. Sewage collection and treatment must be performed, especially during the rainy season. The use of human excreta as fertilizer should be avoided in places where typhoid disease is known to exist [18, 19].

Health education

To raise public awareness about all of the above-mentioned prevention methods, health education is essential. Information about health education for disadvantaged communities must be tailored to local circumstances and translated into local languages. All available means of communication (e.g., media, schools, women's groups, religious groups) must be used to reach communities. The cornerstone of behavior change in terms of cleanliness and the establishment and maintenance of necessary infrastructures is community involvement [18, 19]. All employees in health-care facilities must be continuously trained on the importance of maintaining excellent personal cleanliness at work, patient segregation, and infection control [19].

Conclusion

Treatment options for invasive salmonellosis are limited due to *Salmonella* resistance to fluoroquinolones. To treat invasive *Salmonella* infections or those at risk of developing an invasive infection, the fluoroquinolone (FQ) ciprofloxacin and the third-generation cephalosporin ceftriaxone are being used. An option is azithromycin, a macrolide antibiotic. On the other hand, *Salmonella* resistance to these antibiotics is increasing.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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