NEAR EAST UNIVERSITY

INSTITUTE OF GRADUATE STUDIES

DEPARTMENT OF MEDICAL MICROBIOLOGY AND CLINICAL MICROBIOLOGY

Antibiotic Resistance Rates of *Escherichia coli* Isolates Recovered from Urinary Tract Infections at the Near East University Hospital between 2022 and 2024

M.Sc. THESIS

MOHAMED AHMED DALDOUM MOHAMED

Student number: 20236473

Supervisor:

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Approval

We certify that we have read the thesis submitted by Mohamed Ahmed Daldoum Mohamed titled **"Antibiotic Resistance Rates of *Escherichia coli* Isolates Recovered from Urinary Tract Infections at the Near East University Hospital between 2022 and 2024"** and that in our combined opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

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Declaration of Ethical Principles

I hereby declare that all information, documents, analysis and results in this thesis have been collected and presented according to the academic rules and ethical guidelines of Institute of Graduate Studies, Near East University. I also declare that as required by these rules and conduct, I have fully cited and referenced information and data that are not original to this study.

MOHAMED AHMED DALDOUM MOHAMED

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I dedicate this work to my beloved parents Ahmed and Afaf for their continuous support and heartfelt prayers in this critical time of my life.

MOHAMED AHMED DALDOUM MOHAMED

Abstract

Antibiotic Resistance Rates of *Escherichia coli* Isolates Recovered from Urinary Tract Infections at the Near East University Hospital between 2022 and 2024

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June 19, 2025

Objective: *Escherichia coli* is the most common causative agent of urinary tract infections (UTIs) worldwide. The increasing prevalence of antibiotic-resistant *E. coli* strains presents a growing challenge in clinical management, particularly in healthcare settings. This study aimed to evaluate the antibiotic resistance patterns of *E. coli* isolates obtained from UTI cases at the Near East University Hospital between 2022 and 2024.

Methods: A retrospective analysis was conducted using microbiology laboratory records and patient data from Near East University Hospital. *E. coli* isolates recovered from urine samples between January 2022 and December 2024 were included. Bacterial identification and antibiotic susceptibility were performed by the VITEK-2 system. Antibiotic susceptibility and resistance were determined by using The European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines. Resistance rates to the tested antibiotics were calculated and analyzed to determine trends over the study period.

Results: A total of 203, 167, and 157 *E. coli* UTI cases were recorded in 2022, 2023, and 2024, respectively (Table 1). In 2022, outpatient and inpatient isolates showed

50.4% and 63.2% resistance to ampicillin, respectively. Inpatient isolates also exhibited 80% resistance to cefepime in the same year. In 2023, ampicillin resistance rates displayed a slight increase (54.5%) in outpatient isolates, while more dramatic elevation was detected for intpatient samples (71.7%). While amoxicillin-clavulanate and ciprofloxacin resistance rates were both 60.0%, no resistance was recorded for imipenem (0.0%) among inpatient samples in 2023. In 2024, outpatient isolates showed 69.0% resistance to ampicillin. Inpatient isolates demonstrated high resistance to ciprofloxacin (81.3%) followed by cefixime (77.4%), cefuroxime (71.0%) and ampicillin (67.9%). Moreover, consistently higher prevalence of ESBL-producing *E. coli* strains was detected in inpatient settings (37.0%, 41.8%, and 35.0% for 2022, 2023, and 2024, respectively), compared to those of outpatients (24.6%, 26.8%, and 20.5% for 2022, 2023, and 2024, respectively) throughout the study period.

Conclusion: In the study, highest resistance rates were observed against ampicillin and ciprofloxacin while fosfomycin and carbapenems remained largely effective. The higher rate of ESBL-producing isolates among inpatients underscores the need for strengthened infection control practices and judicious use of antibiotics to mitigate the spread of resistant strains particularly in the hospital settings.

***Key Words**:* antibiotic resistance, *Escherichia coli*, urinary tract infections

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List of Abbreviations

UTIs: Urinary tract infections

FDA: Food and Drug Administration

***E. coli*:** *Escherichia coli*

ESBL: Extended-spectrum beta-actamase

UPEC: Uropathogenic *Escherichia coli*

ETEC: Enterotoxigenic *Escherichia coli*

EHEC: Enterohemorrhagic *Escherichia coli*

CHAPTER I

Introduction

1.1. Background information:

Escherichia coli is a gram negative, non acid fast, non sporulating straight bacillus, flagellated with peritrichous flagella found single or in pairs. It is a facultative anaerobe. It has the ability to survive for lengthy periods in animal droppings, soil, and water. Strains that have pili exist as motile and nonmotile. Some strains which were found to have polysaccharide capsule were recovered from extraintestinal infections. *E coli* grows at 37^{o}C in MacConkey agar producing pink colonies due to its lactose fermentation activity. The bacterium produces also the characteristic green metallic sheen on Eosin-Methylene-Blue agar (Basavaraju & Gunashree, 2023).

Escherichia coli is a bacterium species that belongs to enterobacteriaceae family of the bacterial domain. It is the most prevalent commensal in the alimentary tract of humans and warm-blooded animals. It has a mutually beneficial symbiotic relationship with the hosts. However, it is also among the most commonly encountered pathogens (disease causing) in humans and animals with a variety of possible morbidities. The feasibility of handling of *E coli* including availability of genome sequence and growth in both aerobic and anaerobic environments makes it a suitable target for medical and industrial applications. It is the most frequently used organism in recombinant DNA technology (Allocati et al., 2013).

At the beginning of classification of *E coli*, the strains were identified using composition of the virulence factors namely O antigen (lipopolysaccharide) and H antigen (flagellar antigen). Later on, the bacterium strains were divided into pathotypes. A pathotype is a group of the bacterium species that are involved in the causation of a common disease. There are multiple pathotypes of *E coli* including those causing intestinal diseases and others which result in extra-intestinal illnesses, with UTIs of this research question as one of the examples.

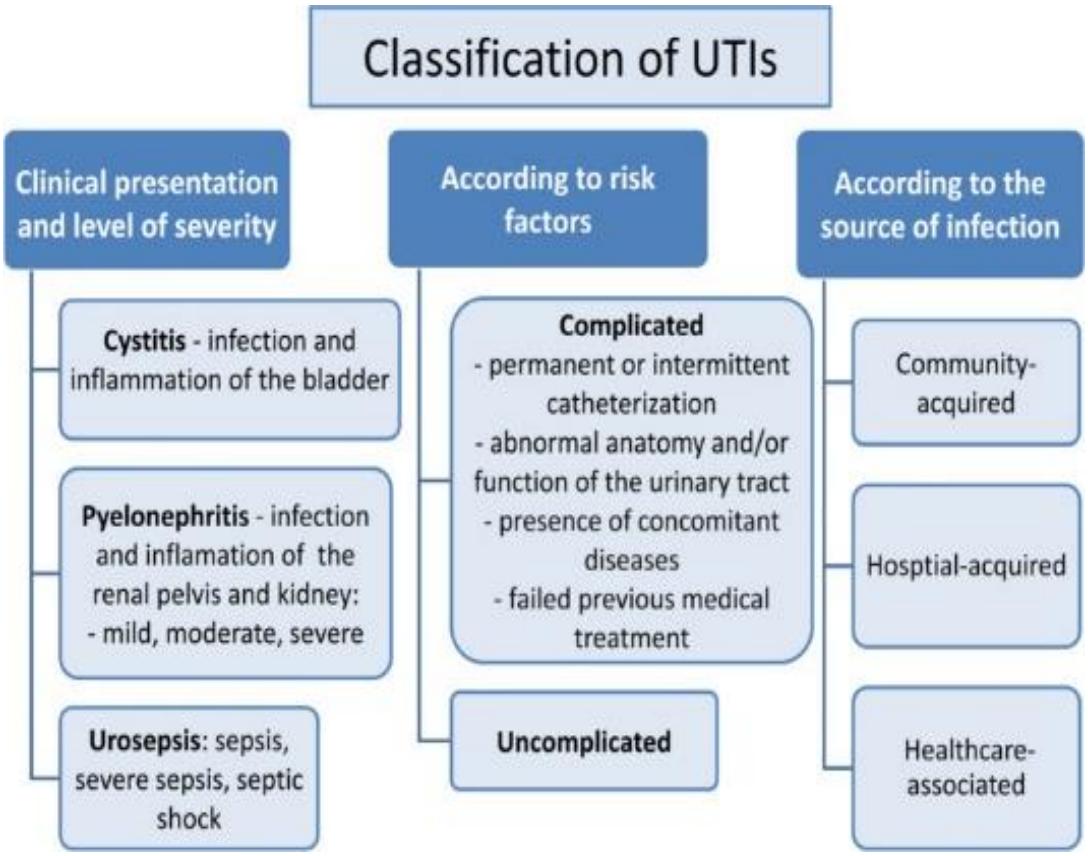
The pathotype of *E coli* causing UTIs is referred to as uropathogenic *E coli* (UPEC). Intestinal pathotypes include for example Entero-toxigenic *E coli* (ETEC) which causes traveler diarrhea and Entero-hemorrhagic *E coli* (EHEC) which produces shiga-like toxin that results in hemorrhagic colitis and hemolytic uremic syndrome (Allocati et al., 2013).

Antimicrobial resistance to antibiotics is a major health concern around the entire globe. Since the introduction of penicillins, the bacteria adapted to the drugs effects by developing resistance mechanisms, plasmid-mediated transfer of resistance genes as an example. The frequent and inappropriate use facilitated the emergence of antibiotic resistance. The continuous migration of people added to the burden and led to development of multidrug resistant strains of bacteria. In *E coli*, beta lactamase secretion is the most significant resistance mechanism against broad spectrum beta lactam drugs, which confers survival against penicillins and cephalosporins to the bacterium (Allocati et al., 2013).

Urinary tract infections is a term that indicates infectious disease that involve a part of the urinary tract: the kidneys, ureters, bladder, and urethra. It is the most common faced bacterial infection in children less than 2 years of age. They are usually benign but some of them progress to renal scarring that culminates in complications in adulthood, for instance: hypertension, proteinuria, and even chronic renal failure that requires dialysis treatment. Among adults, the disease is normally seen in young sexually active women. Generally 40% of women develop UTIs at some point in their lives. Other group of vulnerable patients include the elderly and those who need urethral catheterization (Tan & Chlebicki, 2016).

Figure 1.1.

Classification of Urinary Tract Infections, (Bartoletti et al., 2016).



1.2. Aim of the study:

The rising prevalence of antibiotic resistant uropathogenic *E coli* results in a challenging management of the UTIs. This study aims to update the information about the current antibiotic resistance status of uropathogenic *Escherichia coli* and prevalence of ESBL-producing strains among UTIs cases records in the Near East University Hospital from January 2022 to December 2024.

1.3. Significance of the study:

Studying the antibiotic resistance rates of *E coli* causing UTIs will help develop and strengthen the antibiotic stewardship programs and create new strategies to prevent antibiotic resistance which will ultimately help alleviate and minimize the morbidity and mortality rates, specially within a hospital setting.

CHAPTER II

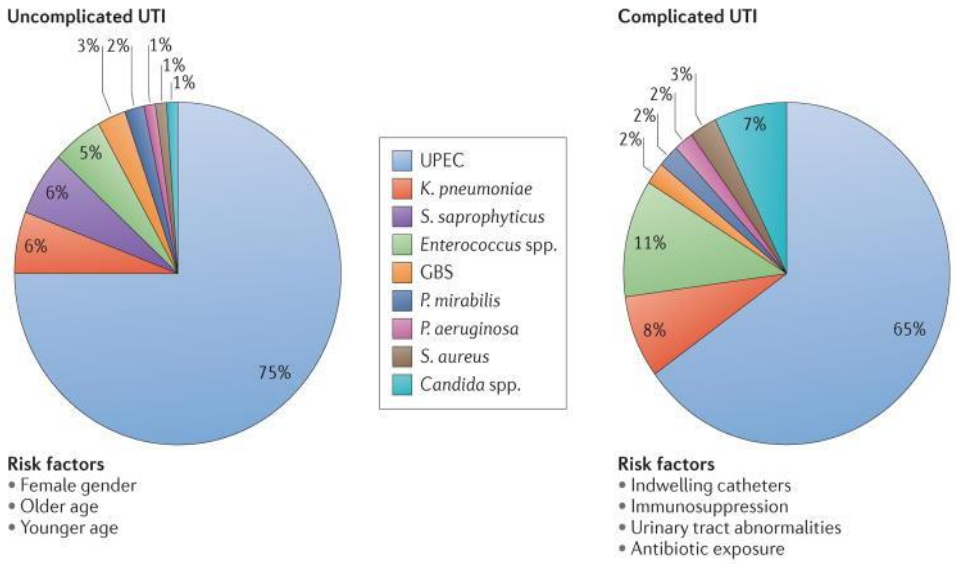
Literature Review

2.1. General Literature:

Urinary tracts infections are caused by a diversity of microorganisms from bacterial to fungal species. The most common causative agent of complicated and uncomplicated UTIs is uropathogenic *E coli.* Other causative agents to uncomplicated UTIs are *Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis, group B Streptococcus (GBS), Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus and Candida spp.* On the other side the causative agents of complicated UTIs are *Enterococcus spp., K. pneumoniae, Candida spp., S. aureus, P. mirabilis, P. aeruginosa and GBS* (Flores-Mireles et al., 2015).

Figure 2.1.

The Most Common Causative Agents of UTIs (Flores-Mireles et al., 2015).



Urinary tract infections are among the most common bacterial infections with 400 million cases and 230,000 deaths in 2019. They are second to respiratory infections as a cause of hospitalization for adults above 65 years of age. *Escherichia coli* is the most commonly encountered bacterium in UTIs cases. The causative species belong to the extraintestinal strains opposite to diarrhea-related *E coli* as they cause urine infections by translocating from the gut into the urethra. They ascend then through urogenital system urethra up to the bladder. The pathotype known as uropathogenic *E coli* is responsible for most of the community acquired UTIs (Whelan et al., 2023).

Untreated UTIs or those caused by antibiotic resistant bacteria can commence into bacteremia and blood sepsis, which will lead to kidney damage, multiple organ failure and death. *E coli* has molecular factors which it utilizes to evade the immune response. These molecules or virulence factors facilitate infection, tract invasion, and antibiotic resistance and most of them are connected to mechanisms of biofilm formation. The bacterium uses adhesins (fimbriae) to invade surfaces and attach and secretes toxins (hemolysin, necrotizing factor...etc) for tissue damage. For survival in the urinary tract where iron concentrations are extremely low the bacterium is highly dependent on siderophore iron transporter protiens (Whelan et al., 2023).

The uropathogenic *E coli* are known for their possible resistance to beta lactam antibiotics in which the beta lactam ring is an integral part of the chemical structure. These include penicillins, cephalosporins, monobactams and carbapenems. It has three possible mechanisms of resistance described in the literature. First, beta lactamase production is the main way for resistance, and frequently encountered with uropathogenic *E coli* is the CTX-M type extended-spectrum beta lactamase (ESBL), which cleaves the beta lactam ring in the antibiotics making them inactive. The other two mechanisms are through target site mutations and efflux pumps. The beta lactamase genes are mainly found in the plasmids and are transferred readily between *E coli* strains (Whelan et al., 2023).

2.2. Antibiotics:

2.2.1. Penicillins:

They are a significant part of antibiotics, characterized by their bacteria killing capacity, perfect diffusion throughout the body tissues, low level of toxicity and their ability to treat bacterial infections caused by bacteria sensitive to their effects. First use of penicillins started with penicillin G for staphylococcal and streptococcal infections. Then by the rise of penicillinase producing staphylococcus, penicillinase resistant penicillins were developed. These included for instace: methicillin, oxacillin, and nafcillin. Their properties of surviving the bacterial penicillinase is related to the acyl side chain that blocks the disruption of the beta lactam ring. Later on, aminopenicillins were added to enable this class of antibiotics the ability to target gram negative bacteria. The initial range of the drugs involved gram negative bacteria like *Escherichia coli, Proteus mirabilis, Shigella, Salmonella, Listeria, Haemophilus, and Neisseria*. In the effort to fight Enterobacteriacae and *Pseudomonas aeruginosa* another two categories of pencillins were developed: the carboxypenicillins (Carbenicillin and Ticarcillin), and the ureidopenicillins (Mezlocillin, Azlocillin, and Piperacillin). Lastly, the combined use of aminopenicillins, ticarcillin, or piperacillin with beta lactamase inhibitors like clavulanic acid, sulbactam, and tazobactam has enhanced the spectrum of the drugs to involve bacteria that particularly produce beta lactamases (Alan J. Wright, 1999).

2.2.2. Cephalosporins:

This group of antibiotics are synthesized from a filamentous fungus of the specie Acremonium chrysogenum. The first chemical isolated was called cephalosporin C. It has a wide antibacterial range from gram positive to gram negative. These antibiotics are necessary in the hospital to prevent and treat skin, ear, and bone infectious diseases as well as upper respiratory and urinary tract infections. In the recent decades a diversity of very effective cephalosporins were created and prescribed around the globe. Cephalosporins are bactericidal antibiotics that destroy the bacterial pathogens through the disruption of cross linkage between peptidoglycan chains of bacterial cellular wall. This occurs during the last stage of peptidoglycan wall synthesis as the drugs mimic the glycopeptides of the cellular wall and bind the penicillin binding proteins preventing their catalysis of the production of the three dimensional structure characteristic of the bacterial cellular wall. They are classified into five generations according to timeline of discovery and spectrum of activity. First generation cephalosporins are effective against gram positive cocci including Streptococci like *Streptococcus pneumoniae* and methicillin sensitive *Staphylococcus aureus*. This generation is well distributed throughout the body except middle ear fluid and cerebrospinal fluid. Important to mention is their weak effects against gram negative bacteria like *Pseudomonas aeruginosa* and *Enterobacter*, species putative as multidrug resistant bacteria, which identified as having resistance against different three antibiotic classes. And due to this limited efficacy, second generation cephalosporins were introduced. This class exhibited stability against gram negative bacteria beta lactamases and a prolonged half life. They proved to be effective against *Haemophilus influenzae* and some Enterobacteriacae species. Then the third generation of cephalosporins exhibited increased activity against gram negative bacteria to include meningococci and proved effective in the treatment of sepsis of unknown origin. In addition to the fact that second and third generation does not show allergy in patients with penicillins allergy, on the contrary to the first generation cephalosporins to which the allergy arises from similarity in the beta lactam ring side chains hence, they can be safely administered to patients with allergy to penicillins. Despite their broad spectrum effectivity most of the third generation cephalosporins have faced

resistance from multidrug resistant bacteria. A prominent specie is *Pseudomonas aeruginosa*, which is an opportunistic nosocomial bacterium that causes ventilator associated pneumonia and blood infections. With only ceftazidime and cefoperazone retaining effectivity against such bacteria. However, all antibiotics from the fourth generation cephalosporins that were developed are effectively wroking against the resistant species. The fourth generation cephalosporins have further increased efficacy toward gram negative bacteria by altering the side chain orientation. By this adaptation affinity of gram negative bacteria beta lacamases to the beta lactam ring is minimized. This generation is effectively targeting also gram positive bacterial species, for instance pneumococci with penicillin resistance, some of the streptococci, and methicillin sensitive *Staphylococcus aureus*. The drugs were helpful for treatment of hospitalized patients with severe infections, but the selection load resulted in further resistance. To combat the rise of the multidrug resistant bacterial strains, the fifth generation of cephalosporins were introduced. The methicillin resistant *Staphylococcus aureus* species are the second leading cause of death among antibiotic resistant pathogens in the year 2019, with the number one leading death causing pathogen being the bacterium under this study the *E coli*. These bacteria developed resistance by the frequent exchange of resistance genes encoding mutated penicillin binding proteins that bind the beta lactam rings of all the previous antibiotic generations making them inactive, where the fifth generation drugs remain effective. Mechanisms of resistance to cephalosporins include the following: (i) Beta lactamase enzyme production, which is the most crucial mechanism for gram negative bacteria, the enzymes inactivate the drug by binding the beta lactam ring and causing hydrolysis. (ii) Mutation of the penicillin binding proteins into variants with lower affinity to beta lactam drugs, or encoding a novel penicillin binding proteins that do not bind the beta lactam ring. (iii) Porins alterations, which are outer membrane proteins transporting hydrophilic molecules, and this results in reduction of the antibiotic penetration. (iv) Efflux pumps: which externalize the antibiotic out of the periplasmic space of the bacterium where the peptidoglycan layer is located. The resitance can be intrinsic to the bacterium or from mobile genetic elements transmitted through chromosomes, plasmids, transposons, and integrons. Antibiotic resistance can result from horizontal transmission of genetic elements through conjugation,

transformation, or bacteriophage transduction. Significant to mention is the developement of extended spectrum beta lactamase production, a plasmid encoded enzyme that confers resistance to third generation cephalosporins (Lin & Kück, 2022).

2.2.3. Carbapenems:

Among the distinct classes of beta lactam drugs, carbapenems are considered the most potent with the widest bactericidal spectrum including gram positive and gram negative aerobic and anaerobic bacteria. It is also considered the currently recommended regimen effective against extended spectrum beta lactamase producing strains. They bind to penicillin binding proteins and inactivate them and stop bacterial cellular wall synthesis. They resullt in accumulation of nascent peptidoglycans and activation of autolytic hydrolases that destroy the peptidoglycans without formation of new ones. Carbapenems fused beta lactam ring is resistant to most beta lactamases. They are significantly effective against streptococci, enterococci, staphylococci, listeria, eneterobacteriacae, most pseudomonas, bacteroides, and acinetobacter species. Despite that, majority of methicillin resistant staphylococci are also resistant to carbapenems. Biosafety of carbapenems is good and similar to the penicillins and the cephalosporins. Most common side effects include: injection site reaction, diarrhea, nausea, vomiting, skin rash, and itching. The carbapenems are excreted unchanged in the urine due to minimal liver metabolism, indicating that hepatotoxicity is rare. Members of this group of antibiotics include for instance imipenem, meropenem, and ertapenem (National Institute of Diabetes and Digestive and Kidney Diseases, 2017).

2.2.4. Aminoglycosides:

This is an old class of antibiotics. They possess a broad spectrum capacity against aerobic bacteria including the gram negative and mycobacteria. There are several drugs within this class, for example: gentamicin, tobramycin, amikacin, neomycin, plazomicin, and streptomycin. They are indicated for empirical treatment of patients with severe disease, as they tested effective against gram negative mutlidrug resistant bacteria. Diseases where aminoglycosides are indicated include infective endocarditis, complicated intra-abdominal infections, sepsis, and genitourinary system infective disease. Under such indications it is recommended not to use the drug for more than two days because of the risk of toxicity. Otherwise, for direct treatment a duration above 2 days is acceptable. They are used in combination with other antibiotics to treat brucellosis, listeriosis, central nervous system nocardiosis, and *Pseudomonas aeruginosa* infections. Other indications are for monotherapy, for instance: Tularemia, resistant mycobacteria, and bacteremia of *Campylobacter spp* and *Yersinia spp*. These antibiotics mechanism of action are through inhibition of bacterial protein synthesis. They bind the aminoacyl site of 16SrRNA, a constituent of the 30S ribosomal subunit of the bacteria, leading to misreading of the bacterial proteins genetic codes and impaired production of cellular proteins. The aminoglycosides are available for administration as oral doses, parenterally, intraperitoneal, or intraventricular. The most common form is parenteral or intravenous, and common antibiotics used by this route are gentamicin, amikacin, and tobramycin. Intraperitoneal use of gentamicin in patients who are having peritoneal dialysis and developed peritonitis has proven to be effective. Gentamicin can also be introduced intraventricularly in pateints with central nervous system infections which proved beneficial. Adverse events of aminoglycosides include ototoxicity (toxicity in the ear), nephrotoxicity (toxicity of kidneys), and neuromuscular block. Aminoglycosides ototoxicity occurs in 2% to 45% of adults. It is dose dependent. Gentamicin, tobramycin, and streptomycin commonly cause vestibular damage, while amikacin and kanamycin precipitate cochlear damage. It is found that the mechanism of these toxicities involve

production of reactive oxygen species. It is noteworthy to mention that toxicity that result in vestibular damage is reversible while hearing loss is permanent. Regarding nephrotoxicity, it was found to occur in 10% to 25% of the drug consumers. The mechanism of such toxicity is related to tubular damage that culminates in a reduced glomerular filtration rate and decreased blood flow to the kidneys. Fortunately, kidney damage by amioglycosides is reversible. The predisposing risk factors are dehydration, pregnancy, and hepatic impairment. The concurrent use of non-steroidal anti-inflammatory drugs, cyclosporine and diuretics, which also have deletrious effects on kidney functions increase the risk of renal problem to the patients. Check of renal function and monitoring when using aminoglycosides is an important measure to avoid toxicity. Finally, the neuromuscular blockade requires deep precaution specially in patients with neuromuscular junction disease or on drugs that prolong neuromuscular block, calcium channel blockers as an example. Therapeutic monitoring have proven important to reduce toxicities and have good impact on mortality rates. Also, clearance monitoring is crucial in critically ill, burn, and obese patients due to their altered distribution volume. Further important measures in monitoring to avoid toxicity is serial audiometry for the ear, and serum creatinine for renal function. No specific antidote available for aminoglycosides, but administration of N-acetylcysteine has protective effects against the drug harm on the ear and the kidney (Block & Blanchard, 2025).

2.2.5. Fluoroquinolones:

Fluoroquinolones are broad spectrum antibiotics that can be used to treat a plenty of bacterial infections due to their perfect oral bioavailability. Their use is though restricted to outpatient prescriptions due to their possible dangerous side effects. They are not indicated as a first line by the FDA as long as there are alternatives with less potential for adverse effects. Up to date there are four generations of quinolones with the initial ones active against only gram negative bacteria, the subsequent generations gained effects against *Pseudomonas spp.*, gram positive bacteria, and the atypical strains. The currently approved for systemic use fluoroquinolones include: Moxifloxacin, ciprofloxacin, gemifloxacin, levofloxacin, delafloxacin, and ofloxacin. There is a little difference in efficacy between quinolones. For instance, Ciprofloxacin is not working against *Streptococcus pneumoniae,* while moxifloxacin lacks effectivity towards *Pseudomonas aeruginosa,* but remains functional against anaerobes similar to delafloxacin, the only quinolone that produces effects against methicillin resistant *Staphylococcus aureus*. The FDA approved indications for adults for use of quinolones encompass the following: urinary tract infections, pyelonephritis, sexually transmitted infections, prostatitis, gastrointestinal system infections, intra-abdominal infections, skin and soft tissue infections, hospital and community pneumonias, and bone and joint infections. The quinolones also recently are on the off-label use as alternatives for drug resistant tuberculosis or intolerable anti-tuberculous medications, and these are moxifloxacin, gatifloxacin, and levofloxacin. FDA also has limited the use of fluoroquinolones in children due to the possible destructive effect on immature cartilages. As a result, only ciprofloxacin and levofloxacin are approved for the treatment of plague and inhalational anthrax. Ciprofloxacin is indicated also for the management of complicated UTIs. The scope of quinolones extends to the treatment of multiple drug resistant diseases in cystic fibrosis patients, in addition to ongoing efforts to introduce the use of these antibiotics in the management of cancer and protozoan parasitic infections. The mechanism of the bactericidal effect of quinolones relies on the supress of bacterial type II topoisomerases,

DNA gyrase, and type IV topoisomerase and change their function to cause constant double strands breaks in the bacterial DNA. Topoisomerases are essential for normal physiology of bacterial bioprocesses like transcription, replication, and condensed remodeling. They introduce transient breaks single or double stranded to help the bacterium relieve torsion and knots that develop during nucleic acid regular processes. In other words, they stabilize the cleavage complexes by suppressing DNA ligation. The resultant DNA fragmentation exceeds the bacterial cell DNA repair mechanisms leading to cellular death. Resistance to quinolones goes through three important mechanisms: (i) target-mediated resistance, this one occurs through significant mutaions in the DNA enzymes resulting in mitigated interaction between the quinolone active site and the enzyme, (ii) Plasmid-mediated resistance, this one is becoming common with extrachromosomal horizontal transfer of resistance genes that encode proteins responsible of diminishing the quinolone-enzyme interaction. (iii) Chromosomal-mediated resistance, occurs by two possible outcomes, firstly, underexpression of porins through which the quinolone diffuses into the cell, secondly, overexpression of efflux pumps that actively pump the quinolone out of the cell lowering its intracellular concentrations. The quinolones can be administered through oral or intravenous routes. Topical preparations are also available for external use in case of eye infections. They are distributed throughout the whole body with varying degrees of penetration into bodily fluids which depends on the individual fluorquinolone characteristics. A good example to this phenomenon is the poor distribution of levofloxacin to cerebrospinal fluid opposite to moxifloxacin which became indicated in treatment of tuberculous meningitis due to its readily availability and penetration into the cerebrospinal fluid. The quinolones are eleminated from the body by the kidneys unchanged through glomerular filtration and some tubular secretion. They are rarely excreted by the hepatic and intestinal route, with pefloxacin being the only fluoroquinolone eleminated mainly by the liver. The quinolones are unaffected when taken with food however, metallic cations containing compounds (like multivitamin tablets) can result in chelation and affect the drug bioavailability, so it is recommended to take the antibiotic 1 to 2 hours prior or 3 to 4 hours after ingestion of the metallic cation compound. Side effects of fluoroquinolones include gastrointestinal upset (nausea, vomiting, and diarrhea). They are also strongly associated with

antibiotic associated colitis with higher rates of *Clostridium difficile* pseudomembranous colitis than other classes of antibiotics. Arthralgias are common in children but are reversible and resolve after completion of treatment. Some patients may develop anaphylaxis ranging from skin rash and photosensitivity to toxic epidermal necrosis. There is also an increased risk to achilles tendon bilateral rupture with prolonged use that is theorized by researchers to be permanent. Other side effects include QTc interval prolongation on the ECG, dysglycemia, nephropathy, neuropathy, exacerbation of myasthenia gravis, ocular toxicity, aortic aneurysm/dissection, aortic and mitral valve regurgitation. There are central nervous system related adverse effects, for example: confusion, weakness, headache, anxiety, loss of appetite, tremor and depression euphemistically attributed to other conditions in the elderly patients. Fluoroquinolones are contraindicated in pregnant women and children due to mechanism of action and cartilage effects. There is theoretical concerns that taking quinolones in the first trimester can affect the fetus growth and DNA synthesis resulting in organ agenesis, mutagenesis, and carcinogenesis (Yan & Bryant, 2025).

2.2.6. Nitrofurantoin:

It is an antibiotic prescribed for lower urinary tract infections. It can cure gram positive as well as gram negative infections. It is characterized by its low serum concentration and accumulation in the lower urinary tract organs, in addition to the finding that it does not alter the bowel flora. It was used until 1970, the year new beta lactam antibiotics and trimethoprim-sulfamethoxazole were introduced to clinical practice. The development of resistance to new antibiotics and increasing prevalence of ESBL-producing bacteria has led to a return in the use of this antibiotic. The stable effect of nitrofurantoin and constant preservation of low resistance rate is attributed in the literature to its low effects on bowel flora. The drug effectively destroys the most common uropathogens, and this includes *E coli, Enterococci, Klebsiella, Staphylococcus saprophyticus, and Enterobacter*. Other susceptible organisms that lie within the spectrum of activity of Nitrofurantoin also include *Shigella, Salmonella, Citrobacter, Neisseria, Bacteroides, group B streptococcus, Staphylococcus aureus, and Staphylococcus epidermidis.* Moreover, there has been no recorded difference in capacity of nitrofurantoin when treating ESBL-producing *E coli* and non-ESBL-producing strains. The drug maintained low resistance for a considerable period that counts in decades of widespread use. In terms of long-term prophylaxis the drug demonstrated good efficacy. A population survey in the united states that tested antimicrobial resistance of uropathogenic ***E coli*** to nitrofurantoin recorded a very low resistance of **1.6%.** Meta-analysis studies show equivalence between nitrofurantoin and other competetor drugs in the management of uncomplicated urinary tract infections. Mechanism of action of nitrofurantoin is still not well understood, But it is referred to action by bacterial flavoproteins that internalize the drug and break it down into intermediate metabolites that act on bacterial ribosomes to prevent production of bacterial DNA, RNA, and bacterial cellular wall proteins. This wide spectrum of activity explains the poor bacterial resistance toward nitrofurantoin, nevertheless, mutations in *nfs*A and *nfs*B have been reported to develop resistance among *E coli* strains. The drug is readily absorbed through the gastrointestinal system. The active ingredient is in powder form that forms gel matrix that release the drug over time during exposure to

gastric and intestinal fluids. The drug is excreted unchanged and soluble in the urine turning its color into brown. Studies show a 40% increase in urine concentrations of the drug when taken with food. The drug is available in oral formulations, and dosage is 100mg twice daily for 5-7 days. While long term prophylaxis dosage is 50mg or 100mg consumed once daily. The drug use is contraindicated in cases of patients with history of cholestatic jaundice/Liver toxicity, renal creatinine clearance <60ml/minute, pregnant women at term or during labor, neonates, and patients with glucose-6-phosphate dehydrogenase deficiency mainly due to hazardous risk of hemolysis. Regarding side effects, nitrofurantoin is considered a safer drug in comparison with equivalents like trimethoprim-sulfamethoxazole and ciprofloxacin. The most commonly reported side effects are nausea, vomiting, loss of appetite, and diarrhea. Nitrofurantoin has uncommon sinistor side effect, pulmonary toxicity, which can be acute with sudden onset fever, chills, cough, muscle pain and shortness of breath, or can be subacute with persistent non-productive cough, fever, and shortness of breath, or it can be chronic pulmonary toxicity with insidious course of fever and shortness of breath. The prevalence recorded in the literature for pulmonary toxicity though is as low as 0.001%. The hepatotoxic effects of the drug can manifest as elevated liver transaminases, cholestatic jaundice, inflammation, and necrosis. The drug must be stopped immediately after development of hepatotoxic reaction, and due to the autoimmune nature of this side effect the corticosteroids can be prescribed to alleviate toxicity further, but should be used precautiously to avoid relpases. Lastly among the rare adverse events of nitrofurantoin is the neurotoxicity. It occurs due to lengthy use in patients with poor kidney function. The form of toxicity is commmonly seen as fiber length dependent sensori-motor polyneuropathy with abnormal nerve conduction studies and axonal degeneration of sural nerve biopsy. Drug studies also show non-dose non-length dependent neuropathy has been reported (Squadrito & del Portal, 2023).

2.2.7. Trimethoprim-sulfamethoxazole:

Also known as cotrimoxazole, is an antibiotic used for a variety of infections. These are: infective exacerbation of chronic bronchitis, otitis media in children, traveler diarrhea management and prophylaxis, urinary tract infections, shigellosis, *Pneumocystis jirovecii* pneumonia, and management and prophylaxis of toxoplasmosis. Sulfamethoxazole mechanism of action is direct on folate synthesis within the bacteria. It interferes with the synthesis process of dihydrofolate by inhibition of dihydropteroate synthase by competing with p-aminobenzoic acid. It is an immediate competitor of dihydrofolate reductase preventing the production of tetrahydrofolate, the folic acid active form. It is an essential vitamin for the production of purines which are crucial for the synthesis of DNA and proteins. This is however, a bacteriostatic effect, but when combined together with trimethoprim the antibiotics achieve their bacterial killing capacity. Sulfamethoxazole metabolism occurs in the liver through the CytochromeP450 with half life of 6-12 hours, while trimethoprim is minimally metabolized and excreted in the urine unchanged with half life of 8-10 hours. The compound drug is available in oral and intravenous formulations. It can be administered with or without food. Adverse effects of the drug include photosensitivity, rash, and folate deficiency. Other common reactions are anorexia, nausea/vomiting, painful swollen tongue, dizziness, tinnitus, fatigue, and insomnia. Dangerous reactions reported are steven johnson syndrome, agranulocytosis, *Clostridium difficile* associated diarrhea, myelosuppression, kidney failure, pancreatitis, and hepatotoxicity. Hemolytic anemia is possible with sulfur containing drug like this antibiotic especially in patients with glucose-6-phosphate dehydrogenase deficiency and sulfa allergy can result in anaphylaxis. The drug is particularly contraindicated in pregnancy because of the folate deficiency risk that can result in multiple possible congenital malformations of the fetus significant to mention are: neural tube defects (eg:spina bifida), urinary tract defects, oral clefts, and clubbed feet. With initiation of therapy it is warranted to test the blood urea nitrogen, serum creatinine ratio, serial full blood count and electrolyte measures if the patient is taking along a drug that interacts with potassium (Kemnic & Coleman, 2022).

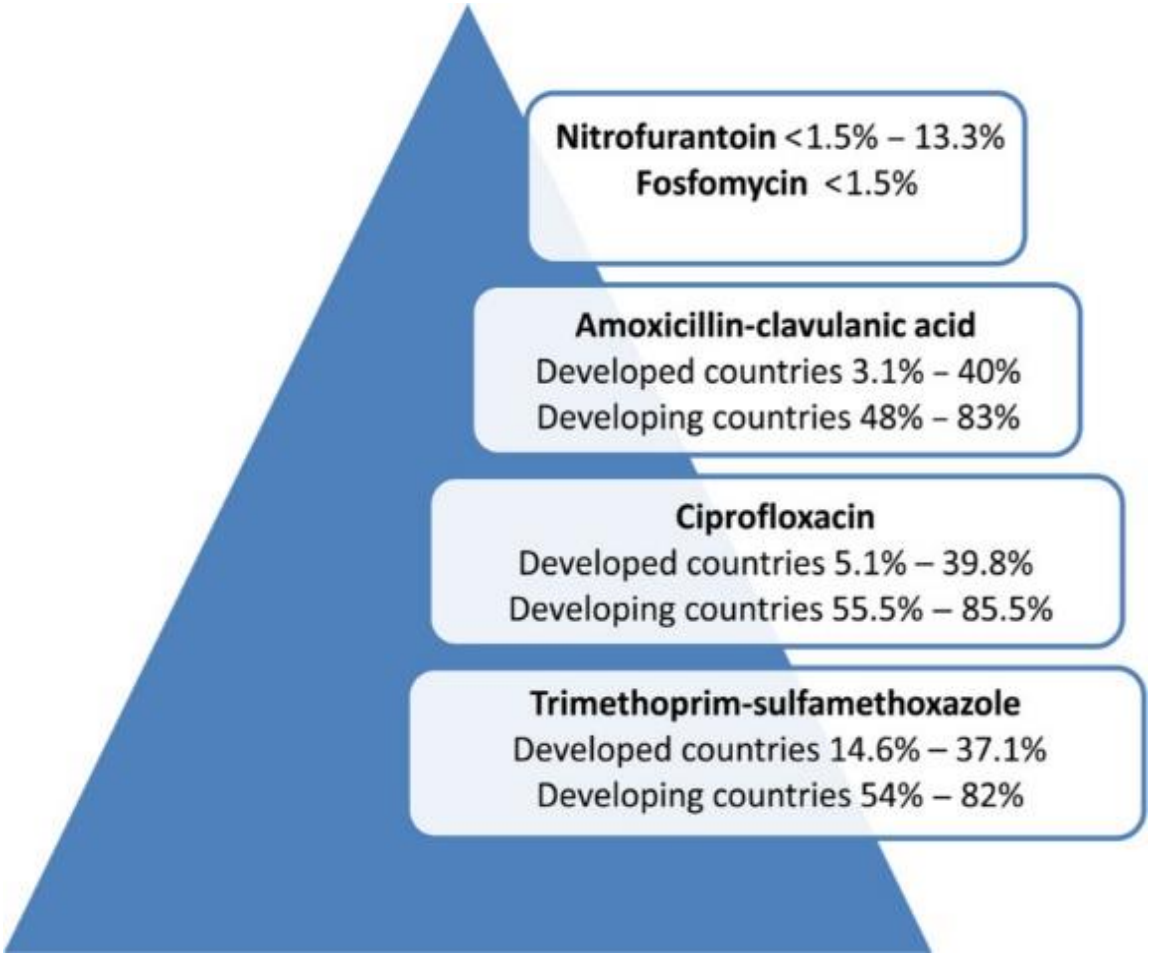
2.3. Related Research:

In Europe, it was found that resistance of uropathogenic *E coli* reached average of 11.8% for cephalosporins of the third generation and 22.3% for quinolones. The resistance for quinolones was 31.3% among isolates of hospital bed ridden patients during 2007 to 2010 in the United States of America. In comparison with the rest of antibiotics, imipenem remains the best effective antibiotic with full sensitivity (100%), then ertapenem (99.98%), then amikacin (99.94%), and finally nitrofurantoin (99.91%). The rising survival of uropathogenic *E coli* strain isolates towards ampicillin (96.42 %), tetracycline (85.71 %), amikacin (71.42 %), ciprofloxacin (67.85 %), and gentamycin (58.71 %) is reported to occur in **pregnant women** with history of recurrent urinary tract infections (Terlizzi et al., 2017).

In recent time it was observed that there is rising resistance rates toward trimethoprim-sulfamethoxazole with European countries having rates for the antibiotic range between 14.6% to 60% among the uropathogenic *E coli* strains. This drug is commonly used as first line treatment of uncomplicated urinary tract infections. Regarding fluoroquinolones, the resistance is also rising due to establised practices of frequently prescribing the drug for outpatient cases of urinary tract infections with continuous increment. This is remarkably higher in developing countries (55.5-85.5)% than developed countries (5.1-32.0)%. Amoxicillin-clavulanic acid which is indicated for pyelonephritis and complicated urinary tract infections has variable resistance rates in European regions that range from 5.3% in Germany to 37.6% in France (Kot B., 2019).

Figure 2.2.

Antibiotic resistance rates of uropathogenic E Coli, (Kot B., 2019).



In a review done in 2022 about the current and emerging treatment options for multidrug resistant uropathogenic *E coli,* Fluoroquinolones recorded in a study carried out in the united states in 2016 a resistance rate of 28.2%, while another study in Iran in 2019 revealed resistance rate of the bacterium to the same antibiotic of 45.2%. Although not a first line medication in UTIs cases, the review reports indicate prescription of the antibiotic in approximately 50% cases of uncomplicated UTIs. ESBL-producing strains are resistant to most cephalosporins, with exceptions as CTX-M producing pathotypes susceptible to ceftazidime and cefepime. It is reported in the review literature though, in a randomized controlled trial that cefepime susceptibility was only 33.3% in comparison to piperacillin-tazobactam of 93% and that of ertapenem 97%. Another trial report revealed that intravenous fosfomycin monotherapy to have a susceptibility of 64.7% in comparison with that of piperacillin-tazobactam of 54.5%. While a multi center trial revealed a rate of intravenous fosfomycin of 68.6% against 78.1% with meropenem or ceftriaxone suggesting fosfomycin monotherapy as not effective as other antibiotics or combinations in patients with urosepsis. The use of fosfomycin in combination regimen with a carbapenem or a third/fourth generation cephalosporin had a high cure rate in a couple of trials with rates of 81.3% and 84.8%. Carbapenems resistance was very low when combined with a beta lactamase inhibitor, meropenem-vaborbactam as an example with 98.4% susceptibility in comparison with 94% susceptibility with piperacillin-tazobactam. In the case of carbapenemase positive *E coli* or resistance to the antibiotic, it is recommended to go for a combination with an aminoglycoside. In a trial comparative analysis between plazomicin and meropenem, plazomicin recorded composite cure rate-that is both clinical and microbiological- of 81.7% in comparison with 70.1% for meropenem (Walker et al., 2022).

CHAPTER III

Methods and Materials

3.1. Research Design

This research overviewed and analysed retrospectively the hospital records of cross-sectional data from the recent last three years (2022,2023,2024) of E coli caused UTIs for the number of cases, and antimicrobial testing data in the Near East University Hospital in the Turkish Republic of Northern Cyprus.

3.2. Participants/Population and Sample

The study included all UTI cases, among all age groups from birth up to late adulthood. Urine samples that isolated other bacterial species along with *E coli* were excluded. Sample size was 203 for 2022, 167 for 2023, and finally 157 cases for the year 2024.

3.3. Data Collection Tools/Materials

-The data was collected previously in the hospital records in microsoft excel sheets. Urine cultures were used to isolate causative agent (*E coli*). Data is divided into outpatient clinics, and inpatient data.

-Identification of the bacteria and antimicrobial susceptibility testing was done using the VITEK-2 system and followed the European Committee on Antimicrobial Susceptibility testing (EUCAST) guidelines.

3.4. Data Analysis Procedures

-Data analysis was carried out by Microsoft Excel tool to estimate the prevalence of *E coli* UTI cases and determine the antibiotic resistance rates, in addition to the study population characteristics including age and gender which were calculated using the same tool. These characteristics included gender composition of the sample and the age distribution by calculating the average, median, and standard deviation with maximum and minimum age groups.

3.5. Study Plan

The study was retrospective and done through analysis of hospital records data of the previous three years, in order to identify UTI cases casued by antibiotic resistant *E coli* and reveal the current antibiotic resistance status of the bacterium.

3.6. Ethical Clearance:

This study was approved by the Near East University Scientific Research Ethics Committee (Project No: NEU/2024/129-1921). Data collection and analysis was discrete and maintained the anonymity and integrity of the test subjects. Since the study was retrograde through already recorded data, individual informed consents were overcome nevertheless, patients data were exclusively used for the research purposes.

CHAPTER IV

Research findings

4.1. Study population characteristics:

-For the year 2022 there was a total of 203 UTI cases, 73 were inpatient with males making around 31.5% and females around 68.5%. The average age for the study samples was approximately 70 years. For the outpatient there was 130 cases with males constituting around 23% and females around 77%. Average age for the outpatient sample was approximately 44 years old.

-For the year 2023 the total was 167 cases. 55 cases inpatient where males made 36% of the sample and females made 63%, average age was 71 years old. On the other side the outpatients were 112 with males around 22% and females around 78%. The average age 47 years old.

-And finally for the year 2024 with total of 157 cases. Inpatients were 40 cases which is the lowest in the study, males were 45% and females were 55% with average age 69 years old approximately. While the outpatients were 117, males 23% and females 77% approximately. The average age being near 46 years old.

-It is noteworthy that average ages for inpatients samples were around seventies and for outpatient samples around forties.

Table 4.1.

Characteristics of the Study Population.

Year	Males	Females	Mean age ± Standard deviation	Median age (minimum - maximum)	Total Cases
2022 inpatient	23 (31.51%)	50 (68.49%)	68.97±18.48	72.5 (0.00-95.00)	73
2022 outpatient	30 (23.08%)	100 (76.92%)	43.85±25.61	35 (0.00-95.00)	130
2023 inpatient	20 (36.36%)	35 (63.64%)	71.02±17.07	72 (23.00-95.00)	55
2023 outpatient	25 (22.32%)	87 (77.68%)	47.09±23.58	48 (0.00-86.00)	112
2024 inpatient	18 (45.0%)	22 (55.0%)	68.92±23.36	76 (0.00-96.00)	40
2024 outpatient	27 (23.08%)	90 (76.92%)	45.60±23.96	43 (1.00-92.00)	117

4.2. Antibiotic resistance rates findings:

-For the year 2022 outpatient samples the antibiotic testing results were as follows: Highest resistance recorded in outpatient for Ampicillin 50.4%, while lowest resistance was for Fosfomycin and Imipenem of 0%. While inpatient antibiotic resistance rates showed a rise in cefepime resistance from 25% to 80%, and ampicillin to 63.2%

-For the year 2023 outpatient rates showed increase in Ampicillin resistance from 50.4% in previous year to 54.5%. Amoxicillin-clavulanate resistance jumped from 18.9% in 2022 to 42.7% in this year. Other antibiotics showed slight insignificant rise. At the inpatients of year 2023, Ampicillin recorded its highest rate during the study period 71.7%, while in comparison with outpatient amoxicillin-clavulanate continued to increase in resistance rate up to 60% along with ciprofloxacin with the same rate.

-Finally the last year 2024: in outpatient samples Ampicillin showed the highest resistance of 69% and slightly lower in inpatients 67.9%. It is found that Amoxicillin-clavulanate in this year recorded its highest resistance rate throughout the study period of 63%. Also ciprofloxacin resistance reached 81.3%. Cephalosporins rates during this year in inpatient samples were the highest with Cefixime getting 77.4% and cefuroxime 71%.

-It is particularly concerning for carbapenems and nitrofurantoin in this last year 2024 that *E coli* resistance increased more than four folds, with Ertapenem from 3% to 12.5%, Imipenem from 1.4% to 12.5%, Meropenem from 1.4% to 10.3%, and lastly Nitrofurantoin from 7.5% to 21.4%. This rise from 2022 to 2024 in inpatient samples is strongly related to *E coli* beta lactamase production.

Table 4.2.

Antibiotic Resistance Rates of Escherichia coli Isolates Recovered from Urinary Tract Infections, 2022-2024.

Antibiotic	Resistance rates among outpatient isolates (%)			Resistance rates among inpatient isolates (%)		
	2022	2023	2024	2022	2023	2024
Amikacin	2.3	6.5	1.6	5.5	9.8	6.3
Amoxicillin-Clavulanate	18.9	42.7	50.0	28.6	60.0	63.0
Ampicillin	50.4	54.5	69.0	63.2	71.7	67.9
Cefepime	25.0	26.7	35.2	80.0	29.4	45.4
Cefixime	28.5	36.0	48.4	36.8	47.9	77.4
Cefoxitin	8.1	13.3	18.9	6.6	5.4	38.9
Ceftazidime	22.5	32.4	23.3	36.1	48.6	41.7
Ceftriaxone	23.5	30.7	23.4	32.8	47.4	50
Cefuroxime	30.7	43.3	54.0	42.6	52.1	71
Ciprofloxacin	32.3	42.4	48.5	43.1	60.0	81.3
Ertapenem	0.8	6.7	3.3	3.0	2.0	12.5
Fosfomycin	0.0	8.1	0.0	10.5	3.4	0.0
Gentamicin	8.5	15.2	13.5	18.1	21.8	17.1
Imipenem	0.0	1.5	0.0	1.4	0.0	12.5
Meropenem	0.8	5.7	3.4	1.4	2.1	10.3
Nitrofurantoin	4.8	6.4	2.7	7.5	9.3	21.4
Piperacillin-Tazobactam	7.7	18.2	22.6	16.4	31.6	25.0
Trimethoprim-Sulfamethoxazole	26.2	35.1	43.5	35.1	56.4	42.9

4.3. ESBL producing *E coli* prevalence:

- Data analysis showed higher ESBL producing strains in the inpatients samples throughout the study period, with outpatients' rates of 24.6%, 26.8%, 20.5%, and inpatients rates of 37%, 41.8%, 35% for 2022, 2023, 2024 respectively. This indicates increased resistance genes transfer in healthcare setting.

Table 4.3.

E. coli Extended Spectrum Beta Lactamase (ESBL) Isolates.

	Outpatients			Inpatients		
Year	2022	2023	2024	2022	2023	2024
ESBL+ve	24.6% (32)	26.8% (30)	20.5% (24)	37% (27)	41.8% (23)	35% (14)
ESBL-ve	75.4% (98)	73.2% (82)	79.5% (93)	63% (46)	58.2% (32)	65% (26)
Total isolates	130	112	117	73	55	40

CHAPTER V

Discussion

This Study analysed recorded data for annual prevalence of *E coli* urine tract infections and the antibiotic susceptibility profile with data divided into outpatients and inpatients. With *E coli* being the most common uropathogen, some strains have shown multiple drug resistance. This finding indicates the importance of judicious antibiotic use as the first line antimicrobials are becoming less effective in the treatment of the bacterium urinary infections. There are multiple studies that evaluated the antibiotic resistance behaviour of *E coli.* These studies show a considerable drop in effectivity of beta lactam drugs against the bacterium. The following paragraphs discuss these observations and correlate them to the findings of this study.

In a cross-sectional study carried out in Bangladesh, that focused on outpatient UTIs to isolate bacterial uro-pathogens and observe antimicrobial resistance patterns from January 2024 to June 2024, female cases showed dominance 89.6%. *E coli* was the most commonly isolated bacterium 85.4%. The study found full sensitivity of the isolated bacteria toward Meropenem, Imipenem, and Amikacin (100%), then Nitrofurantoin by 96.6%, Gentamicin 90% and Cefepime 80%. While the top resistance rates were against beta-lactam drugs, namely Ampicillin 62.5% and Cephalosporin groups 52.1% (Mazumder et al., 2025). This Study resistance rates are conforming with the research findings as aminoglycosides and carbapenems remained effective through the study period and penicillins namely Ampicillin and cephalosporins recorded increased rates.

Another study done in Iraq from August 2024 to October 2024, tested the antibiotic susceptibility of *E coli* isolated from UTI patients. It was found that there is 100% resistance to Ampicillin, and 53.33% resistance to Levofloxacin. The study used the Gram stain, culture, and biochemical tests to diagnose the bacterium (Abbas & Hussein, 2025). A further evidence of resistance to beta lactam drugs where in our research Ampicllin resistance reached 71.7%. Ciprofloxacin instead of levofloxacin was tested but both papers support the increasing resistance of the bacterium to fluoroquinolones.

A study that lasted a decade in Bangladesh from 2011 to 2021 assessed the antibiotic resistance trend of *E coli*. It showed females were 32.06% against males 22.56%. 410 isolates of *E coli* were established in a tertiary health facility. Resistance to Cephalosporins was found to reach 83.33% and that of fluoroquinolones up to 51.72%. Trimethoprim-sulfamethoxazole resistance recorded 52.79%, while lowest resistance rates were for Carbapenems 3.92%, aminoglycosides 20.79% and Piperacillin-Tazobactam 11.55%. The study emphasized the importance of urine culture and susceptibility tests (Majumder et al., 2025). This paper in literature recorded lower female to male ratio. However, findings are closer and congruent with the rising resistance to cephalosporins and fluoroquinolones, while carbapenems and aminoglycosides remain effective.

In a retrospective analysis of antibiotic resistance patterns of uro-pathogenic *E coli* with focus on ESBL-producing bacteria in a tertiary hospital in Saudi Arabia from January 2022 to March 2023, the prevalence of ESBL-producing *E coli* was reported to be 31%. Females constituted 78.9% of the study subjects. Among all the isolates Ampicillin had the highest resistance at 69.3%, Aztreonam 66.7%, and Colistin showed the lowest 0%. The study concluded the need for antibiotic stewardship programs and infection control measures as ESBL-producing *E coli* are prevalent (Alameer et al., 2025). Again this study supports the finding that *E coli* is highly resistant to Ampicillin and the fact that ESBL producing strains has a considerable prevalence similar to the rates recorded in the Near East University hospital outpatients, which is slightly higher.

A cross-sectional research carried out in Kenya to evaluate the prevalence, antimicrobial profiles, and carriage of ESBL resistance genes of *E coli*, found that the prevalence was 13.3%. Regarding antibiotics, high resistance to Trimethoprim-sulfamethoxazole was shown of 81.3%, Amoxicillin-clavulanate 66.7%, and intermediate resistance-around 50%- for Cephalosporins. Meropenem and Nitrofurantoin recorded the lowest resistance 14.6% and 8.3% respectively. ESBL

genes most common prevalent gene was found to be the TEM gene comprising 84% of the isolated genes. The paper concluded the importance of updating treatment guidelines with respect to rising prevalence of ESBL genes (Chelangat et al., 2025). These literature findings differ in two points. First, the resistance rate to Trimethoprim-sulfamethoxazole is higher than the highest recorded rate of our research 56.4% in 2023 inpatients. Second, the ESBL-producing *E coli* prevalence was found to be remarkably lower 13.3% than our research lowest recodring in outpatients of the year 2024 of 20.5%. This could be attributed to the observation that ESBL-producing strains specialize in resistance to beta lactam drugs than Trimethoprim-Sulfamethoxazole where high prevalence of non-ESBL producing strains encode more resistance genes to the drug.

CHAPTER VI

Conclusions, Limitations, and Recommendations

Conclusions:

- *E coli* has high and rising resistance rates against penicillins generally and ampicillin specifically.

-The bacterium recorded its highest resistance against ciprofloxacin 81.3% with similar results in the literature.

- There is a relatively growing resistance against carbapenems and nitrofurantoin but the rates remain low with carbapenems and aminoglycosides efficacy maintained along with fosfomycin.

-This growing resistance during the three years period and the striking rise of resistance to cephalosporins in 2024 indicates the possiblity of increased beta lactamase production as evidenced by the high inpatients ESBL- producing *E coli* prevalence rates.

Limitations of the study:

- The scope of the study did not include other significant uro-pathogens.

-The study focused on UTIs generally with no age group specifications.

- Risk factors for increasing *E coli* antibiotic resistance were not assessed.

Recommendations:

-Continuous monitoring of the antibiotic resistance status of *E coli* is needed with the growing concern that beta lactam resistant strains are becoming prevalent specially in hospital setting through transfer of resistance genes.

-A solid antibiotic stewardship program with continuous update of the prescription guidelines is in need to avoid development of resistance against the remaining effective antibiotics.

-The management of UTIs should always include the lab request of urine culture and antimicrobial susceptibility testing to pick the most appropriate medication.

-Patient education about the appropriate use of antibiotics according to the correct dosage and duration.

-Development of guidelines that regulate the use of over the counter antibiotics to minimize inappropriate and unnecessary consumption.

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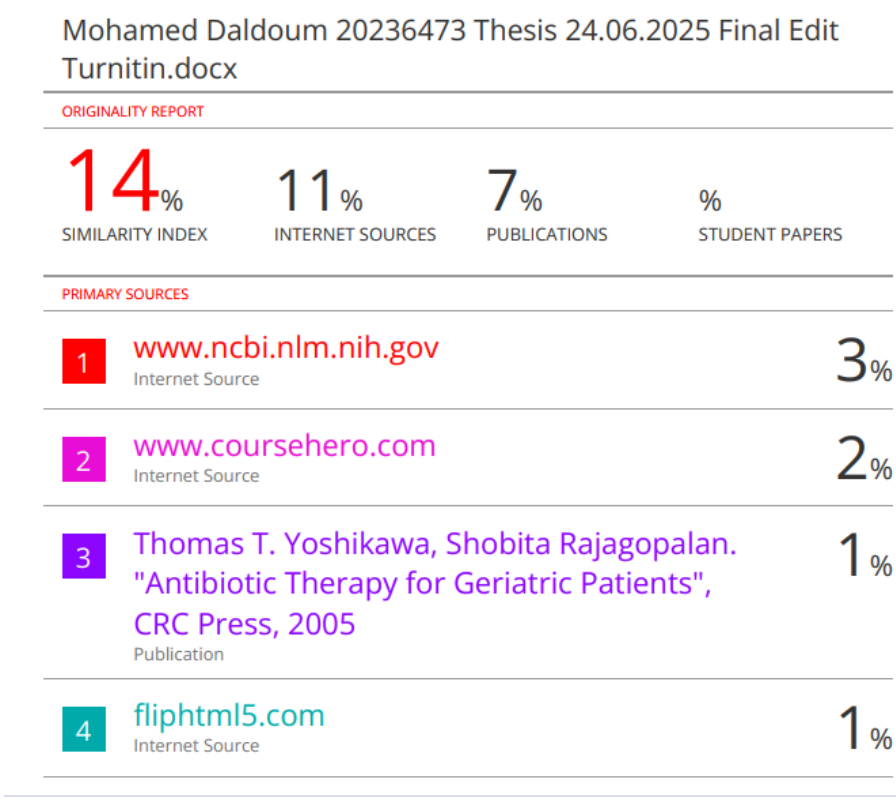

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