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Topic

Study of Antibiotic Resistance and Multiresistance in Bacterial Strains Isolated from Urine Culture (UC) in Hospital and Community Settings at Medical Analysis Laboratory Dr. Haouri in Ksar El Boukhari

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Dedication

In memory of my Dad,
Whose encouragement and support have been my strength.
This thesis is for you.

I dedicate this thesis to the unwavering love and support of my extended family, whose encouragement has been my guiding light throughout this journey.

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RAHMA

Summary: Study of Antibiotic Resistance and Multiresistance in Bacterial Strains Isolated from Urine Culture (UC) in Hospital and Community Settings at Medical Analysis Laboratory Dr. Haouari in Ksar El Boukhari.

The thesis investigates the resistance patterns of bacterial strains isolated from urine cultures (ECBU) in both hospital and community settings in Ksar El Boukhari. The study focuses on understanding the prevalence and resistance profiles of common pathogens such as *E. coli*, *Klebsiella*, *Candida*, *Streptococcus*, *Pseudomonas*, *Enterococcus*, and *Enterobacter*. Data was collected from 738 urine cultures, including 673 negative cases and 65 positive cases. Among the positive cases, pathogens were identified: 39 cases of *E. coli*, 18 cases of *Klebsiella*, 2 cases of *Candida*, 3 cases of *Streptococcus*, 1 case each of *Pseudomonas*, *Enterococcus*, and *Enterobacter*. The study utilized tables, graphs, and pie charts to organize and visualize data by age and gender.

The results showed that *E. coli* was the most prevalent pathogen (39 cases), followed by *Klebsiella* (18 cases). A detailed analysis revealed varying degrees of resistance and multiresistance among different bacterial strains. Charts and graphs depicted age and gender-specific distribution of infections, highlighting demographic trends in susceptibility. The findings underscore the complexity of antibiotic resistance among bacterial strains isolated from urine cultures at Medical Analysis Laboratory Dr.Haouari in Ksar El Boukhari. The study emphasizes the need for tailored antibiotic stewardship programs and infection control measures in both hospital and community settings to mitigate the spread of resistant pathogens.

Keywords: *Bacterial resistance, urine cultures, ECBU, E.coli, Klebsiella, Candida, Streptococcus, Pseudomonas, Enterococcus, Enterobacter, antibiotic resistance, antibiotic stewardship, infection control, pathogen prevalence*.

Résumé: Étude de la résistance aux antibiotiques et de la multirésistance dans les souches bactériennes isolées des cultures d'urine (UC) en milieu hospitalier et communautaire au Laboratoire d'analyses médicales Dr. Haouri à Ksar El Boukhari.

Cette thèse examine les schémas de résistance des souches bactériennes isolées des cultures d'urine (UC) dans les environnements hospitaliers et communautaires à Ksar El Boukhari. L'étude se concentre sur la prévalence et les profils de résistance des pathogènes courants tels que *E.coli, Klebsiella, Candida, Streptococcus, Pseudomonas, Enterococcus* et *Enterobacter.* Les données ont été recueillies à partir de 738 cultures d'urine, comprenant 673 cas négatifs et 65 cas positifs. Parmi les cas positifs, les pathogènes identifiés étaient : 39 cas *d'E.coli,* 18 cas de *Klebsiella,* 2 cas de *Candida,* 3 cas de *Streptococcus,* 1 cas chacun de *Pseudomonas, Enterococcus et Enterobacter*. L'étude a utilisé des tableaux, des graphiques et des diagrammes circulaires pour organiser et visualiser les données par âge et par sexe.

Les résultats ont montré que *E. coli* était le pathogène le plus courant (39 cas), suivi de *Klebsiella* (18 cas). L'analyse détaillée a révélé des degrés variables de résistance et de multirésistance parmi les différentes souches bactériennes. Les graphiques ont montré la répartition spécifique par âge et par sexe des infections, mettant en évidence les tendances démographiques de susceptibilité. En conclusion, les résultats soulignent la complexité de la résistance aux antibiotiques parmi les souches bactériennes isolées des cultures d'urine Au laboratoire d'analyse médicale Dr. Haouari à Ksar El Boukhari. L'étude met en avant la nécessité de programmes adaptés de gestion des antibiotiques et de mesures de contrôle des infections, tant dans les milieux hospitaliers que communautaires, pour limiter la propagation des pathogènes résistants.

Mots Clés: Résistance bactérienne, cultures d'urine, ECBU, *E. coli, Klebsiella, Candida, Streptococcus, Pseudomonas, Enterococcus, Enterobacter,* antibiotiques, résistance aux antibiotiques, gestion des antibiotiques, contrôle des infections, prévalence des pathogènes.

ملخّص: دراسة مقاومة ومتعدد المقاومة الخاصة بالبكتيريا ضد المضادات الحيوية للسلالات المعزولة من الفحوصات البكتيرية الخلوية في البيئة الاستشفائية والمجتمعية

تهدف هذه الدراسة إلى تحليل أنماط مقاومة المضادات الحيوية في السلالات البكتيرية المعزولة من فحص البكتيريا الخلوية في البيئات المستشفوية والمجتمعية في قصر البخاري. يركز البحث على فهم مدى انتشار وأنماط المقاومة في الممرضات الشائعة مثل الإشريكية القولونية، الكليبسيلا، المبيضة، العقدية، الزائفة، المعوية، والمعوية الأخرى

تم جمع البيانات من 738 عينة فحص البكتيريا الخلوية، منها 673 حالة سلبية و65 حالة إيجابية. ضمن الحالات الإيجابية، تم تحديد الممرضات كالتالي: 39 حالة للإشريكية القولونية، 18 حالة للكليبسيلا، حالتان للمبيضة، 3 حالات للعقدية، وحالة واحدة لكل من الزائفة، المعوية، والمعوية الأخرى. استخدمت الدراسة الجداول والرسوم البيانية والمخططات الدائرية لتنظيم وتوضيح البيانات حسب الفئة العمرية والجنس.

كانت الإشريكية القولونية الأكثر انتشاراً بين الحالات الإيجابية (39 حالة)، تليها الكليبسيلا (18 حالة) .أظهرت التحليلات درجات متفاوتة من المقاومة والمقاومة المتعددة بين السلالات البكتيرية المختلفة.

عرضت الرسوم البيانية والمخططات توزيع الإصابات حسب الفئة العمرية والجنس، مما أظهر الاتجاهات الديموغرافية في قابلية الإصابة.

تؤكد النتائج على التعقيد المتزايد في مقاومة المضادات الحيوية بين السلالات البكتيرية المعزولة من فحص البكتيريا الخلوية في قصر البخاري. تبرز الدراسة أهمية تبني برامج توجيهية دقيقة لإدارة استخدام المضادات الحيوية وإجراءات صارمة لمكافحة العدوى في كل من البيئات المستشفوية والمجتمعية للحد من انتشار الممرضات المقاومة.

الكلمات المفتاحية:

مقاومة المضادات الحيوية، مقاومة متعددة، السلالات البكتيرية، فحص البكتيريا انتشار العدوى، البيئات المستشفوية، البيئات المجتمعية، برامج إدارة المضادات المعوية الحيوية، إجراءات مكافحة العدوى، توزيع الفئة العمرية والجنس، تحليل البيانات البيانية.

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List of Abbreviations

- **ECBU**: Examen CytoBactériologique des Urines
- **UTI**: Urinary Tract Infection
- **WHO**: World Health Organization
- **MDR**: Multidrug-Resistant
- **ESBL**: Extended-Spectrum Beta-Lactamase
- **AMR**: Antimicrobial Resistance

Introduction

Introduction

As stated by Muteeb et al. (2023), antibiotic resistance has emerged as a significant global health challenge, closely linked to increased mortality and morbidity rates. Infections caused by both Gram-positive and Gram-negative bacteria have become increasingly difficult to treat due to multidrug resistance, rendering traditional antibiotics ineffective. This issue has persisted across both the pre-antibiotic and antibiotic eras, severely impacting the efficacy of antibiotics in clinical settings **(Muteeb et al., 2023).** The first instance of antibiotic resistance was reported shortly after the introduction of sulfonamides in the 1930s, suggesting that antibiotic resistance existed in the natural environment even before the widespread use of antibiotics, although without the presence of highly resistant deadly pathogens. The development and extensive application of antibiotics marked the beginning of the antibiotic era. However, the misuse and overuse of antibiotics, resulting in high concentrations of toxic doses, have significantly altered their effectiveness and led to the rapid proliferation of antibiotic-resistant bacteria **(Muteeb et al., 2023).**

As explained by Muhigwa et al. (2024), urinary tract infections (UTIs) caused by E. coli are considered priority infections for disease surveillance systems due to their high frequency, significant virulence, and increasing resistance to antibiotics. The prevalence of these infections, coupled with the potential for overdiagnosis, poses a substantial risk of antibiotic overuse. This overuse can promote the development of single or multi-drug resistant bacterial strains. The rising trend in antibiotic resistance in UTIs has prompted numerous studies aimed at identifying the most effective antimicrobial agents and determining the optimal treatment duration for mild cystitis **(Muhigwa et al., 2024).**

Discoverer of penicillin Alexander Fleming, in December 1945, during his acceptance speech of the Nobel Prize in Medicine, announced the risk of the inevitable phenomenon of antibiotic resistance, already observed in laboratories, with the following words:

“it’s not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them…there is the danger that the ignorant man may easily under-dose himself and, by exposing his microbes to non-lethal quantities of the drug, make them resistant.” **(A. Fleming, Penicillin, Nobel Lecture, 11 December 1945).**

According to Terreni et al. (2021), Fleming’s predictions have proven to be accurate: the misuse and overuse of antibiotics accelerate the development and spread of antibiotic-resistant bacteria. Taking penicillin as an example, when bacteria are exposed to “non-lethal levels” of the antibiotic, they can use it for signaling with regulatory functions. Bacteria can release β-lactamase enzymes, which hydrolyze the amide bond of the four-membered β-lactam ring, inactivating the β-lactam antibiotic **(Terreni et al., 2021).**

Introduction

As indicated by Terreni et al. (2021), this example is just one of many defense mechanisms that bacteria have developed against antibiotics. Antibiotics have undoubtedly been a milestone in the history of humanity and modern medicine, serving as an indispensable and life-saving weapon against numerous infectious diseases, including those associated with organ transplants, cancer chemotherapies, and intensive therapies **(Terreni et al., 2021).** While the last century saw the discovery of many new antibiotics, the number of antimicrobial agents discovered has sharply declined since the 1990s. This decline is accompanied by a simultaneous and worrying increase in antibiotic resistance. Multidrug-resistant (MDR) bacteria, which are resistant to at least three different classes of antimicrobials, have become common, especially in hospitals. There is a looming risk of entering a so-called “post-antibiotic era” within a few years, where infections currently under control could easily become lethal threats **(Terreni et al., 2021).**

Chapter I

Urinary Tract Infection

Chapter I: Urinary Tract Infection

Understanding bacterial analysis, including detection, identification, discrimination, and antibiotic resistance, is crucial in the context of food safety, infectious disease prevention, and environmental control **(Váradi et al., 2017; Law et al., 2015).** Culture-based methods remain the most commonly used techniques for bacterial detection and identification **(Gracias & McKillip, 2004).**

Bacteria, a vernacular term, refers to microscopic, prokaryotic organisms found in all environments. They are primarily unicellular but can sometimes be multicellular, generally in filamentous forms **(O'Toole et al., 2009).**

Bacteria exhibit a wide range of sizes and shapes. Typical bacterial cells range from 0.5 to 5 µm in length, though some species like Thiomargarita namibiensis and Epulopiscium fishelsoni can reach up to 750 µm (0.75 mm) and be visible to the naked eye **(Schulz, 2001; Lecointre, 2001).**

Bacteria commonly take spherical or rod-like shapes, referred to as cocci and bacilli, respectively. Intermediate forms, such as coccobacilli, also exist. Some rod-shaped bacteria are slightly curved, like Vibrio. Additionally, some bacteria have a helicalshape, known as spirilla if rigid and spirochetes if flexible.

Bacteria are ubiquitous and present in all environments on Earth, including soil, fresh and marine waters, air, ocean depths, and radioactive waste (Fredrickson et al., 2004). The human body hosts a significant number of bacteria, equivalent to the number of human cells, though their mass is higher. While most of these bacteria are harmless or beneficial, many pathogenic species are responsible for numerous infectious diseases.

I. Anatomical and Physiopathological Analysis of the Urinary System

The urinary system is one of the body's excretory systems **(Lepot, 2011).** Its primary function is to purify the blood by extracting metabolic waste and excreting it as urine. This selective elimination also helps maintain the constancy of the internal environment **(Lacombe, 2005).**

I.1. Anatomy of the Urinary System

The organs of the urinary system are responsible for the production, storage, and elimination of urine. It can be divided into two distinct regions based on the relation to the ureteral orifice in the bladder:

-The upper body, consisting of the kidneys and ureters, which produce and transport urine to the storage compartment.

-The lower compartment, which includes the bladder, urethra, and in men, the prostate. This compartment stores urine and provides a system for its evacuation **(Drake et al., 2020).**

I.2. The Physiology of the Urinary System

I.2.1. Characteristics and Composition of Urine

Urine is a sterile organic liquid produced by the kidneys after blood filtration, transported by the ureters, stored in the bladder, and excreted during urination. It is yellow with a distinctive odor, slightly acidic (pH 5-6), with a specific gravity of 1.016 to 1.020, and a slightly salty taste. Daily urine output ranges from 0.5 to 2 liters, depending on age **(Belmellat & Igoudjil, 2022).**

Urine consists of 95% water, with urea, creatinine, ammonia, and potassium. It also contains solutes like uric acid, sodium, magnesium, sulfate, chloride, and calcium ions. Abnormal constituents or unusual quantities of normal constituents may indicate disease **(Tortora & Derrickson, 2017).**

II. Urinary Tract Infection (UTI)

II.1. Definition

A urinary tract infection (UTI) is an invasion of the urinary tract by one or more microorganisms, causing inflammation and clinical symptoms. It is defined by clinical signs and significant leukocyturia **(Raghu, 2016).**

II.2. Epidemiology of Urinary Infections

The urinary tract is the second most common site of community-acquired infections after respiratory infections **(Sbiti et al., 2017).** Globally, there are over 150 million cases annually **(Mancuso et al., 2023).** UTIs are a major cause of morbidity and mortality in some patients **(Martin et al., 2019).** They are much more prevalent in women, with 40% to 60% experiencing at least one UTI in their lifetime **(Syed et al., 2019).** Cystitis is the most common type, usually caused by Enterobacteriaceae, primarily *Escherichia coli*, which is the most frequently isolated bacterium regardless of age or gender **(Bruyère & Pizzighella, 2018).**

II.3. Classification of Urinary Infections

II.3.1. Uncomplicated UTIs

These are simple UTIs affecting generally healthy individuals without structural or functional urinary tract abnormalities **(Mancuso et al., 2023).**

II.3.2. Complicated UTIs

These are defined as UTIs occurring in the presence of risk factors and are caused by pathogens other than E. coli **(Truls et al., 2011).**

II.4. Types of Urinary Infections

II.4.1. Lower Urinary Tract Infections

II.4.1.A.Urethritis

Affects the urethra and is a sexually transmitted infection (STI), primarily affecting men but can also occur in women. It can be caused by various pathogens, with Chlamydia and gonococci being the most common **(Guy Albert, 2008).**

II.4.1.B.cystitis

Acute bacterial cystitis is an infection-induced inflammation of the bladder, confined to the urine and urothelium **(Dalibon, 2015).**

II.4.1.C. Prostatitis

Refers to inflammatory or infectious processes affecting the prostate gland, common in men and not directly linked to benign prostatic hyperplasia or prostate cancer **(Francolugo Vélez, 2003).**

II.4.2. Upper Urinary Tract Infections

II.4.2.A.Pyelonephritis

Is a more severe condition involving inflammation of the renal pelvis and kidney, typically resulting from bacterial infection. It can arise as a complication of untreated or poorly treated cystitis, allowing bacteria to proliferate from the bladder to the kidneys. Acute pyelonephritis is more common in women, especially pregnant women **(Guy Albert, 2008).**

II.5. Forms of Contamination

II.5.1. Ascending Route

Bacteria can enter the urethra and ascend into the bladder. Saprophytic bacteria often ascend and remain in the bladder, and then travel up the urinary tract due to weakened host defenses and favorable conditions **(Caron, 2003).**

II.5.2. Hematogenous Route

The kidney is colonized by blood-borne pathogens during septicemia or bacteremia via glomerular filtration. Hematogenous pathogens often include specific bacteria like Staphylococcus aureus, Candida, and the tuberculosis bacillus **(Bruyère et al., 2008).**

II.5.3. Lymphatic Route

This controversial route suggests potential lymphatic pathways between the colon and kidney, but there is no experimental evidence to confirm this **(Bamba, 2000).**

II.6. Risk Factors

II.6.1. Bacterial Factors

Adhesion and virulence factors developed by uropathogenic bacteria and the presence of a significant bacterial inoculum in the urinary tract are considered risk factors for UTI **(Lobel & Soussy, 2007).**

II.6.2. Host Factors

-Anatomical or functional abnormalities of the urinary tract (congenital malformations, tumors, stones, vesicoureteral reflux, bladder diverticula).

-Advanced age.

-Gender: a short urethra in women facilitates the ascent of bacteria to the bladder, explaining the higher incidence in women.

-Urinary stasis due to external compression (pregnancy, severe chronic renal failure, genital prolapse, prostatic hypertrophy).

-Certain conditions: diabetes, severe immunodeficiency

-Gynecological infections (vaginitis and vulvovaginitis).

-Poor perineal hygiene, sexual activity.

-Insufficient fluid intake and infrequent urination **(Bouakkaz & Boucherbit, 2017).**

II.7. Germs Causing Urinary Tract Infections

-**Enterobacteriaceae**: Commonly found in the gastrointestinal flora, these bacteria are frequent in clinical specimens and cause many infections, including UTIs. They can be parasites (Shigella and Yersinia pestis), commensals (Escherichia coli, Proteus mirabili, and Klebsiella pneumoniae), or saprophytes (Serratia marcescens and Enterobacter cloacae) (Boivin et al., 2016). They are oxidase-negative, glucose-fermenting, nitrate-reducing, non-sporulating, immobile or mobile by peritrichous flagella, facultative anaerobes, with an optimal temperature of 37°C **(Freney et al., 2006).**

-**Pseudomonas**: A Gram-negative, strictly aerobic, non-fermenting bacillus, ubiquitous in the environment. It causes opportunistic infections, mainly in nosocomial settings, and is characterized by blue-green pigment production and natural resistance tomany antibiotics **(Dousquet & Mérens, 2018).**

-Streptococci: Streptococci are commensal species but also responsible for infections in humans. They are Gram-positive bacteria, coccoid or ovoid in shape, and group in pairs or chains. They are facultative anaerobes and are classified based on their hemolytic properties, with blood agar being their medium of choice. These bacteria are

lactic acid fermenters and nutritionally demanding. They are highly sensitive to environmental changes and do not survive long outside the body **(Gaschignard et al., 2019).** Streptococcus group D is the most commonly found in urinary infections **(Wainsten, 2012).**

- Staphylococci: Staphylococci are commensal bacteria in humans, ubiquitous, and facultative anaerobes. They appear as Gram-positive cocci grouped in clusters. These bacteria are highly resistant in the external environment and have low nutritional requirements, with a short growth time in culture (Tran, 2020).

II.8-Fungal Pathogens

The most common non-bacterial pathogens are fungi (usually species of Candida), and less frequently, mycobacteria, viruses, and parasites. Non-bacterial pathogens typically affect immunocompromised patients, those with diabetes, urinary tract obstructions or structural abnormalities, or those who have recently undergone urinary tract instrumentation **(Talha, 2024).** Candida is a species within the human microbiome found on mucosal surfaces. Pathogenesis by Candida is triggered by disruptions in the host's environmental regulation, such as the loss of commensals after antibiotic therapy, inflammation, or breaches in mucosal surfaces. This initial dysregulation of Candida commensalism is necessary for both superficial mucocutaneous infections and systemic diseases in individuals without primary immunodeficiency. C. albicans is the main cause of candidiasis but is not the only species responsible for diseases in humans **(Papon et al., 2013).**

Candida albicans, a member of the Candidaceae family **(Hazen & Howell, 2007),** is a diploid and encapsulated fungus classified among the polymorphs as it can appear as yeast or pseudohyphae depending on temperature, pH, and nutrients **(Ryan, 2004).** The yeast form is associated with the production of blastoconidia and is the most commonly observed form of C. albicans. Pseudohyphae lack the parallel walls and septa characteristic of true hyphae, appear as long filaments, and can produce thick-walled chlamydospores **(Ryan, 2004).** Asexual reproduction occurs by budding to produce blastoconidia **(Ryan, 2004; Hazen, 2007).** Colonies appear 48 to 72 hours after culture at 37°C on fungal isolation media, such as Sabouraud agar; initially wrinkled, they become smooth upon reculturing.

II.9.Diagnosis of Urinary Infections

Several urinary tests are available and are specific concerning their indications and diagnostic values for detecting urinary infections. It is crucial to identify and pinpoint the microorganisms responsible for urinary infections, which involves the use of urine dipsticks (BU) and urine culture and cytobacteriological examination (ECBU).

II.9.1-Urine Collection

Urine collection for UC is done using a sterile container (available at pharmacies or provided by the primary care physician) with the first morning urine. Depending on the patient (young children, etc.), urine collection for UC can sometimes be done using an adhesive sterile pouch (collector bag) placed around the genitalia for at least 30 minutes. Urine collection for ECBU can also be done at the end of the day with urine that has remained in the bladder for at least 4 hours. The first stream of urine should be discarded into the toilet. For newborns or children who are not yet toilet trained, collection is done via a collector bag **(Jean, 2021).**

II.9.2-Urine Dipsticks

The urine dipstick is a plastic stick with reagents that react to different components in the urine **(Latini et al., 2010).** The dipstick is a quick and simple test for screening healthy individuals without symptoms or signs of infection. However, its positive predictive value remains insufficient, requiring a cytobacteriological examination **(Teng & Robain, 2022).**

II.9.3-Urine Culture and Cytobacteriological Examination (ECBU)

The UC is the definitive test for confirming a urinary infection. It aims to reveal the presence of pathogens responsible for the infection. For accurate results, it is essential to follow proper collection, conservation, and transportation conditions **(Ait Miloud, 2011).**

- Men: Thorough washing of the glans with quaternary ammonium, followed by physiological serum, and then midstream urine collection.
- Women: Thorough washing and midstream urine collection.
- Obese or incontinent individuals: Collection by catheterization.
- Children: Collection using sterile adhesive bags **(Ouamrouche, 2019).**

The presence of bacteria, leukocytes, and epithelial cells is assessed. The test includes direct microscopic examination of the urine and culture to identify the causative pathogen. If a pathogen is found, an antibiotic susceptibility test (Antibiogram) is performed to guide the physician in choosing an effective treatment (**Qebibo, 2014).**

III-Antibiogram

The antibiogram is a technique systematically associated with ECBU. The test determines the sensitivity or resistance of a bacterial strain when exposed to specific antibiotics. Based on the incubation results, the appearance of inhibition zones indicates whether the cultured bacteria are sensitive, resistant, intermediate, or undetermined **(Seakhri, 2011).**

These diagnostic methods enable precise targeting of microorganisms responsible for urinary infections, ensuring appropriate therapeutic management **(Seakhri, 2011).**

Chapter II

Antibiotics and Resistance

Chapter II: Antibiotics and Resistance

II-1- Antibiotics

Abdus Salam et al. (2023) emphasized that antibiotics, often referred to as "magic bullets" for their effectiveness against bacteria, are considered one of the most important medical discoveries of the 20th century. Their introduction revolutionized medical treatment, saving millions of lives from bacterial infections. Beyond their medical applications, antibiotics have also been widely used in animal husbandry and production as preventive measures, especially in many underdeveloped and developing countries **(Abdus Salam et al., 2023).**

However, the extensive use and misuse of antibiotics have led to the emergence of antimicrobial resistance (AMR). AMR refers to the ability of microorganisms—including bacteria, viruses and fungi—to survive and grow despite the presence of drugs designed to kill them. This resistance complicates the treatment of infections, often leading to more severe illness and higher mortality rates. Various antimicrobial agents, such as antibiotics, antifungals, antivirals, disinfectants, and food preservatives, work to inhibit or kill microbial growth. Among these agents, antibiotics are specifically used to combat bacterial infections and are more commonly employed than any other type of antimicrobial, underscoring the urgency of addressing antibiotic resistance **(Abdus Salam et al., 2023).**

II-1-1. Definition

Cook and Wright (2022) argued that antibiotics are among the most transformative medications in human history, significantly altering both mortality rates and the quality of life. They noted that before the advent of antibiotics, over half of all deaths were due to infectious diseases. With the introduction of antibiotics and improved infection control measures, mortality rates from infections have drastically declined **(Cook & Wright, 2022).** This development has contributed to a global increase in life expectancy by one to two decades within less than a century. Antibiotics have not only directly treated infections but have also facilitated life-saving medical procedures such as cancer chemotherapy, organ transplants, and complex surgeries. According to Cook and Wright (2022), the reliable infection control provided by antibiotics is essential for the success of these interventions, underscoring their indispensable role in modern medicine.

II-1-2. History

On the authority of Walesh et al (2022), in the earliest contemporary clinical method, pyocyanase, an extract from Pseudomonas aeruginosa, was employed by Emmerich and Löw between 1890 and 1910 to treat infectious illnesses. Paul Erlich's synthetic prodrug salvarsan marked the beginning of the concept of small-molecule antibiotics. The dye's source, which selectively strains bacterial cells, also served as an inspiration for Gerhard

Domagk's creation of prontosil. The first of the broad-spectrum antibiotics known as sulfonamides—which are still in use today—was prontosil. **(Walesh et al., 2022).** Antibiotics have become more popular since Alexander Fleming's 1929 discovery of the natural substance penicillin, which was later refined by Healthy and associates. The discovery of soil-dwelling actinomycetal and its ability to generate naturally occurring antibiotic compounds by Salman Waksman, Albert Schatz, and Elizabeth Bugie marked the beginning of the period known as the "golden age of antibiotics," which lasted from the 1940s to the 1960s. During those decades, the majority of antibiotic classes currently in use were discovered and produced **(Walesh et al., 2022).** With the exception of tuberculosis treatment, the 22 antibiotic classes currently approved for the systemic treatment of bacterial infections have five general mechanisms to kill or inhibit the growth of bacteria: 1. interfering with the synthesis of cell walls; 2. protein biosynthesis; 3. DNA synthesis; 4. folic acid metabolism; or 5. compromising the synthesis and integrity of cell membranes. The general modes of action appear to be associated with blocking the cellular machinery that forms complex biological structures like proteins, DNA, RNA, and cell walls **(Walesh et al., 2022).**

II-1-3. Classification

Etebu and Arikekpa (2016) explained that antibiotics can be classified in several ways, with the most common schemes based on their molecular structures, mode of action, and spectrum of activity. Another classification criterion includes route of administration, such as injectable, oral, or topical forms. Antibiotics within the same structural class typically exhibit similar patterns of effectiveness, toxicity, and potential allergic reactions. Common classes of antibiotics based on chemical or molecular structures include Beta-lactams, Macrolides, Tetracyclines, Quinolones, Aminoglycosides, Sulphonamides, Glycopeptides, and Oxazolidinones **(Etebu & Arikekpa, 2016).**

Isha et al. (2020) found that antibiotics are categorized into three groups: Access, Watch, and Reserve, with some combinations labeled as "not recommended." The Access group consists of antibiotics commonly used as first or second choices for a wide range of pathogens and are less prone to antibiotic resistance. Watch antibiotics are deemed "Critically Important Antimicrobials for Human Medicine" but have a higher risk of developing resistance **(Isha et al., 2020).** Reserve antibiotics are reserved for specific treatments, such as multidrug-resistant infections, and should be used as a last resort when other options fail. The World Health Organization (WHO) aims for 60% of antibiotic consumption to come from the Access group to promote universal health coverage. A survey was conducted in selected healthcare facilities in Tamil Nadu to evaluate antibiotic prescribing patterns based on the WHO Aware classification **(Isha et al., 2020).**

Table1

*WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use, **2023***

Class	Antibiotic	ATC code	Category	Listed on EML/EMLc2023
Aminoglycosides	Amikacin	J01GB06	Access	Yes
	Gentamicin	J01GB03	Access	Yes
	Netilmicin	J01GB07	Watch	No
	Streptomycin_IV	J01GA01	Watch	No
	Streptomycin_oral	A07AA04	Watch	No
Penicillins	Ticarcillin	J01CA13	Watch	No
	Amoxicillin	J01CA04	Access	Yes
	Ampicillin	J01CA01	Access	Yes
	Meticillin	J01CF03	Access	Yes (therapeutic alternative to cloxacillin)
Beta-lactam / beta-lactamase-inhibitor	Amoxicillin / clavulanic - acid	J01CR02	Access	Yes
First-generation-cephalosporins	Cefazolin	J01DB04	Access	Yes
Second-generation-cephalosporins	Cefoxitin	J01DC01	Watch	No

Second-generation-cephalosporins	Cefuroxime	J01DC02	Watch	Yes
Third-generation-cephalosporins	Cefotaxime	J01DD01	Watch	Yes
Amphenicols	Chloramphenicol	J01BA01	Access	Yes
Fluoroquinolones	Ciprofloxacin	J01MA02	Watch	Yes
	Levofloxacin	J01MA12	Watch	No
Lincosamides	Clindamycin	J01FF01	Access	Yes
Macrolides	Erythromycin	J01FA01	Watch	Yes (therapeutic alternative to clarithromycin (EMLc))
Carbapenems	Ertapenem	J01DH03	Watch	No
	Imipenem/cilastatin	J01DH51	Watch	Yes (therapeutic alternative to meropenem)
	Imipenem/cilastatin/relebactam	J01DH56	Reserve	No
Nitrofuran-derivatives	Nitrofurantoin	J01XE01	Access	Yes
Sulfonamide-trimethoprim-combinations	Sulfamerazine/trimethoprim	J01EE07	Access	No
Tetracyclines	Tetracycline	J01AA07	Access	No
Glycopeptides	Vancomycin_IV	J01XA01	Watch	Yes

	Vancomycin_oral	A07AA09	Watch	Yes
Streptogramins	Pristinamycin	J01FG01	Watch	No
Phosphonics	Fosfomycin_IV	J01XX01	Reserve	Yes
	Fosfomycin_oral	J01XX01	Watch	No
Rifamycins	Rifampicin	J04AB02	Watch	No

Antibiotics Mode of Action

According to Etebu and Arikekpar (2016), the antimicrobial potency of most classes of antibiotics is directed at some unique feature of bacterial structure or their metabolic processes. The mechanisms of antibiotic actions include inhibition of cell wall synthesis, breakdown of cell membrane structure or function, inhibition of the structure and function of nucleic acids, inhibition of protein synthesis, and blockage of key metabolic pathways **(Etebu & Arikekpar, 2016).**

Table 2

Mechanisms of Action of Various Antibiotic Classes

Mode of action	**Targets**	**Drug class**	**Specific drugs example**
Cell wall synthesis inhibition	**Penicillin-binding protein** **Peptidoglycan subunits** **30 s subunit**	β-lactams Glycopeptides Aminoglycosides and tetracyclines	Penicillin G, amoxicillin, and cephalosporin C Vancomycin Streptomycin, gentamicin, neomycin, tetracycline, and doxycycline
Inhibition of protein synthesis	**50 s subunit**	Macrolides, chloramphenicol, and oxazolidinones	Erythromycin, azithromycin, chloramphenicol, and linezolid
Inhibition of nucleic acid synthesis	**RNA** **DNA**	Rifamycin Fluoroquinolones	Rifampin Ciprofloxacin and ofloxacin
Anti-metabolites	Folic acid synthesis enzymes	Sulfonamides and trimethoprim	Sulfamethoxazole, dapsone, and trimethoprim.
Disrupt membranes	Lipopolysaccharides	Polymyxins	Polymyxin B and colistin

Source: Uddin and colleagues (2021), p. 63.

II-1-4. Antibiotics Side Effects

From the point of view of Mohsen et al. (2020), antibiotics are invaluable in treating severe infections and can save lives, yet their misuse or overuse can lead to bacterial resistance and adverse effects. While much attention is paid to their benefits, the potential harms are often overlooked. Clinicians must carefully assess the benefits of prescribing antibiotics against the risks they carry. For example, chloramphenicol was once a go-to for meningitis treatment despite rare but severe side effects like aplastic anemia **(Mohsen et al., 2020).** However, as safer alternatives became available, the risks associated with such drugs became unacceptable. Similarly, sulfonamides were once hailed as "wonder drugs" but fell out of favor due to the rise in severe skin reactions. It's essential for medical professionals to weigh the potential benefits and risks of antibiotics when making treatment decisions **(Mohsen et al., 2020).**

II-2- Resistance

"AMR is an unavoidable evolutionary phenomenon shown by all organisms through development of genetic mutations in order to safeguard against lethal selection pressure. To withstand environmental selection pressure, bacteria strive to develop resistance against antibacterial drugs, rendering these drugs ineffective. With the ever-increasing use of antibiotics, especially in developing countries, bacteria have ample opportunity to develop AMR with profound consequences including much higher morbidity and mortality" **(Abdus Salam et al., 2023, p. 1946).**

II-2-1. Definition

From the point of view of Edwards et al. (2021), antibiotic resistance in pathogenic bacteria can be defined either microbiologically or clinically.

As explained by Edwards et al. (2021), microbiological resistance is determined through laboratory testing, where an organism's sensitivity or resistance to an antimicrobial agent is assessed based on specific criteria, often using standardized methods such as those set by the European Committee on Antimicrobial Susceptibility Testing. In the UK, for example, this may involve placing antibiotic-impregnated discs on a pure culture of the bacteria and observing the growth inhibition zones around the discs. The presence or absence of growth within these zones helps categorize the bacteria as either sensitive or resistant to the antibiotic **(Edwards et al., 2021).**

According to Edwards et al. (2021), clinical resistance occurs when antibiotic treatment fails to eliminate an infection or contain its spread within a patient, even when the antibiotic is prescribed and administered correctly according to clinical guidelines. This definition considers the real-world effectiveness of antibiotics in clinical settings and the treatment outcomes experienced by patients **(Edwards et al., 2021).**

II-2-2. Mechanism of Resistance

Reducing Intracellular Antibiotic Concentrations

- Increased efflux
- Decreased influx **(Patel et al., 2023).**

Antibiotic Inactivation

- Enzymatic modification
- Chemical degradation **(Patel et al, 2023).**

Target Site Alteration

- Mutation of the target site
- Antibiotic modification
- Target site protection
- Elimination of the target site **(Patel et al., 2023).**

II-2-3. Methods to Curb Antibiotic Resistance

As explained by Nadgir et al. (2023), Australian researchers have pinpointed a promising solution in the fight against antibiotic resistance: our own immune systems. They've discovered that a group of proteins called guanylate-binding proteins not only have the ability to detect and eradicate bacteria but also activate the immune system's response against them. These proteins could potentially evolve into standalone treatments over time. To safeguard the effectiveness of antibiotics, efforts are primarily focused on regulating antibiotic distribution in hospitals and ensuring they're not dispensed without proper prescriptions. This underscores the urgent need for novel targets within bacterial mechanisms to combat resistance **(Nadgir et al., 2023).**

II-2-4. Multidrug Resistance

As indicated by Escola Verge et al. (2020), one of the World Health Organization's current priorities is addressing multidrug-resistant bacteria, as they pose a global challenge due to their rapid spread and the difficulty of treatment. These bacteria are linked to high morbidity, mortality, and significant economic costs. Both Gram-positive and Gram-negative multidrug-resistant bacteria are of concern, including carbapenem-resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, carbapenemase-producing *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus* (MRSA) and/or vancomycin-intermediate *Staphylococcus aureus* (VISA), and vancomycin-resistant *Enterococcus faecium* (and less commonly *Enterococcus faecalis*) (**Escola Verge et al., 2020).**

As explained by Catalano et al. (2022), bacteria can develop multidrug resistance (MDR) through various mechanisms. Firstly, they can accumulate multiple resistance genes within a single cell, typically on resistance R-plasmids, each gene conferring resistance to a different drug. Secondly, MDR can result from the overexpression of genes encoding multidrug efflux pumps, which expel a broad range of drugs. Lastly, MDR can arise through the

enzymatic inactivation of drugs, either by degrading them or by attaching a chemical group to them. For instance, some drugs, like penicillin and tetracycline, can be inactivated through hydrolysis **(Catalano et al., 2022, p. 22).**

II-2-5. Mechanisms of Efflux Pump Systems

One significant cause of multidrug resistance (MDR) is the expulsion of antibiotics by drug efflux pumps. These pumps decrease the accumulation of drugs inside cells by enhancing drug efflux and overexpressing drug transporters, leading to clinically significant drug resistance. This mechanism is primarily responsible for resistance to tetracyclines, erythromycin, and fluoroquinolones **(Catalano et al., 2022, p. 22).**

As explained by Catalano et al. (2022), the prokaryotic efflux pumps are divided into six classes, while the eukaryotic ones are divided into five groups. However, the ATP-binding cassette (ABC) efflux pumps are the major efflux pumps involved in multidrug resistance **(Catalano et al., 2022).**

From the point of view of Poole (2001), Gram-negative microorganisms generally exhibit higher resistance to antimicrobials compared to Gram-positive microorganisms **(Poole, 2001).**

II-2-6. Extended-spectrum beta-lactamases (ESBLs)

As stated by Giamarello (2005), ESBL enzymes, belonging to Ambler's molecular class A, typically feature a serine residue at their active site. In a classification system introduced in 1995, β-lactamases were categorized into functional groups based on their biochemical properties, molecular structure, and gene nucleotide sequences. According to this scheme, ESBLs are enzymes that hydrolyze oximino-cephalosporins and are inhibited by clavulanic acid, falling into group 2be (Giamarello, 2005). While ESBLs do not exhibit activity against cephamycins, strains expressing these enzymes should generally be susceptible to cefoxitin and cefotetan. However, due to the loss of an outer membrane porin protein, ESBL-producing strains often develop resistance to cephamycins **(Giamarello, 2005).**

According to Giamarello (2005), the majority of ESBLs are derived from TEM and SHV enzymes, distinguished by specific point mutations at certain locations within the gene. As of January 25, 2005, there were 138 TEM-type (TEM-1 to TEM-139) and 62 SHV-type (SHV-1 to SHV-63) β-lactamases identified. These enzymes are predominantly found in strains of *Klebsiella pneumoniae* and *Escherichia coli* **(Giamarello, 2005).**

II-2-7 Detection Methods for ESBLs

1. The double-disc approximation test **(Giamarello, 2005, p. 53).**
2. The Etest ESBL strip (AB Biodisk, Solna, Sweden) (**Giamarello, 2005, p. 6).**
3. Commercialised tests with discs containing clavulanate plus ceftazidime or cefotaxime (10 µg plus 30 µg, respectively) (**Giamarello, 2005, pp. 54-55).**
4. The three-dimensional test **(Giamarello, 2005, p. 56).**

5. The automated ESBL microbial susceptibility test system Vitek (BioMérieux, Marcy l'Etoile, France) **(Giamarello, 2005, p. 6).**
6. Recently, the NCCLS has recommended initial screening by testing for growth in a broth medium containing 1 μg/mL of one of five extended-spectrum β-lactam antibiotics **(Giamarello, 2005, p. 52).**

On the authority of Giamarello (2005), it's important to emphasize that upon detecting an ESBL, the strain should be reported as non-susceptible to all extended-spectrum cephalosporins (ESCs) and aztreonam, irrespective of the susceptibility test outcome. However, it's worth noting that false-positive ESBL results may occur in strains producing elevated levels of SHV-1 or when an AmpC-type enzyme is co-expressed in the same isolate. In conclusion, the double-disc approximation test and broth dilution MIC reduction method appear to be the simplest and most cost-effective options for implementation in clinical laboratories **(Giamarello, 2005).**

Chapter III

EPIDEMIOLOG

Chapter III: EPIDEMIOLOGY

Mullner (2024) found that a variety of tools, such as mortality rates, incidence rates, and prevalence rates, are utilized in epidemiology to gain a deeper understanding of disease characteristics within and across populations. Additionally, epidemiologic studies can be classified as either descriptive or analytic. Descriptive studies aim to characterize disease, while analytic studies test conclusions drawn from descriptive surveys or laboratory observations **(Mullner, 2024).**

III.1-Epidemic

In 2016, the WHO projected that by 2050, 10 million people could die annually from antibiotic-resistant infections if no measures are taken. Consequently, the WHO declared the rise and spread of bacteria resistant to antibacterial agents as "a growing threat to public health worldwide, requiring action across all sectors and throughout society" **(World Health Organization [WHO], 2016).** The MOOC "Resistance to Antibacterial Agents" tackles the significant public health issue of the emergence of multi-drug resistant bacteria, which leads to higher morbidity and mortality rates from various bacterial infections **(Institut Pasteur, 2021).**

III.1.1-Europe

As stated by Institut Pasteur (2021), in Europe, the European Centre for Disease Prevention and Control (ECDC) estimates that 33,000 deaths are caused by infections with antibiotic-resistant bacteria. A similar mortality rate is observed in the United States, according to the Centers for Disease Control and Prevention (CDC) in Atlanta. Data are lacking for low-income countries, but the increase in resistance in these regions, coupled with limited access to safe antibiotics when needed, is likely responsible for numerous deaths. The rise in resistance could lead to a dramatic increase in these numbers, as modeled in Lord J. O'Neill's report on the impact of antibiotic resistance by 2050 **(Institut Pasteur, 2021).**

III.1.2-France

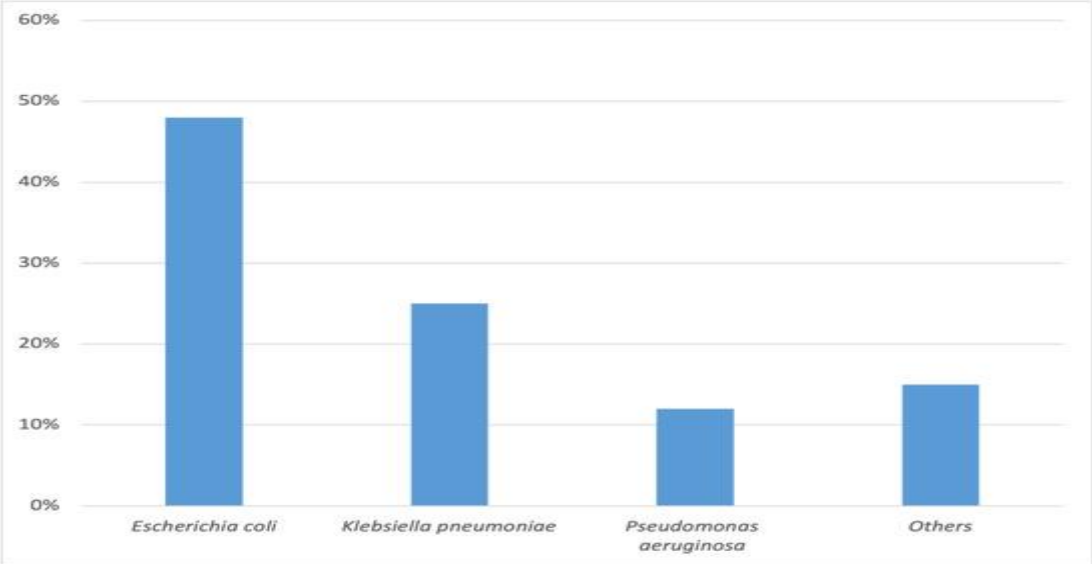
As indicated by Institut Pasteur (2021), in France, since the early 2000s, the National Plan to Preserve the Effectiveness of Antibiotics has established a surveillance system for bacterial resistance to antibiotics, overseen by Santé Publique France (formerly the Institute for Public Health Surveillance - InVS). In a surveillance report published in November 2020, French health authorities emphasized that "the massive and repeated use of antibiotics in human and animal health over time leads to an increase in bacterial resistance. Antibiotics not only target the specific bacteria responsible for the infection but also affect other bacteria, such as the beneficial commensal bacteria in the digestive tract." Despite this plan, antibiotic consumption in France remains abnormally high. In outpatient care, prescriptions are twice as high in France compared to Germany or England, two socioeconomically comparable countries **(Institut Pasteur, 2021).**

III.1.3-Saudi Arabia

Alhazmi et al. (2023) found that a comprehensive analysis of 1082 urinary bacterial samples revealed several key findings. *Escherichia coli* emerged as the predominant etiologic agent responsible for community and hospital-acquired infections. The overall prevalence of bacterial infections was higher in females (62.66%) than in males (37.34%). *Escherichia coli* accounted for the majority of UTI cases (47.97%), followed by *Klebsiella pneumoniae* (24.58%) and *Pseudomonas aeruginosa* (11.55%). Other pathogens, including *Enterobacter cloacae, Streptococcus agalactiae, Enterococcus faecalis, Staphylococcus aureus, Proteus mirabilis,* and *Acinetobacter baumannii,* represented more minor cases. The distribution of uropathogens can be visualized in Figure 1 **(Alhazmi et al., 2023).**

Figure 1

The most common reported organisms in this study.

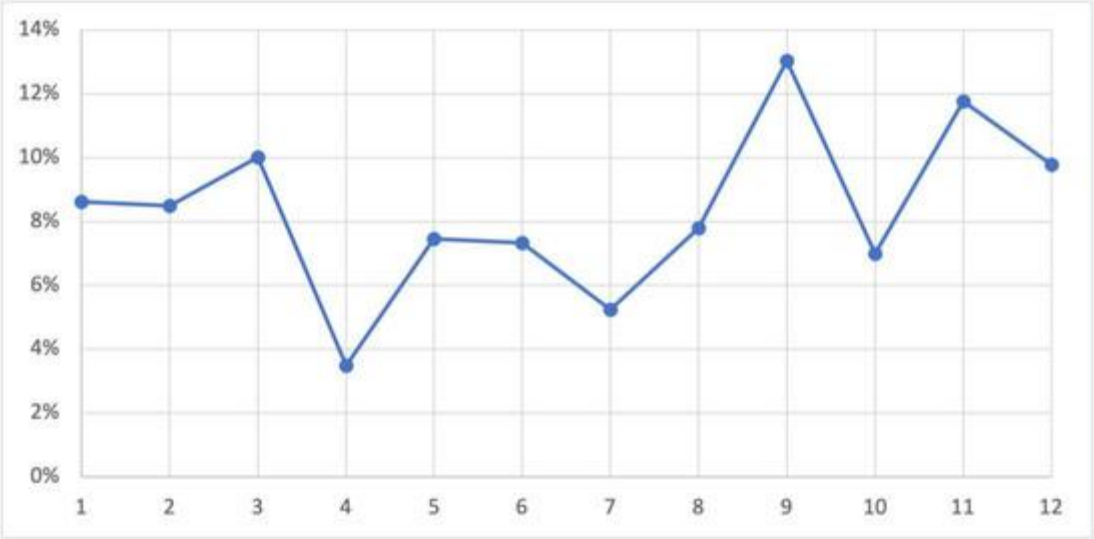


As indicated by Alhazmi et al. (2023), regarding antibiotic resistance patterns, the reported UTIs were classified into four groups. Extended-spectrum beta-lactamase (ESBL) was detected in 30.13% of cases, while carbapenem-resistant Enterobacteriaceae (CRE) accounted for 1.94% of cases. Methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant Enterococcus (VRE) were less common, comprising 0.74% and 0.18% of cases, respectively **(Alhazmi et al., 2023).**

According to Alhazmi et al. (2023), the temporal distribution of UTIs throughout the study duration was reported. September had a higher prevalence of UTIs (13%) compared to other months, while in April, the lowest prevalence was recorded, as illustrated in **Figure 2** **(Alhazmi et al., 2023).**

Figure 2

Distribution of the positive cases of UTI during the months of 2022 (n = 859).



According to Alhazmi et al., (2023). Gram-negative bacteria constituted the majority of UTI cases (94%), while Gram-positive bacteria represented a smaller proportion (6%). Among 1015 identified Gram-negative bacteria, 361 cases (36%) exhibited multidrug resistance (MDR), indicating resistance to three or more tested antibiotics. On the other hand, 654 cases (64%) were susceptible to the tested antibiotics. Notably, *Escherichia coli* (34.42%), *Klebsiella pneumoniae* (13.95%), and *Pseudomonas aeruginosa* (1.63%) were the most prevalent MDR Gram-negative species **(Alhazmi et al., 2023).**

According to Alhazmi et al., (2023), provides further details on MDR infections caused by Gram-negative organisms. The analysis of gender distribution showed that 128 (12.61%) of the Gram-negative bacteria with MDRO were isolated from male patients, while 223 (21.97%) were from female patients. Regarding the location of isolation, the ER had 144 (14.19%) Gram-negative bacteria with reported MDRO, followed by the wards with 86 (8.47%), ICU with 39 (3.84%), and clinics with 92 (9.06%). Considering nationality, 310 (30.54%) of the Gram-negative bacteria with reported MDRO were isolated from non-Saudi patients, while 534 (52.61%) were from Saudi patients (*p*-value = 0.096). Regarding the origin of infections, HAI (Healthcare-Associated Infection). Showed the highest number of Gram-negative bacteria with reported MDRO, with 82 (8.08%), followed by community-acquired infections (CAI) with 183 (18.03%). Among the Gram-negative isolates, *Escherichia coli* demonstrated the highest prevalence of MDRO, with 232 (34.42%) cases, followed by *Klebsiella pneumoniae* with 94 (13.95%), Pseudomonas aeruginosa with 11 (1.63%), and others with 12 (1.78%). **(Alhazmi et al., 2023).**

III.1.4-Morocco

According to Jaouhar et al. (2023), urinary tract infection is one of the most common infectious diseases worldwide. This study aimed to determine the frequency of urinary tract infections, identify the microorganisms involved, and determine the antibiotic resistance pattern of Escherichia coli. Conventional biochemical techniques identified isolates. The antibiogram was produced using the Muller-Hinton agar disc diffusion method according to the recommendations of the Antibiotic Committee of the French Microbiology Society. During the study period, 21.4% of the samples were identified as positive. The microorganisms isolated were: Escherichia coli (47%), Klebsiella pneumoniae (19%), followed by Trichomonas vaginalis (9%), Candida albicans, and Pseudomonas sp (8%). Finally, *Staphylococcus aureus* and Proteus rettgeri represent 4% of isolates. The dominant resistance of *E. coli* was to amoxicillin and ticarcillin (55%), followed by cefalotine (39%). Resistance to fluoroquinolones was 27% (norfloxacin). The resistance rates to amikacin and gentamicin were 12.5% and 10.5%, respectively. Resistance to third-generation cephalosporins (ceftazidime, cefotaxime) was 10.5%. E. coli showed resistance rates to nitrofurantoin and fosfomycin at 10.5% and 6.6%, respectively. However, resistance to imipenem did not exceed 2%. Increasing rates of *E. coli* antibiotic resistance indicate that careful monitoring of their use is necessary **(Jaouhar et al., 2023).**

III.1.5-Algeria

According to Benmoumou et al. (2023), urinary tract infections (UTIs) are currently one of the most important medical practice visits. The spread of antibiotic-resistant bacteria in the community complicates the therapeutic management. The aim of this study is to investigate the bacteria associated with community-acquired urinary tract infections (CA-UTIs) and the antibiotic resistance pattern of bacterial isolates during 2021 in Algiers, northern Algeria. A total of 548 urine samples from patients with CA-UTI symptoms were analyzed. Pure bacterial isolates were identified using morphological and biochemical characteristics and subjected to antibiogram evaluation using the disk diffusion method. A total of 133 out of 548 patients (24.27%) had positive CA-UTIs, mainly affecting women (84.21%). A percentage of 87.22% of isolates were identified as Enterobacteriaceae, which were represented mostly by Escherichia coli (76 isolates), Klebsiella pneumoniae (13 isolates), and Proteus mirabilis (13 isolates). A number of 125 isolates (93.98%) were resistant to at least one antibiotic tested (Benmoumou et al., 2023). The results showed the highest antibiotic resistance to ampicillin (92.24%) and amoxicillin-clavulanic acid (91.37%) and revealed the most sensitivity to cefotaxime and nitrofurantoin (95.69%) and colistin (93.11%). The results of this study revealed high concerns about CA-UTIs caused by multidrug-resistant Enterobacteriaceae **(Benmoumou et al., 2023).**

III.1.6.Tunisia

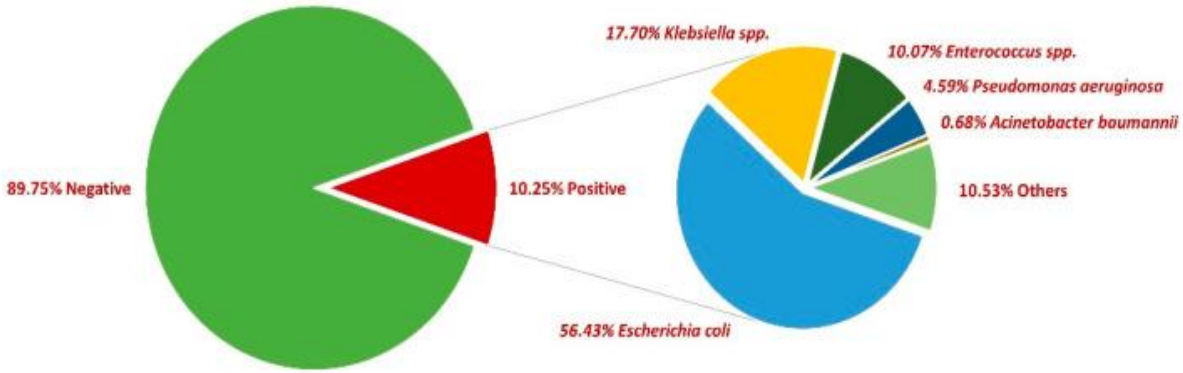
According to Kilani et al. (2023), a total of 1313 strains were isolated. The bacteriological study showed the predominance of *Enterobacteria* (96.8%), especially *E. coli* (52.2%) and *K. pneumoniae* (19.3%). Overall resistance rates to antimicrobial agents were as follows: for hospital settings, *E. coli* strains exhibited descending resistance to amoxicillin (73.05%), trimeth / sulfamethoxazole (46.9%), ofloxacin (40.3%), amoxicillin/clavulanic acid (35.05%), and gentamicin (20.5%). Results indicated low resistance to fosfomycin for *E. coli* at 2.6% in hospitals, while *K. pneumoniae* showed ≥12.1%. Amikacin resistance remained medium-low for *E. coli* at ≥20% and for *K. pneumoniae* at 10% **(Kilani et al., 2023).** Nitrofuran resistance affected 1.06% of *E. coli* strains in hospital settings and 21.5% of *K. pneumoniae.* Extended Spectrum Beta-Lactamases (ESBLs) production was present in a number of *Enterobacteria* (19.3% of *K. pneumoniae* and 14.4% of *E. coli*). Increasing rigorous surveillance of resistance rates is necessary to determine appropriate empirical treatment and limit the spread of multiresistant strains **(Kilani et al., 2023).**

III.1.7-Romania

According to Borcan et al. (2024), first, 54,114 midstream urine samples collected between 2018 and 2022 were examined, with a positivity rate of 10.25% (5548). More than two-thirds of positive samples were collected from female patients (73%). The most common pathogen incriminated was *E. coli* (56.43%), followed by *Klebsiella* spp. (17.70%), *Enterococcus* spp. (10.07%), *Pseudomonas aeruginosa* (4.59%), and *Acinetobacter baumannii* (0.68%). In what concerns the rest of the positive urine samples, other bacteria were incriminated, such as *Enterobacter* spp., *Proteus* spp., *Morganella morganii*, and *Staphylococcus saprophyticus*, etc. **(Borcan et al., 2024).**

Figure 3

Distribution of bacteria in positive urine cultures between 2018 and 2022.



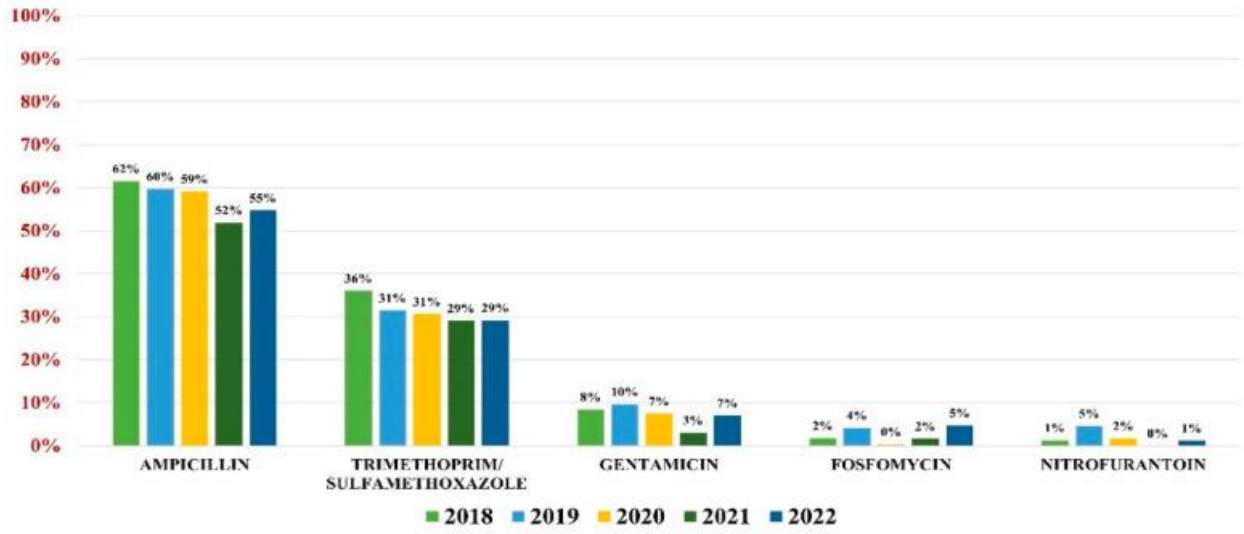
A/- Escherichia coli

As explained by Borcan et al. (2024), E. coli was responsible for 56.43% of all UTIs (3131 samples). The highest overall antibiotic resistance was to ampicillin (59%) and trimethoprim/sulfamethoxazole (32%), while the lowest rate of resistance was to gentamicin (8%), fosfomycin (3%), and nitrofurantoin (2%).

In what concerns the overall antibiotic resistance trends, a slight decrease in resistance was observed every year, with the lowest value being recorded in 2021. In 2022, however, the trend resumed its growth **(Borcan et al., 2024).**

Figure 4

Antibiotics resistance trends for E. coli.

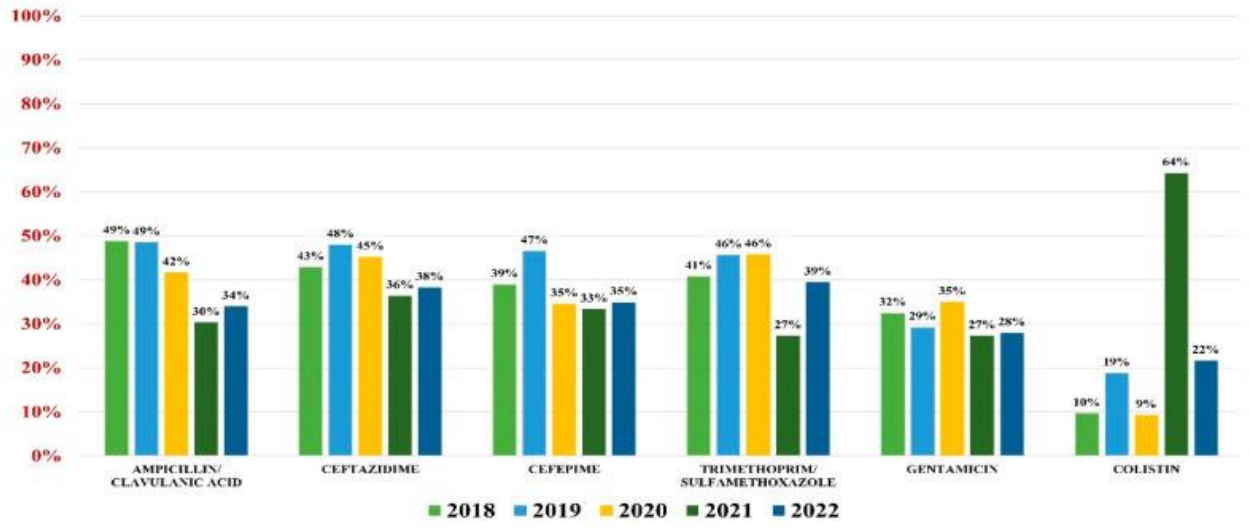


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In what concerns the overall antibiotic resistance trends, a slight decrease in resistance was observed every year, with the lowest value being recorded in 2021. In 2022, however, the trend resumed its growth **(Borcan et al., 2024).**

Figure 5

Antibiotics resistance trends for Klebsiella spp.



B/-Klebsiella *spp*

Klebsiella spp. were identified as pathogens for 982 urine samples, representing 17.70% of all positive results; 94% were *Klebsiella pneumonie*, while the rest of them were *K. oxytoca* and *K. aerogenes*. Overall resistance to antibiotics was as follows: amoxicillin/clavulanic acid (44%), ceftazidime (43%), cefepime (40%), gentamicin (31%), trimethoprim/sulfamethoxazole (41%), and colistin (15%).

Of these, 32.90% were ESBL producers and 10.20% were carbapenemases producers. A percentage of 48% were MDR.

In what concerns the general antibiotic resistance trends, a downward trend in resistance similar to *E. coli* was noted. The trend reached a minimum in 2021 for most antibiotics (excluding colistin) and resumed its growth in 2022 **(Borcan et al., 2024).**

The Practical Section

The objective

The objective of this thesis is to investigate and analyze the resistance and multidrug resistance patterns of bacterial strains isolated from urine cultures (UC) at Medical Analysis Laboratory Dr.Haouari in Ksar El Boukhari, Medea, focusing on both hospital and community settings. Specifically, the study aims to compare resistance levels and multidrug resistance between these two environments within the region. By identifying prevalent antibiotic resistance trends and assessing their implications for treatment strategies in hospital-acquired and community-acquired infections, this research seeks to contribute to the understanding of antibiotic resistance dynamics in the local context.

I- Materials and Methods

I.1-Study Design and Population

This study was a retrospective analysis of urinary tract infections (UTIs) conducted at Medical Laboratory Dr. Haouari. The study included patients diagnosed with UTIs over a specific time period, from 4th November 2023 to 14 Mai 2024. The population comprised both male and female patients across various age groups ranging from 1 to 100 years.

I.2 Data Collection

I.2.1- Patient Records

- Inclusion criteria: Patients with laboratory-confirmed UTIs.

- Exclusion criteria: Patients with incomplete records or those diagnosed with UTIs without laboratory confirmation.

I.2.2 -Variables Collected

- Demographic Information: Age, sex and Antibiotics.

I.2.3- Clinical Data

- Laboratory Data: Results of urine cultures and sensitivity tests.

I.3. Laboratory Procedures

I.3.1-Urine Sample Collection

- Midstream urine samples were collected in sterile containers following standard guidelines.

- For catheterized patients, samples were collected from the catheter using aseptic techniques.

I.3.2-Microbiological Analysis

- Culture: Urine samples were cultured on appropriate media (blood agar, Nutrient, Hektoen, Sabouraud and Chapman agar) and incubated at 37°C for 24-48 hours.

- Identification: Bacterial isolates were identified based on colony morphology, Gram staining, oxydase, Catalase ,Chrom and Gallery API 20 E.

- Antibiotic Sensitivity: Sensitivity testing was performed using Kirby-Bauer disk diffusion method was employed on Mueller-Hinton agar plates.

I-4. Antibiotic Susceptibility Testing

1. **Selection of Antibiotics:** Commonly prescribed antibiotics for UTIs, including amoxicillin, ciprofloxacin, ceftazidime, gentamicin, and trimethoprim-sulfamethoxazole.
2. **Method:** Kirby-Bauer disk diffusion method was employed on Mueller-Hinton agar plates.
3. **Procedure:**
    - Bacterial suspensions were adjusted to a 0.5 McFarland standard.
    - Sterile swabs were used to inoculate the entire surface of the agar plate.
    - Antibiotic disks were placed on the inoculated plates using a disk.
    - Plates were incubated at 37°C for 18-24 hours.
4. **Interpretation:** Zones of inhibition were measured and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

I.5. Statistical Analysis

I.5.1- Data Analysis

- Data were entered into SPSS software version 26.0 and Excel for statistical analysis.

- Descriptive statistics were used to summarize demographic and clinical characteristics, including frequencies and percentages for categorical variables.

I.5.2-Specific Analyses

- Sex Distribution: The proportion of male and female patients infected with different pathogens was calculated and compared.

- Age Distribution: Patients were categorized into age groups (1-20, 21-40, 41-60, 61-80, and 81-100 years), and the frequency of infections within each group was analyzed.

- Pathogen Distribution: The distribution of specific pathogens (e.g., *E. coli*, *Klebsiella*, and *Candida*) was analyzed across different age groups and sexes.

I.5.3-Visualization

- Pie charts were created to represent the distribution of UTI cases by sex.

- Histograms were used to depict the age distribution of UTI cases.

- Tables summarized the frequencies and percentages of different pathogens across various demographic categories.

I.6. Ethical Considerations

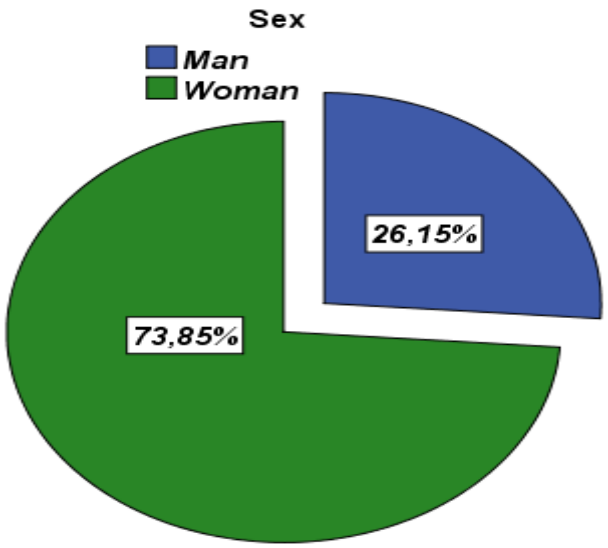
-Confidentiality

- Patient confidentiality was maintained by anonymizing data before analysis. Unique patient identifiers were removed to ensure privacy.

II. Results

Figure 01

The patiens infected with UTIs according to gender



II.1-Interpretation

- Female Patients: The pie chart indicates that 73.85% of the patients infected with UTIs are female.

- Male Patients: Conversely, 26.15% of the patients infected with UTIs are male.

II.2.Analysis

II.2.1- Dominance of Female Cases

- The substantial majority of UTI cases are among females, comprising nearly three-quarters of the total cases (73.85%).

- This is a significant difference compared to the male segment, which accounts for just over a quarter (26.15%) of the cases.

II.2.2- Medical Context

- This distribution aligns with known medical observations. UTIs are more prevalent in females due to anatomical and physiological factors. For instance, the female urethra is shorter and closer to the anus, which can facilitate the entry of bacteria into the urinary tract.

II.2.3- Visual Representation

- In the pie chart, the segment representing females would be markedly larger than the segment representing males.

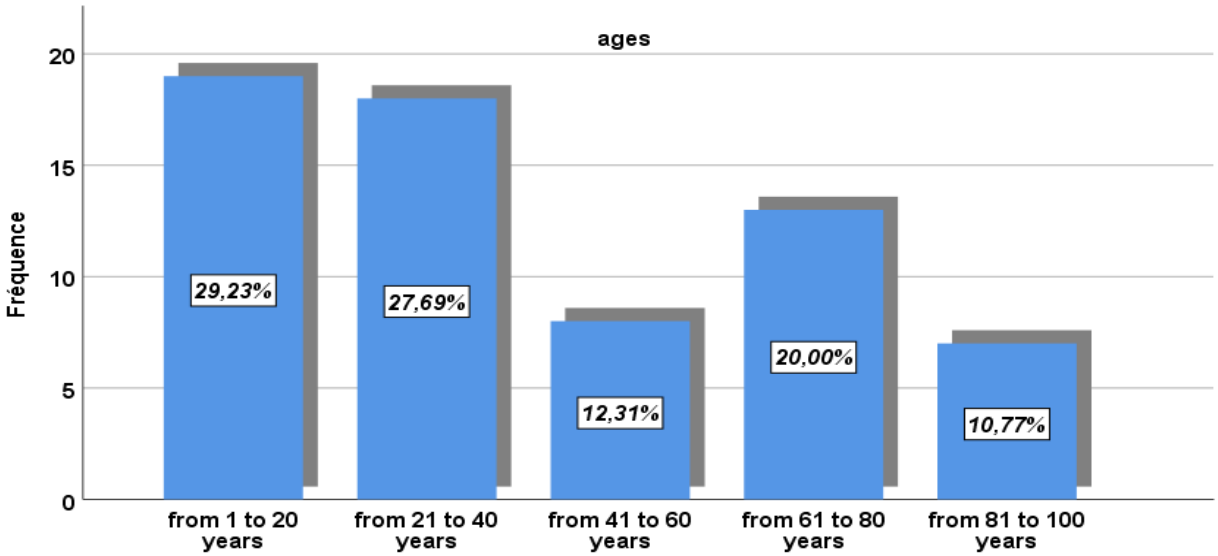
- The visual difference in segment size helps quickly convey that UTIs are more common among female patients compared to male patients.

- The pie chart clearly demonstrates a higher incidence of UTIs among females (73.85%) compared to males (26.15%).

II.3.Interpretation

Figure 02

Distribution of patient according to age groups.



II.3.1-Young Patients (1-20 years)

- **Frequency:** 29.23%

- **Analysis:** The highest frequency of UTI cases is found in the youngest age group (1-20 years), accounting for nearly one-third of the total cases. This could be due to various factors such as the higher incidence of UTIs in children, particularly young girls, due to shorter urethras and the potential for poor hygiene practices.

II.3.2-Young Adults (21-40 years)

- **Frequency:** 27.69%

- **Analysis:** The second highest frequency is among young adults. This group often includes women of childbearing age, who are more prone to UTIs due to sexual activity and pregnancy.

II.3.3- Middle-aged Adults (41-60 years)

- **Frequency:** 12.31%

- **Analysis:** The frequency of UTIs in this age group is significantly lower. This might be because individuals in this age range generally have established hygiene practices and may have fewer physiological changes impacting their urinary tract compared to younger and older adults.

II.3.4- Older Adults (61-80 years)

- **Frequency:** 20.00%

- **Analysis:** There is a notable increase in UTI frequency among older adults. Factors contributing to this include the increased prevalence of chronic conditions, weakened immune systems, and for post-menopausal women, decreased estrogen levels affecting the urinary tract.

II.3.5- Elderly (81-100 years)

- **Frequency:** 10.77%

- **Analysis:** The frequency slightly decreases in the oldest age group but remains significant. Elderly individuals are at higher risk due to factors such as immobility, use of catheters, and more complex health conditions.

Table 01

Presentation of different bacteria with frequencies and percentages

		Fréquence	Pourcentage	Pourcentage valide	Pourcentage cumulé
Valide	E.coli	39	60,0	60,0	60,0
	Klebseilla sp	18	27,7	27,7	87,7
	Candida sp	2	3,1	3,1	90,8
	Enterobacter sp	1	1,5	1,5	92,3
	Streptococcus sp	3	4,6	4,6	96,9
	Enterococcus sp	1	1,5	1,5	98,5
	Pseudomonas sp	1	1,5	1,5	100,0
	Total	65	100,0	100,0	

II.4.Interpretation of the Table of Bacteria Frequencies and Percentages

II.4.1. *E. coli* (*Escherichia coli*)

- **Frequency:** 39 cases

- **Percentage:** 60.0%

- **Analysis:** *E. coli* is the most common bacterium causing UTIs, responsible for 60% of cases. This aligns with existing medical literature, as *E. coli* is known to be a predominant uropathogen due to its ability to adhere to the lining of the urinary tract.

II.4.2. *Klebsiella*

- **Frequency**: 18 cases

- **Percentage:** 27.7%

- **Analysis:** *Klebsiella* is the second most common pathogen, accounting for 27.7% of cases. This bacterium is also a well-known cause of UTIs, particularly in hospital settings where it can be resistant to multiple antibiotics.

II.4.3. *Candida*

- **Frequency:** 2 cases

- **Percentage:** 3.1%

- **Analysis:** *Candida*, a type of fungus, causes a smaller proportion of UTIs (3.1%). These infections are often associated with immunocompromised individuals, diabetes, or prolonged use of antibiotics.

II.4.4. *Enterobacter*

- **Frequency:** 1 case

- **Percentage:** 1.5%

- **Analysis:** *Enterobacter* accounts for 1.5% of UTI cases. This bacterium is less common but can cause UTIs, particularly in healthcare settings or in patients with underlying health conditions.

II.4.5. *Streptococcus*

- **Frequency:** 3 cases

- **Percentage:** 4.6%

-**Analysis:** *Streptococcus* species contribute to 4.6% of UTI cases. These bacteria are not typical uropathogens but can cause infections, especially in individuals with predisposing factors.

II.4.6. *Enterococcus*

- **Frequency:** 1 case

- **Percentage:** 1.5%

- **Analysis:** *Enterococcus* is responsible for 1.5% of cases. It is a common cause of hospital-acquired infections and is known for its resistance to many antibiotics.

II.4.7. *Pseudomonas*

- **Frequency:** 1 case

- **Percentage:** 1.5%

- **Analysis:** *Pseudomonas* also accounts for 1.5% of UTI cases. This bacterium is often associated with complicated UTIs, particularly in patients with catheters or those who are immunocompromised.

- Predominance of *E. coli*: The data shows a clear predominance of *E. coli* in UTI cases, highlighting its role as the primary pathogen. This underscores the importance of targeting *E. coli* in both treatment and preventive strategies.

- Significant Presence of *Klebsiella*: *Klebsiella's* significant proportion indicates its importance, particularly in healthcare-associated infections. This suggests a need for stringent infection control practices to manage its spread.

- Diverse Range of Pathogens: The presence of multiple other bacteria (*Enterobacter, Streptococcus, Enterococcus and Pseudomonas)* at lower frequencies indicates that UTIs can be caused by a variety of pathogens. This diversity necessitates a broad approach to diagnosis and treatment, considering potential antibiotic resistance patterns.

Table 02

Cross Table Sex / Bacteria

			Bacteria							Total
			E.coli	Klebseilla	candida	enterobacter	steptococcus	enterococcus	pseudomenas	
sex	Man	Effectif	6	5	2	1	1	0	1	16
		% du total	9,4%	7,8%	3,1%	1,6%	1,6%	0,0%	1,6%	25,0%
	Woman	Effectif	33	12	0	0	2	1	0	48
		% du total	51,6%	18,8%	0,0%	0,0%	3,1%	1,6%	0,0%	75,0%
Total		Effectif	39	17	2	1	3	1	1	64
		% du total	60,9%	26,6%	3,1%	1,6%	4,7%	1,6%	1,6%	100,0%

II.5.Interpretation

II.5.1. *E. coli* as the Dominant Pathogen

- Women: *E. coli* accounts for 51.6% of infections, making it the most common pathogen by a significant margin.

- Men*: E. coli* also leads but at a much lower rate (9.4%).

II.5.2. *Klebsiella*

- **Women:** Klebsiella is the second most common bacterium, responsible for 18.8% of infections.

- **Men:** Klebsiella accounts for 7.8% of infections.

II.5.3. *Candida*

- **Men:** Candida is responsible for 3.1% of infections.

- **Women:** No cases of Candida infections were reported (0.0%).

II.5.4. Other Bacteria

- *Enterobacter*, *Streptococcus*, *Enterococcus*, and *Pseudomonas*: These bacteria have a minimal presence in both men and women, with small percentages and frequencies.

II.6.Detailed Analysis

II.6.1. Sex-Specific Trends

- Women

- The data shows that *E. coli* is overwhelmingly the most frequent cause of UTIs in women, consistent with the anatomical predisposition that facilitates bacterial entry into the urinary tract.

- *Klebsiella* also poses a significant risk, being the second most common pathogen.

- Candida and Pseudomonas are absent, indicating these pathogens are not a common cause of UTIs in women within the dataset.

- Men

- *E. coli* and *Klebsiella* are also leading causes of UTIs in men but at much lower percentages than in women.

- *Candida* is present in men but not in women, suggesting different risk factors or sources of infection.

- Other bacteria like *Enterobacter*, *Streptococcus*, *Enterococcus*, and *Pseudomonas* appear in minor percentages.

Table 03

Age / Bacteria Cross Table

			Bacteria							
			E.coli	Klebseilla	candida	enterobacter	steptococcus	enterococcus	pseudomenas	Total
Ages	from 1 to 20 years	Effectif	14	5	0	0	0	0	0	19
		% du total	21,5%	7,7%	0,0%	0,0%	0,0%	0,0%	0,0%	29,2%
	from 21 to 40 years	Effectif	13	3	0	0	2	0	0	18
		% du total	20,0%	4,6%	0,0%	0,0%	3,1%	0,0%	0,0%	27,7%
	from 41 to 60 years	Effectif	6	1	0	0	0	1	0	8
		% du total	9,2%	1,5%	0,0%	0,0%	0,0%	1,5%	0,0%	12,3%
	from 61 to 80 years	Effectif	2	7	2	1	0	0	1	13
		% du total	3,1%	10,8%	3,1%	1,5%	0,0%	0,0%	1,5%	20,0%
	from 81 to 100 years	Effectif	4	2	0	0	1	0	0	7
		% du total	6,2%	3,1%	0,0%	0,0%	1,5%	0,0%	0,0%	10,8%
Total		Effectif	39	18	2	1	3	1	1	65
		% du total	60,0%	27,7%	3,1%	1,5%	4,6%	1,5%	1,5%	100,0%

II.7.Interpretation

II.7.1. High Incidence in Younger Age Groups

- 1 to 20 years: *E. coli* infections are most frequent in this age group, accounting for 21.5% of the total cases. This high incidence could be due to anatomical and behavioral factors in children and teenagers, such as shorter urethras in females and potentially less stringent hygiene practices.

- 21 to 40 years: This group also has a high incidence of *E. coli* infections, representing 20% of the cases. Factors contributing to this may include sexual activity, pregnancy, and other hormonal changes that affect the urinary tract in adults.

II.7.2. Middle Age Group (41 to 60 years)

- The frequency drops to 9.2% in the 41 to 60 age group. This decline might be due to better-established hygiene practices and fewer physiological changes compared to younger adults and teenagers.

II.7.3. Older Adults (61 to 80 years)

- E. coli infections further decrease in the 61 to 80 years age group, representing only 3.1% of the cases. Although UTIs are still a concern in this age group, the lower percentage might reflect better management of risk factors and possibly the influence of competing health issues that overshadow the reporting of UTIs.

II.7.4. Elderly (81 to 100 years)

- There is a slight increase in *E. coli* infections in the 81 to 100 years age group, with 6.2% of the cases. This increase may be due to age-related factors such as weakened immune systems, increased use of catheters, immobility, and other chronic conditions that predispose the elderly to infections.

II.8.Interpretation of the Table of *Klebsiella* Infections by Age

II.8.1. Young Age Groups (1 to 20 years)

- **Frequency:** 4 cases
- **Percentage:** 7.7%

- **Analysis:** *Klebsiella* infections in the 1 to 20 years age group account for 7.7% of the total cases. This relatively higher frequency in younger individuals might be due to hospitalizations, congenital urinary tract abnormalities, or other pediatric health issues that predispose this age group to infections.

II.8.2. Young Adults (21 to 40 years)

- **Frequency:** 3 cases
- **Percentage:** 4.6%

- **Analysis**: In the 21 to 40 years age group, the frequency of *Klebsiella* infections decreases to 4.6%. This may be due to stronger immune systems and fewer underlying health conditions compared to other age groups.

II.8.3. Middle Age Group (41 to 60 years)

- **Frequency:** 1 case
- **Percentage:** 1.5%

- **Analysis:** The frequency of *Klebsiella* infections is the lowest in this age group at 1.5%. This suggests that middle-aged individuals are the least susceptible to *Klebsiella* UTIs, potentially due to better overall health and immune function.

II.8.4. Older Adults (61 to 80 years)

- **Frequency:** 7 cases
- **Percentage:** 10.8%

- **Analysis:** The frequency of *Klebsiella* infections significantly increases in the 61 to 80 years age group, accounting for 10.8% of cases. This increase can be attributed to age-related factors such as weakened immune systems, higher likelihood of hospitalization, and increased use of medical devices like catheters which can introduce bacteria into the urinary tract.

II.8.5. Elderly (81 to 100 years)

- **Frequency:** 2 cases
- **Percentage:** 3.1%

- **Analysis:** There is a decrease in the frequency of *Klebsiella i*nfections in the 81 to 100 years age group to 3.1%. While still vulnerable, the lower frequency might reflect competing health issues that overshadow the reporting of *Klebsiella* UTIs or perhaps more stringent infection control measures in elderly care settings.

II.9.Interpretation

II.9.1-*Enterobacter* Infections

- 1 to 20 years:

- Frequency: 1 case

- Percentage: 1.5%

- Analysis: *Enterobacter* infections are relatively rare in this age group, accounting for only 1.5% of the cases. This low frequency might suggest that *Enterobacter* is not a common pathogen in pediatric UTIs, possibly due to less frequent exposure to hospital environments where *Enterobacter* is more prevalent.

II.9.2-Candida Infections

- 1 to 20 years:

- Frequency: 2 cases

- Percentage: 3.1%

- Analysis: *Candida* infections represent 3.1% of the cases in this age group. This higher frequency compared to *Enterobacter* and *Pseudomonas* indicates that fungal infections, although still uncommon, are more likely to occur in children and young adults, possibly due to antibiotic use that disrupts normal bacterial flora or immunocompromised conditions.

II.9.3-Pseudomonas Infections

- 1 to 20 years:

- Frequency: 1 case

- Percentage: 1.5%

- Analysis: *Pseudomonas* infections are as rare as *Enterobacter* infections in this age group, also accounting for 1.5% of the cases. *Pseudomonas* is typically associated with healthcare settings and immunocompromised individuals, which may explain its low incidence in the general pediatric population.

II.10. Interpretation:

The table below presents the resistance of *Escherichia coli (E. coli)* to various antibiotics, showing the number of resistant responses, the percentage of observations, and the percentage of total observations for each antibiotic.

Table 4

Resistance of Escherichia coli to Various Antibiotics

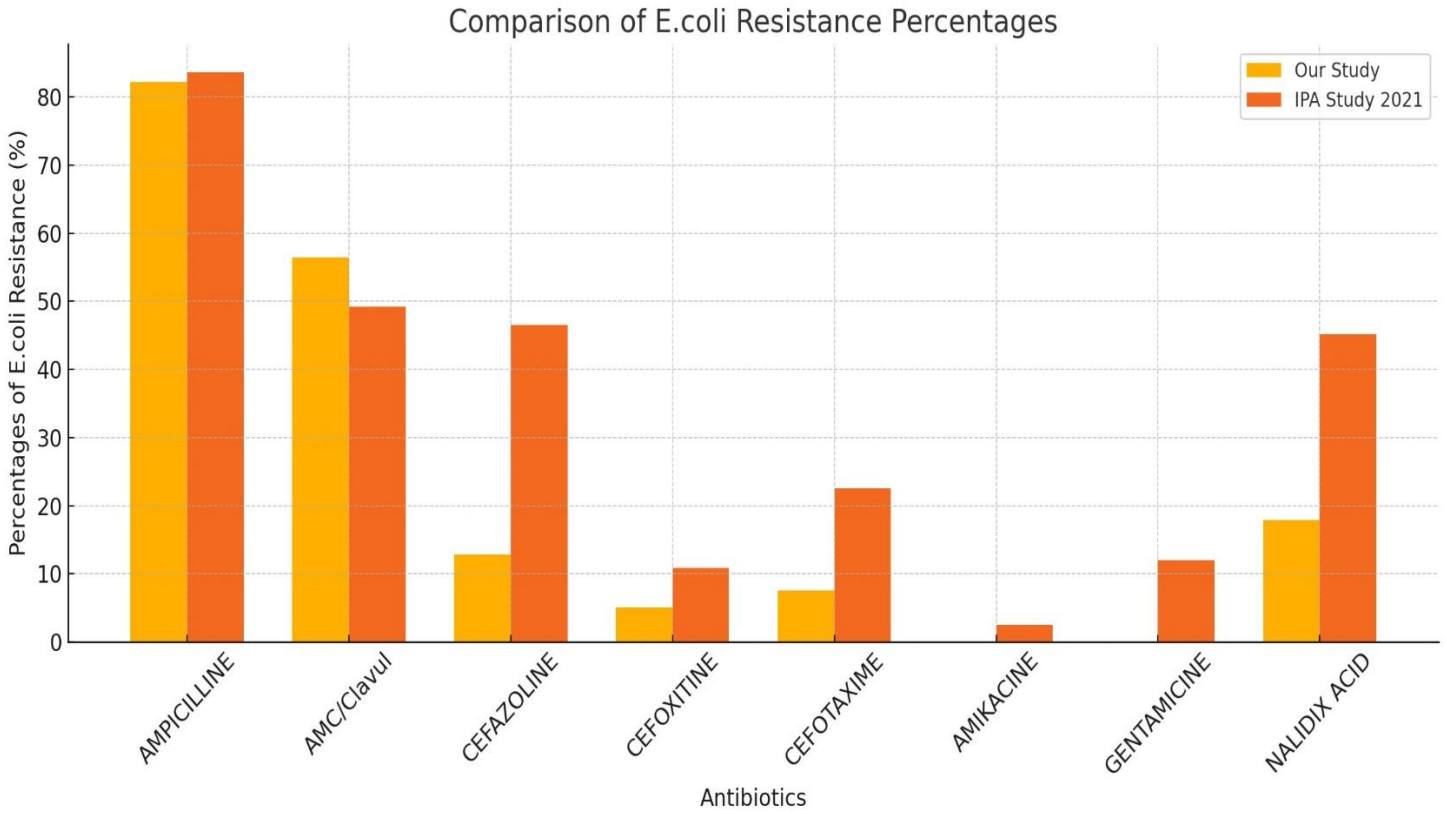
Antibiotics	Frequency of E.coli Resistance in our Study	Pourcentages of E.coli in our Study %	Pourcentages of E.coli in IPA Study 2021 %
Ampicillin	32	82,2	83,62
AMC/Clavul acid	22	56,4	49,17
Cefazolin	5	12,8	46,54
Cefoxitin	2	5,1	10,81
Cefotaxim	3	7,6	22,53
Amikacin	0	0	2,53
Gentamicin	0	00	11,99
Nalidixic Acid	7	17,9	45,21

Interpretation:

The percentages of Ampicillin resistance in our study and in the IPA study are similar. However, the percentages of resistance to AMC/Clavulanic Acid, Cefoxitin, Cefotaxime, and Cefazolin are higher in the IPA study compared to our study. This difference can be attributed to the fact that the patients in our study are from the community, while the patients in the IPA study are hospitalized. Additionally, the resistance percentages for Amikacin and Gentamicin are higher in the IPA study compared to our study, where they are 0%. This discrepancy is likely due to the smaller sample size in our study, whereas the IPA study includes a larger sample size

Figure 1

`Comparaison of E.coli `Resistance Percentages



The graph compares the percentages of E. coli resistance to different antibiotics between our study and the IPA Study 2021. Here are the key points:

1. **Ampicillin**:
   - Our Study: 82.2%
   - IPA Study: 83.62%
   - Interpretation: Both studies show a very high and similar resistance rate to Ampicillin.
2. **AMC/Clavulanic Acid**:
   - Our Study: 56.4%
   - IPA Study: 49.17%
   - Interpretation: Resistance to AMC/Clavulanic Acid is higher in our study compared to the IPA study, though both have moderately high resistance rates.
3. **Cefazoline**:
   - Our Study: 12.8%
   - IPA Study: 46.54%
   - Interpretation: The IPA study shows significantly higher resistance to Cefazoline compared to our study.
4. **Cefoxitine**:

- Our Study: 5.1%
- IPA Study: 10.81%
- Interpretation: The IPA study has more than double the resistance rate to Cefoxitine compared to our study.

5. **Cefotaxime**:
   - Our Study: 7.6%
   - IPA Study: 22.53%
   - Interpretation: Resistance to Cefotaxime is substantially higher in the IPA study.
6. **Amikacine**:
   - Our Study: 0%
   - IPA Study: 2.53%
   - Interpretation: The IPA study shows a small percentage of resistance to Amikacine, while our study shows none.
7. **Gentamicine**:
   - Our Study: 0%
   - IPA Study: 11.99%
   - Interpretation: There is a notable resistance to Gentamicine in the IPA study, while our study shows no resistance.
8. **Nalidix Acid**:
   - Our Study: 17.9%
   - IPA Study: 45.21%
   - Interpretation: The IPA study reports a much higher resistance rate to Nalidix Acid compared to our study.

Overall Interpretation:

- The resistance rates to most antibiotics are higher in the IPA study, which could be attributed to the fact that the IPA study involves hospitalized patients who are more likely to have been exposed to antibiotics and thus have higher resistance rates.
- In contrast, our study involves community patients who generally show lower resistance rates, except for AMC/Clavulanic Acid where the resistance is somewhat higher. This suggests that antibiotic resistance in community settings is generally lower than in hospital settings, but certain antibiotics still show significant resistance.

III. Discussion

In this section, we will discuss the implications of the results obtained from the analysis of urinary tract infections (UTIs) by sex and age, as well as the distribution of various bacterial pathogens.

III.1.Sex-Based Analysis of UTIs

The analysis reveals a significant difference in the prevalence of UTIs between sexes, with women showing a much higher incidence (73.85%) compared to men (26.15%). This disparity can be attributed to anatomical and physiological differences. Women have a shorter urethra, which facilitates easier access for bacteria to the bladder. Furthermore, the proximity of the urethra to the anus increases the likelihood of bacterial contamination. Hormonal fluctuations, particularly during pregnancy, also play a crucial role in increasing the risk of UTIs in women.

The predominant pathogen, *E. coli*, accounts for 51.6% of infections in women and 9.4% in men. The higher prevalence of *E. coli* in women aligns with existing literature that identifies this bacterium as the most common cause of UTIs due to its ability to colonize the periurethral area. *Klebsiella*, the second most common pathogen, also shows a higher incidence in women (18.8%) than in men (7.8%), reinforcing the need for targeted preventive measures in females.

III.2.Age-Based Analysis of UTIs

The age distribution of UTI cases highlights specific trends:

III.2.1. Higher Incidence in Younger Age Groups

- **1 to 20 years:** The high incidence of *E. coli* infections (21.5%) in this age group may be due to developmental factors, including behavioral hygiene practices and anatomical factors in children and adolescents.

- **21 to 40 years:** This group also shows a high incidence (20%), likely due to factors such as sexual activity and pregnancy, which are known to increase UTI risk.

III.2.2. Middle Age Group Resilience

- **41 to 60 years:** There is a noticeable decline in UTI incidence in this age group (9.2% for *E. coli*). This could be attributed to more stable immune function and established hygiene practices. However, *Klebsiella* infections remain relatively low (1.5%).

III.2.3. Older Adults and Elderly

- **61 to 80 years:** A resurgence in UTI cases is observed (10.8% for *Klebsiella*), which may be due to age-related factors such as weakened immune systems, increased use of catheters, and higher hospitalization rates.

-**81 to 100 years:** While E. coli infections increase slightly to 6.2%, *Klebsiella* infections decrease (3.1%).

III.3.Pathogen Distribution

E. coli remains the predominant pathogen across all age groups, but its prevalence decreases with age, especially in the middle-aged group. Conversely, *Klebsiella* shows a different pattern, with higher frequencies in young and older adults. This dual peak could indicate different risk factors affecting these age groups, such as varying exposure to healthcare environments and differing immune responses.

Candida infections, although rare, are present in the 1 to 20 years age group, indicating the potential for fungal infections in pediatric patients, especially those with prolonged antibiotic use or compromised immune systems. *Enterobacter* and *Pseudomonas* are also noted, albeit infrequently, in the same age group, underscoring the importance of considering a broad spectrum of pathogens in pediatric UTI management.

III.4. Implications for Healthcare

III.4.1- Sex-Specific Preventive Measures

- For women, emphasize hygiene practices, particularly in perineal care, and educate on risk factors related to sexual activity and pregnancy. Routine screening during pregnancy can help in early detection and management.

- For men, while the incidence is lower, awareness and preventive measures should not be neglected, especially for those with predisposing factors like urinary tract abnormalities or prostate issues.

III.4.2- Age-Specific Strategies

- Younger age groups require education on proper hygiene and possibly prophylactic measures for those with recurrent infections.

- Middle-aged adults benefit from standard hygiene practices and regular health check-ups to manage other potential risk factors.

- For older adults and the elderly, implement stringent infection control measures in healthcare settings, regular screening for UTIs, and careful management of catheter use to prevent nosocomial infections.

III.4.3-Clinical Focus

- Tailor empirical antibiotic treatments based on prevalent pathogens, with a primary focus on *E. coli* and *Klebsiella.* Consider fungal infections like Candida in pediatric and male patients with atypical symptoms or treatment-resistant UTIs.

- Regular monitoring and early intervention are crucial for preventing complications and managing infections effectively.

The findings of our study align with and contribute to the broader understanding of urinary tract infections (UTIs), particularly regarding the demographic distribution and bacterial prevalence. The higher prevalence of UTIs among females, particularly in the age groups of 1-20 and 21-40 years, is consistent with global trends that identify women as more susceptible to UTIs due to anatomical and hormonal factors.

The age distribution data in our study, where the highest frequencies of UTI cases were found in the 1-20 years (29.23%) and 21-40 years (27.69%) age groups, mirrors the findings in other recent studies. For instance, research conducted in Tanzania indicated that the prevalence of UTIs was 41% (141/344) and elders (>=60 years) had five times higher odds of having UTI as compared to adolescents ($p < 0.001$). *E. coli* was the most predominant bacteria (47%; 66/141). Female participants had almost two times higher odds of having UTI as compared to male participants at the borderline $p = 0.05$ **(Mlugu et al., 2023).** All isolated bacteria demonstrated high resistance (> 85%) against ampicillin and co-trimoxazole **(Mlugu et al., 2023).** In other recent study, the predominant uropathogens are Escherichia coli (n = 284), *staphylococcus aureus* (n = 122), and *Klebsiella pneumoniae* (n = 112). Presents the regional distribution of the predominant uropathogens in Uganda **(Makeri et al., 2023).**

In agreement with previous studies, we found that *E. coli* is the predominant strain in both hospital and community settings. In study The analysis reveals a significant difference in the prevalence of UTIs between sexes, with women showing a much higher incidence (73.85%) compared to men (26.15%).In other study in Saudi Arabia The number of positive UTI cases was slightly higher in women (n = 2051; 52.1%) than in men (n = 1886; 47.9%) **(El Mutawif et al. 2023).** The most commonly isolated bacterium was *Escherichia coli*, followed by *Klebsiella pneumoniae.* Multidrug resistance (MDR) was found in 67.7% (149/220) of patients with hospital-acquired UTIs and in 49.4% (83/168) of patients with community-acquired UTIs **(Shaker et al., 2024).** In community acquired UTIs, the top five most susceptible antibiotics against E. coli were Imipenem, Meropenem, Amikacin, Ertapenem, and Colistin. In the hospital acquired UTIs, the top five most susceptible antibiotics against E. coli were Fosfomycin, Meropenem, Imipenem, Ertapenem, and Chloramphenicol **(Shaker et al., 2024).**

These results confirm the findings of Sahilu et al, (2023), a total of 600 prescriptions containing antibiotics prescribed for patients with UTIs were observed during the study period. Of these, 415 (69.19%) were females and 210 (35%) were in the age group of 31–44 years **(Sahilu et al., 2023).** The percentage of antibiotics per prescription was found to be 27.83%. About 88.40% of antibiotics were prescribed by generic names. Fluoroquinolones were the most frequently prescribed class of drugs for the treatment of patients with UTIs **(Sahilu et al., 2023).**

Discussion

Our data show a different pattern of prevalence as two Cameroonian towns, Uropathogens were recovered from 137 (58.3%), with prevalence rates in Buea and Bamenda being 65.9% and 54% respectively. Predominant pathogens were *Escherichia coli* (31.4%), *Klebsiella oxytoca* (25.5%) and *Staphylococcus spp* (24.1%) **(Akoachere, 2012).** Compared to earlier studies, our data indicate the predominant pathogen, *E. coli*, accounts for 51.6% of infections in women and 9.4% in men. The higher prevalence of E. coli in women aligns with existing literature that identifies this bacterium as the most common cause of UTIs due to its ability to colonize the periurethral area. *Klebsiella*, the second most common pathogen, also shows a higher incidence in women (18.8%) than in men (7.8%), reinforcing the need for targeted preventive measures in females **(Akoachere, 2012).** The antimicrobial potency and spectrum of 8 classes of antibiotics against uropathogens is summarized in Table4. Cotrimoxazole was the most inactive drug as isolates showed very low susceptibilities: 12.5% for Buea and 1.9% for Bamenda. However, all (100%) *E. coli* isolates from Buea were sensitive to the drug. Isolates were also resistant to ampicillin and nitrofurantoin. *E. coli* isolates from Bamenda were most sensitive to ceftriaxone (65%) **(Akoachere, 2012).**

We observed a higher incidence of *E.coli* compared to the prevalence among females 6/32 (18.75%) was higher among males 5/42 (11.9%) without significant association (COR = 2.09, 95% CI = 1.04–8.45, $P = 0.253$). Urinary tract infection was higher in the age group of 35–49 years old (19.3%). Age was statistically significant and stronger independent associated risk factor with crude odds ratio = 3.67, 95% CI = 2.89–20.07 and $P = 0.003$, respectively. The most prevalent bacteria isolates were *Escherichia coli* 2(18.2%), *Staphylococcus aureus* 2(18.2%), *Acinetobacter spp*. 2(18.2%), *Enterococcus spp*. 2(18.2%), Coagulase-negative *Staphylococci 2*(18.2%) followed by *Porteus mirabilis* 1(9.1%) **(Kiros, 2019).** The majority (80%) of Gram-negative bacteria were resistant to ciprofloxacin, chloramphenicol, and trimethoprim/sulfamethoxazole. Simultaneously, the multidrug-resistant bacterial isolates accounts for 82% among tested kidney allograft recipients (**Kiros, 2019).**

For future students, I highly recommend focusing on the mechanisms of antibiotic resistance. While our study primarily concentrated on antibiotic susceptibility, understanding the underlying mechanisms of resistance is crucial for developing more effective treatment strategies and combating the growing issue of antibiotic resistance.

Additionally, it's important to note that the surveillance conducted by the Pasteur Institute primarily monitors hospitals in the northern regions. This leaves a significant gap in data from the southern regions, where there is a higher reliance on medicinal herbs. This disparity should be addressed to ensure a comprehensive understanding of antibiotic use and resistance patterns across different regions.

Conclusion

The study of antibiotic resistance and multiresistance in bacterial strains isolated from urine cultures (UC) samples in both hospital and non-hospital settings highlights a critical public health issue. Our findings underscore the pervasive nature of antibiotic resistance, which is not confined to hospital environments but is also prevalent in community settings.

In the hospital environment, the high prevalence of resistant strains, particularly multi-drug resistant organisms (MDROs), reflects the intense selective pressure exerted by the frequent and often broad-spectrum use of antibiotics. This environment fosters the rapid evolution and dissemination of resistance mechanisms. The data indicate that specific bacterial species, such as *Escherichia coli* and *Klebsiella pneumoniae*, are particularly adept at developing and maintaining resistance traits, posing significant treatment challenges.

Conversely, the presence of resistant strains in non-hospital environments reveals the spread of resistance factors beyond clinical settings, likely due to inappropriate antibiotic use in outpatient settings and agricultural practices. The detection of resistance in community-acquired infections signifies a reservoir of resistant bacteria that can transfer between individuals, leading to broader public health implications.

The results emphasize the necessity for stringent antibiotic stewardship programs across all healthcare settings to minimize unnecessary antibiotic usage and curb the spread of resistance. In hospitals, this includes robust infection control measures, routine surveillance, and the judicious use of antibiotics guided by susceptibility testing. In non-hospital environments, public education on the appropriate use of antibiotics, regulation of over-the-counter sales, and reducing the use of antibiotics in agriculture are crucial steps.

Furthermore, ongoing research and surveillance are essential to monitor resistance trends, identify emerging resistant strains, and develop new antibiotics and alternative treatments. Our study reinforces the urgent need for a multi-faceted approach involving healthcare providers, policymakers, and the public to combat the growing threat of antibiotic resistance.

In conclusion, tackling antibiotic resistance requires a comprehensive, integrated strategy that addresses both clinical and community settings. Only through coordinated efforts can we hope to mitigate the impact of resistant bacteria on global health and ensure the continued efficacy of antibiotics for future generations.

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Annexes

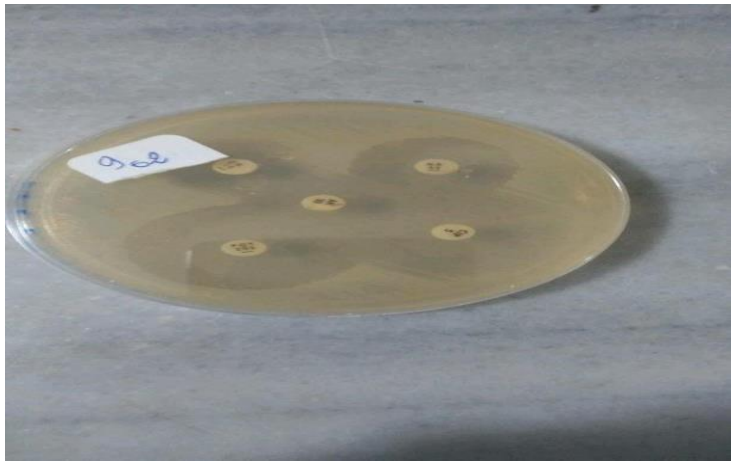
Figure 01

E.coli in nutrient and Hektoen medium of patient Sample No. 38.



Figure 02

The arrangement of antibiotic disks in Muller Hinton medium of patient Sample No.902 and 235.



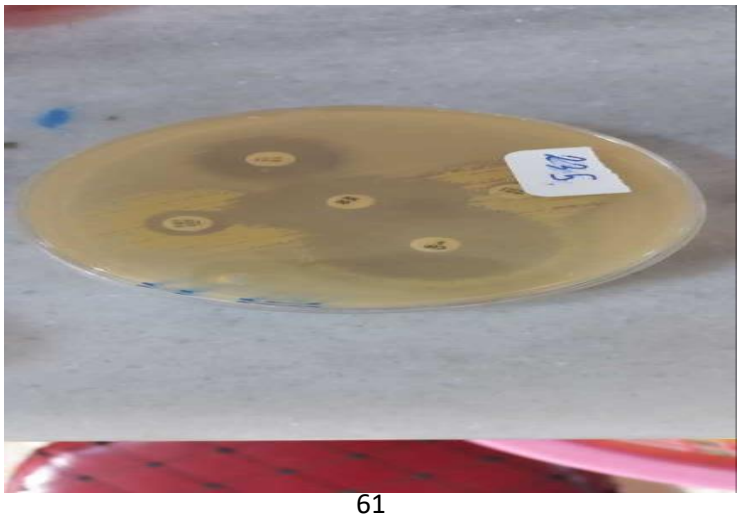
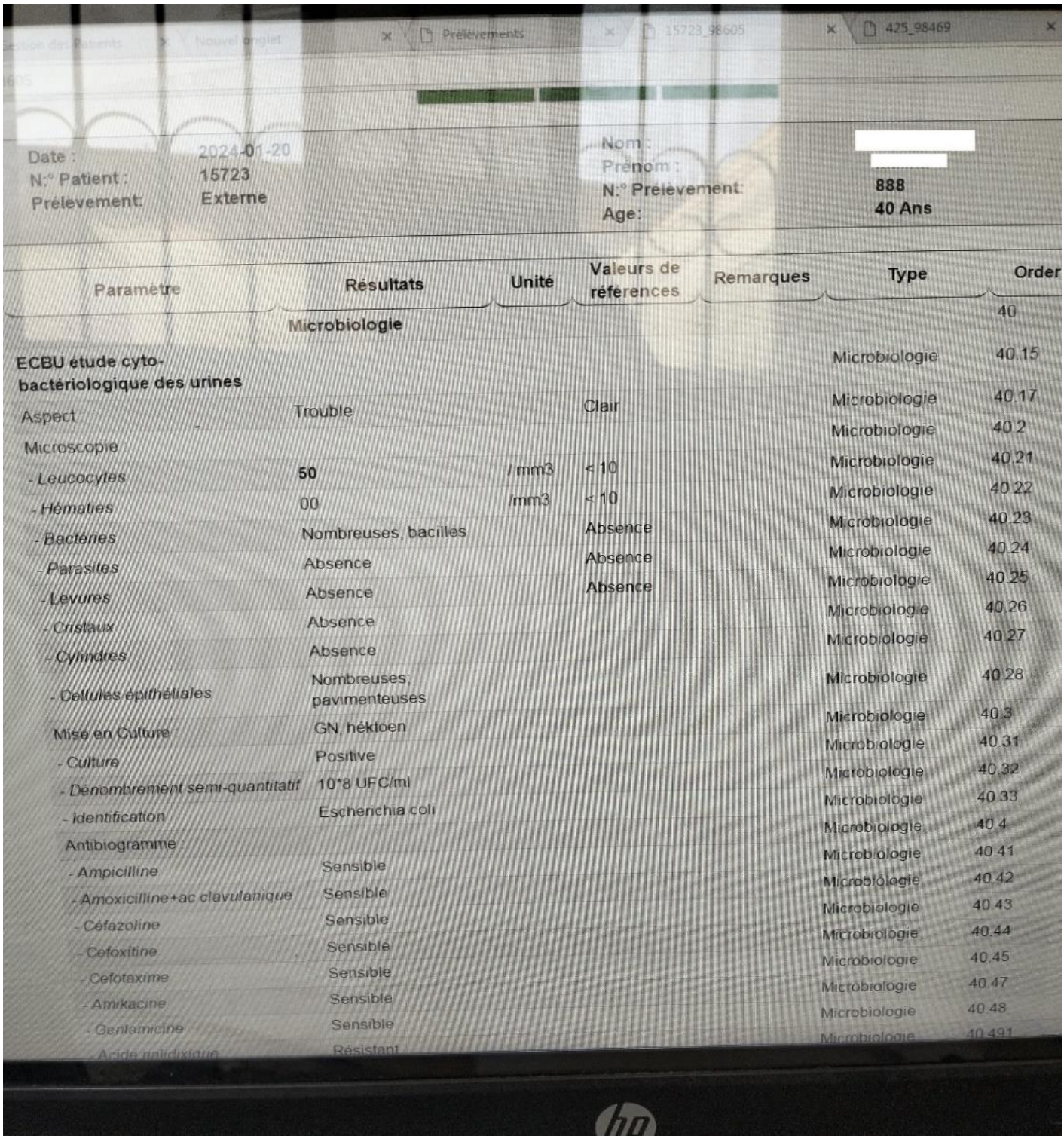


Figure 3

The information sheet.



Date : 2024-01-20
N:° Patient : 15723
Prélèvement: Externe

Nom :
Prénom :
N:° Prelevement: 888
Age: 40 Ans

Parametre	Résultats	Unité	Valeurs de références	Remarques	Type	Order
	Microbiologie					40
ECBU étude cyto-bactériologique des urines					Microbiologie	40.15
Aspect	Trouble		Clair		Microbiologie	40.17
Microscopie					Microbiologie	40.2
- Leucocytes	50	/ mm3	< 10		Microbiologie	40.21
- Hématies	00	/mm3	< 10		Microbiologie	40.22
- Bactéries	Nombreuses, bacilles		Absence		Microbiologie	40.23
- Parasites	Absence		Absence		Microbiologie	40.24
- Levures	Absence		Absence		Microbiologie	40.25
- Cristaux	Absence				Microbiologie	40.26
- Cylindres	Absence				Microbiologie	40.27
- Cellules épithéliales	Nombreuses, pavimenteuses				Microbiologie	40.28
Mise en Culture	GN, héktoen				Microbiologie	40.3
- Culture	Positive				Microbiologie	40.31
- Dénombrement semi-quantitatif	10*8 UFC/ml				Microbiologie	40.32
- Identification	Escherichia coli				Microbiologie	40.33
Antibiogramme					Microbiologie	40.4
- Ampicilline	Sensible				Microbiologie	40.41
- Amoxicilline+ac clavulanique	Sensible				Microbiologie	40.42
- Céfazoline	Sensible				Microbiologie	40.43
- Cefoxitine	Sensible				Microbiologie	40.44
- Cefotaxime	Sensible				Microbiologie	40.45
- Amikacine	Sensible				Microbiologie	40.47
- Gentamicine	Sensible				Microbiologie	40.48
- Acide nalidixique	Résistant				Microbiologie	40.491

Figure 4

Nutrient and Chapman agar.



Figure 5

Antibiotics disks.

