

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. The emergence of more virulent and resistant *Salmonella* species by the development of either mutated DNA-binding proteins or efflux pump mechanism for drugs is considered the main problem associated with the therapeutic use of the fluoroquinolones. 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, Mechanism, infection, enteric fever

1. 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 belong to the *Enterobacteriaceae* family [18]. *Salmonella* is categorized into two major group based on their clinical appearance Typhoidal *Salmonella* and Non-typhoidal *Salmonella* (NTS). Enteric fever is caused by Typhoidal *Salmonella*, which includes the

Salmonella enterica subspecies *enterica* (hereafter *Salmonella*) serovars Typhi and Paratyphi A, B, and C [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 stopping [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]. 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

The fluoroquinolones are a class of broad-spectrum antimicrobial agents, therefore, they are highly active against both aerobic Gram-positive and Gram-negative organisms. Gram-positive includes penicillinase and non-penicillinase-producing staphylococci, *Streptococcus pneumoniae* and *Streptococcus viridans*, *Enterococcus faecalis*, *Listeria monocytogenes*, and *Nocardia*

species. Gram-negative includes *Neisseria meningitidis* and *Neisseria gonorrhoeae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Vibrio* species and most important *Enterobacteriaceae* species, especially against *Salmonella species* [2]. The fluoroquinolone antimicrobials includes ciprofloxacin, ofloxacin, perfloxacin, sparfloxacin antibiotic medications, gemifloxacin, levofloxacin and Moxifloxacin, Nalidixic acid, Cinoxacin, Norfloxacin, Lomefloxacin, Enoxacin, Gatifloxacin, Trovafloxacin [2].

Fluoroquinolones Mechanism of action

Fluoroquinolones show their action by inhibiting the replication and transcription of bacterial DNA that is responsible for proper functioning of the cell [2]. During DNA replication and transcription, double-stranded DNA goes to uncoil into a single-stranded structure by enzymes called DNA gyrase or DNA topoisomerase. DNA gyrase is an essential adenosine triphosphate-hydrolyzing topoisomerase II enzyme that prevents the detachment of gyrase from DNA. It consists of two A subunits (gyrA) and two B subunits (gyrB). DNA gyrase establishes negative super-helical twists in the bacterial DNA Figure 1 [2]. Quinolones and fluoroquinolones inhibit this enzyme by binding to the A subunit of the enzyme due to which the bacteria are unable to replicate or even synthesize proteins. There is DNA-binding groove between the A and B subunits so that binding of the fluoroquinolones to this groove may conformity change the DNA gyrase molecule. Then, DNA becomes another binding site itself; as a result fluoroquinolones bind with both DNA and DNA gyrase. In many bacteria, DNA gyrase acts as the primary site of fluoroquinolone action, including *E. coli* [2]. Fluoroquinolones have also been found to inhibit the *in vitro* activities of topoisomerase IV, having structure similar to DNA gyrase [2]. The 2nd target site for the fluoroquinolones is topoisomerase IV; this is made up from two ParC subunits (parC) and two ParE subunits (parE). The proteins subunits coded for by parC (ParC) and parE

(ParE) are homologous to the A and B subunits of DNA gyrase, respectively. Topoisomerase IV carries out decatenation and relaxation of DNA and assists with the segregation of replicating chromosomes or plasmids in bacteria [2]. The bactericidal activity of the fluoroquinolones is enhanced by inhibition of topoisomerase IV [2].

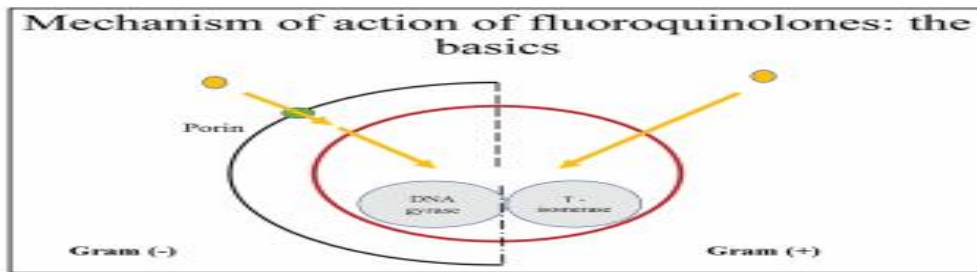


Figure 1: Mechanism of action of fluoroquinolone.

Mechanism of Resistance to fluoroquinolones

Resistance to fluoroquinolones mostly occurs by two mechanisms that are mutations in the both target enzymes DNA gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria. The second way that reduced accumulation of the fluoroquinolones can occur is through an efflux system. Resistance is due to increased expression of chromosomal gene leading to increased efflux of the fluoroquinolones Figure 2 [2].

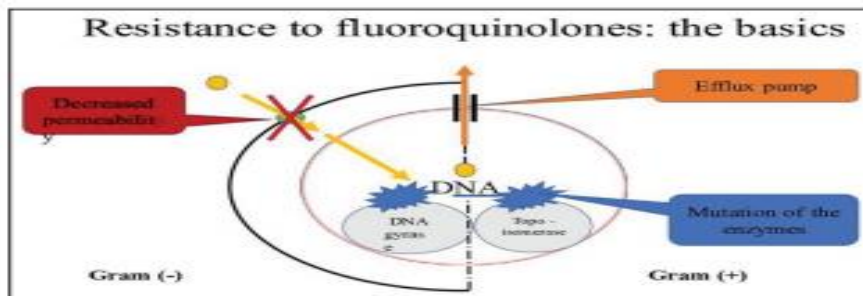


Figure 2: Resistance to fluoroquinolone.

Mechanisms of Antibiotics Resistance 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 pathogenic because they can invade, replicate, and live-in human host cells, causing potentially fatal disease. When *Salmonella* infects non-phagocytic human host cells, it exhibits a unique feature [16]. In order to gain entry to the host cell,

it actually initiates its own phagocytosis. Bacteria may normally penetrate the intestinal epithelial cells when they enter the digestive tract through polluted water or food. *Salmonella* pathogenicity islands (SPIs) encode type III secretion systems, multi-channel proteins that enable *Salmonella* to infuse its effectors through the intestinal epithelial cell layer into the cytoplasm [16].

Salmonella are coated in a vacuole, which is a layer compartment made of the host cell membrane, after being absorbed into the host cell. In normal circumstances, the presence of a bacterial foreign body can cause an immune response in the host cell, resulting in lysosome fusion and the death of intracellular bacteria, a digesting enzyme is released. *Salmonella* is a type of bacteria, on the other hand. It changes the compartment structure by using the type III discharge mechanism to infuse other effector proteins into the vacuole. The lysosomes are prevented from fusing by the rebuilt vacuole, allowing the bacteria to survive and multiply inside the host cells. Since bacteria can reside within macrophages, they can move through the reticuloendothelial system (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 is 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,

toxaemia, and renal failure. On fair skin, a rash on the trunk may develop. The all-out white cell count 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].

2. CONCLUSION

Salmonella fluoroquinolones resistance severely limits treatment options, especially for invasive *salmonellosis*. 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. As an alternative, macrolides antibiotics azithromycin may be used. *Salmonella* resistance to these prescribed antibiotics is, however, becoming much more common.

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