MINI REVIEW

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Urinary Tract Infection and *Klebsiella pneumoniae* as the Second Major Cause: A Mini-Review.

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Abstract

Urinary tract infection (UTI) is a very common infectious condition worldwide that affects people of all genders and ages. Women were more likely than men to have UTIs for a variety of clinical reasons. *Klebsiella pneumoniae* and *Escherichia coli*, the most prevalent causes of UTI in the Enterobacteriaceae family, have gradually increased in prevalence over time. Although *K. pneumoniae* is less common than *E. coli*, it is substantially more dangerous when it comes to causing UTIs. The global prevalence of Extended Spectrum Beta-Lactamase (ESBL) synthesis among *K. pneumoniae* has grown, posing a significant threat to public health. The genes of the *bla-$_{TEM}$* and *bla-$_{CTXM}$* variants are the most important in the many bacterial families that produce ESBLs. Carbapenem hydrolyzing-lactamases are becoming increasingly common. The carbapenemases *bla-$_{KPC}$*, *bla-$_{OXA-48}$*, and Metallo Beta Lactamases, notably *bla-$_{NDM}$*, are presently the most effective at hydrolyzing carbapenems and have a wide geographical spread. *K. pneumoniae* has several virulent features that allow it to spread and evade the host's immune system, resulting in disease in human hosts.

Keywords: Urinary Tract Infection, Klebsiella Pneumoniae, Antimicrobial resistance.

Introduction:

UTI is a highly prevalent infectious disease globally. Every year, around 150 million people worldwide have UTIs. It has major economic effects because it negatively impacts work productivity, personal and family responsibilities, quality of life, and sexual health (Prasada et al., 2019). From 1990 to 2019, the prevalence of UTIs in the general population increased by 60%, demonstrating that UTIs remain a substantial public health concern that has not yet been eliminated.(Abdallah et al., 2023; J. Li et al., 2022; Lila et al., 2023). UTI severity ranges from minor to potentially fatal infections, and it accounts for around 20-25% of global mortality(Makhrmash et al., 2022).

UTIs are a very common condition that affects people of all genders and ages. The prevalence of UTIs was higher in women than in males for a variety of clinical reasons, including anatomical differences, hormonal effects, behavioral patterns, and physiological and structural differences in the female urethra(L. Huang et al., 2022). UTIs are primarily caused by Gram-negative bacteria. *E. coli* is the major organism that causes uncomplicated cystitis and pyelonephritis, accounting for around 80% of UTI cases. Other Enterobacteriaceae species, such as *Proteus. mirabilis* and primarily *Klebsiella* spp., are also responsible for UTIs. (Mazzariol et al., 2017).

The treatment protocol for UTIs differs depending on the patient's age, gender, underlying medical condition, the bacteria causing the infection, and whether the

infection is in the lower or upper urinary tract. Nonetheless, there is a significant increase in antimicrobial resistance among UTI bacteria because of indiscriminate and widespread antibiotic use. The prevalence of MDR has increased worldwide, creating a substantial public health threat. (Prasada et al., 2019). Monitoring the regional antibiotic resistance of Gram-negative bacteria, specifically *E. coli* and *K. pneumoniae*, isolated from urine samples is crucial for making informed decisions about the most suitable antimicrobial treatment for outpatients with UTIs (Rafalskiy et al., 2020).

The progression of UTIs is facilitated by bacterial characteristics and their capacity to evade the human immune system which are called virulence factors (A. Nemr et al., 2021). *K. pneumoniae and E. coli*, the most common cause of UTI within the Enterobacteriaceae family, have seen a gradual rise in prevalence over time, Although *K. pneumoniae* is less common than *E. coli*, it is significantly more harmful when it comes to causing UTIs (Abdallah et al., 2023; Foysal et al., 2018). In 2017, the World Health Organization's (WHO) Bacterial Priority Pathogens List (BPPL) listed *K. pneumoniae*, third-generation cephalosporin-resistant, and *K. pneumoniae* carbapenem-resistant as the top five pathogens; in 2024, the WHO BPPL was updated to include *K. pneumoniae* carbapenem-resistant as the top pathogen(WHO Bacterial Priority Pathogens List, 2024.). *K. pneumoniae* has been the second most prevalent etiological agent of community-acquired (CA) UTI during the previous two decades. (Taraghian et al., 2020).

The global prevalence of ESBL synthesis in *K. pneumoniae* has grown, and it has been identified as a significant public health threat (Hayder Hasan & Alasedi, 2021). The *bla-$_{TEM}$* and *bla-$_{CTXM}$* genes are the most important in the various bacterial groups of ESBLs (Jazayeri Moghadas et al., 2018) Carbapenems, such as imipenem and meropenem, are the only effective therapy options for *K. pneumoniae* strains that produce ESBLs (Saleem et al, 2021). Carbapenem hydrolyzing-lactamases are becoming increasingly common. The carbapenemases *bla-$_{KPC}$*, *bla-$_{OXA-48}$*, and Metallo Beta Lactamases, notably *bla-$_{NDM}$*, are presently the most effective in hydrolyzing carbapenem and have a wide geographical distribution (Hayder Hasan & Alasedi, 2021). *K. pneumoniae* possesses numerous virulence traits that facilitate its proliferation and evasion of the host's immune system, leading to the development of disease in human hosts (Saleem et al, 2021).

1. **Epidemiology and Prevalence of Urinary tract infection**:

UTIs are the second most common infection worldwide, accounting for 1-3% of primary care visits and 13.7% of community-based antibiotic prescriptions. In 2019, there were 405 million UTI infections worldwide, with 236,790 associated deaths, representing a 60% increase in cases and a 140% increase in deaths since 1990 (Basavaraj Bellankimath et al., 2024.). The total number of UTI cases grew by 60.40% from 252.25 million in 1990 to 404.61 million in 2019 (G Mboera et al.,2022).The African region has the highest reported rate of UTI (3.6%). This demonstrates the necessity of implementing safety precautions(Mengistu et al., 2023).

UTI prevalence in Egypt has increased over time. In 2024, the percentage was as high as 69.3%. Women (44.1%) had the highest incidence of CA UTIs, followed by children (32.3%; 19.6% girls and 12.7% boys) and men (23.5%), with age-related differences (Abu-Gharbia et al., 2024). Also, in a Brazilian city in 2024, 72.38% of UTIs were detected in women, and 44.63% of all examined patients were 65 years or older. The frequencies of children (18.61%) and elderly patients (52.98%) were substantially greater in males than in women (13.29% and 41.59%, respectively), while the frequencies of adults (45.12%) were significantly higher in women than in men (29.11%)(Negri et al., 2024).

2. Urinary tract infection during pregnancy:

Pregnancy is widely recognized as a critical stage, and neglecting to provide necessary care may result in negative effects. Complications can arise from a variety of illnesses, including UTIs that affect both the lower and upper urinary tract. UTI is most common during pregnancy, and it is influenced by a variety of factors. Although there is no consensus on the occurrence of UTIs during pregnancy, ongoing research is being conducted to determine the link between pregnancy and UTIs. Pregnancy is generally regarded as a critical phase that requires the use of several preventive measures to ensure the well-being of both the expectant mother and the developing fetus. (Vasudevan, 2014).

3. Stages of Urinary tract infection (UTIs):

3.1. Colonization:

The distinction between UTI and colonization has been heavily discussed. The term colonization may be considered antiquated, or it may be viewed as a clinical occurrence on the same spectrum as infection. The urinary tract is a sterile environment, hence any presence of bacteria in the urine, regardless of symptomatology, should be regarded as an infection. When selecting whether to treat bacteriuria, it is necessary to distinguish between asymptomatic and symptomatic cases (Gordon & Katlic Editors, 2017).

3.2. Uroepithelium penetration:

Uropathogens are thought to live in a reservoir in the gastrointestinal system, causing infection when

introduced into the urethra. It is becoming obvious that the bladder itself can function as a reservoir, with bacteria penetrating the uroepithelium and remaining intracellularly inactive before reemerging to cause another round of infection. It is important to note that the bladder epithelium's high impermeability is thought to be caused not just by urothelial plaques, but also by the unique composition of the lipids associated with them. Thus, urothelial plaques and their accompanying lipid microdomains appear to have parallel roles in preserving the bladder epithelium's exceptional impermeability (Duncan et al., 2004)**.**

3.3. Ascension:

Because UTIs are thought to arise ascendingly, flagellum-mediated motility has been suggested to contribute to pathogenicity by allowing uropathogens to spread to the upper urinary tract (Lane et al., 2007).

3.4. Pyelonephritis:

Pyelonephritis is a type of UTI caused by bacteria traveling from the lower to the upper urinary tract, such as the kidneys. The bacteria have a difficult time surviving inside the kidneys due to the diverse habitats. These include the bacteria themselves, how our cells respond, the circumstances in the diseased organ, and signals from other parts of the body. To completely understand how pyelonephritis works, scientists must employ modern techniques that allow them to observe what is happening inside the body in real-time. This allows us to gain a better understanding of how all these elements interact to generate the infection (Choong et al., 2015)**.**

3.5. Acute Kidney Injury (AKI):

Asymptomatic or symptomatic UTI can cause a wide range of symptoms, including mild irritative voiding, bacteremia, sepsis, shock, and even death. Urosepsis can result in death rates ranging from 25% to 60% in some patient populations. Sepsis is one of the most common causes of AKI, with around 60% of individuals experiencing septic shock developing AKI. Acute UTI can induce abrupt worsening of renal function, particularly in cases of urinary tract blockage. Acute kidney injury is associated with increased morbidity and death during acute care (Hsiao et al., 2015)**.**

AKI is associated with considerable in-hospital mortality, particularly in Intensive Care Units (ICUs), as well as a deterioration in long-term renal function in both native and transplanted kidneys. Urinary sepsis is the leading cause of AKI in kidney transplant recipients, followed by other UTIs (Królicki et al., 2022).

4. Classification of Urinary tract infections (UTIs):

UTIs can be classified into two types: complicated and uncomplicated UTIs. The presence of risk factors distinguishes uncomplicated from complicated urinary tract infections. This differential is used to determine the selection and duration of antibiotic treatment (Tonolini, 2018)**.**

4.1. Uncomplicated Urinary Tract Infection (Cystitis):

Cystitis, an example of UTI, occurs when bacteria enter and infect the bladder. Cystitis (bladder infection or lower UTI) symptoms include dysuria with or without frequency, urgency, suprapubic pain, or hematuria. The most common symptom is frequent urination. Dysuria is common with urethritis or vaginitis, but cystitis is more likely when symptoms include frequency, urgency, or hematuria, as well as when symptoms arise unexpectedly or aggressively, without vaginal discomfort or discharge. Even if left untreated, acute uncomplicated cystitis rarely progresses to more severe illness (Geerlings, 2016)**.**

4.2. Complicated Urinary Tract Infections:

A complicated UTI is a urine infection that occurs in a patient who has a structural or functional dysfunction of the genitourinary system. Complicated urinary infections affect both men and women of any age. Acute urinary infections can cause serious morbidity, including septic shock and death. This is occasionally accompanied by suppurative consequences such as paraurethral, renal, or perirenal abscesses, as well as metastatic infection. These problems, however, are rather rare and occur in patients with comorbidities such as diabetes, chronic urological devices, or bladder blockage (LE Nicolle, 2005).

5. Symptoms of Urinary tract infection:

UTIs can be symptomatic or asymptomatic, caused by bacteria growing in the urinary tract as reported by (Kaur & Kaur, 2021). Symptomatic UTIs present with various noticeable symptoms, including pain during urination, frequent urination, lower abdominal pain, visible blood in urine, fever (greater than 37.7°C), flank pain, chills, vomiting, nausea, itching, burning sensation, blister formation in the vaginal area, and suprapubic discomfort. These infections typically involve inflammation and are characterized by a white blood cell count exceeding 8 cells/mL in urine. Cloudy urine, known as pyuria, is also commonly observed in symptomatic UTIs (Kaur & Kaur, 2021).

6. Recurrency of Urinary tract infection:

Recurrent urinary tract infection: Major cases of UTI are referred to as re-infections, and the patient becomes ill after several weeks of antibiotic therapy. Relapse is an

uncommon kind of recurrent UTI that arises within two weeks of the initial infection because of treatment failure. Relapse UTIs frequently result in pyelonephritis, which can lead to renal failure, kidney stones, and morphological abnormalities in both men and women (Kaur & Kaur, 2021).

Gaining insight into the specific risk factors that contribute to recurrent UTIs in people and populations might help clinicians tailor preventative strategies. Recurrent uncomplicated UTIs are related to multiple documented risk factors, including frequent sexual activity, vulvovaginal atrophy, changes in the local bacterial population, a previous history of UTIs during premenopausal or infancy, and a family history of UTIs(Storme et al., 2019).

Recurrent complicated UTIs pose a risk of ascending infection or urosepsis. To treat recurring complicated UTIs, it's recommended to start with broad-spectrum antibiotics and alter coverage based on culture results. Imaging investigations should also be used to determine any existing urinary blockage(Kodner, 2010).

7. Diagnosis of Urinary tract infection:

The presence of clinical symptoms along with pathogen identification is the gold standard for diagnosing a UTI. Midstream urine culture detects and identifies the pathogen while also allowing for the calculation of bacteriuria levels. Microbiological laboratories have yet to determine or standardize the minimum level of bacteriuria required to diagnose UTI. A bacterial infection level of 10^5 colony-forming units (cfu)/ml in a patient's urine sample is employed as a diagnosis threshold depending on the type of bacteria found. (Schmiemann et al., 2010).

The following methods are used for the diagnosis of UTI bacterial infection:

7.1. Microscopic examination of urine:

After the routine culture technique, the smear was then sent for routine microscopic examination, centrifuged, and examined under the microscope (×400 magnification). White blood cells, red blood cells, organisms, crystals, and casts were looked for. Then the results are discussed as follows positive means the presence of bacteria and pyuria; >5 white blood cells or white blood cell clumps/field objective (×400), negative means < 5 white blood clumps/field (Wiwanitkit et al., 2005)

7.2. Pyuria:

Pyuria occurs in 95% of patients with genitourinary tract infections, although it cannot distinguish between a bacterial UTI and acute urethral syndrome. Pyuria can be caused by a variety of illnesses, including analgesic nephropathy, interstitial nephritis, perinephric abscess, renal cortical abscess, fungal infection, and appendicitis. (Najar et al., 2009).

7.3. Gram stain:

A simple Gram-stained smear may enhance the specificity of the test since morphology and stain features aid in identifying the likely pathogen and directing empiric treatment (Najar et al., 2009). After the routine culture technique, the urine sample was centrifugated and a urine smear was made of the sediment. The smear was then stained with by Gram stain and examined for the presence of bacteria under a microscope (×1,000 magnification). The results were discussed as follows positive means the presence of ≥1 bacteria/field (×1,000), and negative means <1 bacterium/field (Wiwanitkit et al., 2005).

7.4. Urine cultures:

Urine specimens must be cultured immediately within 2 hours or can be stored by refrigeration or a sufficient chemical addition (boric acid sodium formate) (Najar et al., 2009). The results were discussed as follows positive means the presence of CFU of 10^5 /ml or more, and negative means < 10^5 CFU/ml (Wiwanitkit et al., 2005).

7.5. Plain X-ray of the abdomen:

These indicate the existence and degree of calcification in the urinary system. They are less sensitive to detecting ureteral calculi. Plain films are useful for tracking changes in the position, size, and number of calculi. (Najar et al., 2009).

7.6. Ultrasound:

Ultrasound (USG) paired with plain X-ray has emerged as the preferred imaging modality for patients with recurrent infections. It is a sensitive detector of pelvicalyceal dilation, which may indicate an obstruction. Echoes in a dilated pelvicalyceal system, whether diffuse or layered, indicate the presence of pyonephrosis. Ultrasonography can help in the drainage of a blocked kidney. It accurately determines the renal length and detects many renal scars, abscesses, and perinephric fluid collections (Vrtiska et al., 1992).

8. Treatment of Urinary tract infections:

Antimicrobial medications can help to resolve UTI symptoms faster and eliminate bacteria from the urine more effectively. However, this medication promotes the growth of drug-resistant bacteria in the urinary system and harms normal bacteria in the stomach and vagina. Given the growing resistance of uropathogens to current antibiotics, it may be important to investigate alternate approaches for treating UTIs (Foxman, 2010).

9. Antibiotics used for the treatment of Urinary tract infection:

9.1. Nitrofurantoin:

Nitrofurantoin is a synthetic antibiotic used for treating UTIs for over 50 years. The newest form, macrocrystalline, allows for fewer daily doses due to slower absorption and excretion. Its effectiveness lies in

altering bacterial molecules, leading to their death. Resistance to nitrofurantoin is relatively low due to its broad spectrum of targets within bacterial cells. It works against common uropathogens like *E. coli*, *Klebsiella* spp., *Staphylococcus*, and *Enterococcus* but not *Pseudomonas* or *Proteus* (Nickel, 2005). It is considered a First-line agent for uncomplicated UTIs, and treatment duration is typically 100 mg twice daily for 5 days. For Pyelonephritis Avoid due to suboptimal concentrations in renal parenchyma(Al Lawati et al., 2024).

9.2. Beta-Lactams:

Beta-lactams, a class of antibiotics, include penicillin, aminopenicillins, clavams, extended-spectrum penicillin, carbapenems, and cephalosporins. They all work by blocking cell wall formation in bacteria. Aminopenicillins like ampicillin and amoxicillin are effective against *E. coli* and *P. mirabilis*, making them useful for treating UTIs. Later-generation cephalosporins and carbapenems like imipenem are used for serious UTIs and are highly effective against various bacterial infections. However, beta-lactams are generally less effective for UTIs compared to sulfamethoxazole/trimethoprim or fluoroquinolones, and resistance to them is common among uropathogens (Nickel, 2005)**.** Treatment duration for UTIs with beta-lactams in case of Acute Uncomplicated Cystitis Use only if the first-line agents cannot be utilized Examples: Amoxicillin/clavulanic acid 500/125 mg twice a day for 5-7 days. Cefpodoxime 100 mg twice daily for 5–7 days. In the case of Pyelonephritis not advised as the first agent. Consider employing an oral β-lactam drug if the pathogen is sensitive and after an initial intravenous dosage of a long-acting parenteral antibiotic, such as 1 g of ceftriaxone(Al Lawati et al., 2024).

9.3. Aminoglycosides:

Aminoglycoside antibiotics were discovered in the 1940s, initially with streptomycin being the first used to treat tuberculosis. They are derived from bacteria like Streptomyces and Micromonospora, or through chemical modifications. Aminoglycosides like neomycin, kanamycin, and gentamicin kill bacteria rapidly and are effective against a wide range of Gram-negative and Gram-positive bacteria, including some drug-resistant strains. They are particularly useful against *Enterobacteriaceae* but not *P. aeruginosa* or *Acinetobacter* spp. They also combat biothreat pathogens like *Yersinia pestis* and *Francisella tularensis*. Aminoglycosides are crucial in treating severe infections like UTIs, sepsis, and pneumonia. They are commonly used intravenously, with amikacin and gentamicin being preferred for MDR Gram-negative bacteria (Serio et al., 2018)

It is recommended for the treatment of complicated UTIs in combination with amoxicillin or a second-generation cephalosporin(Bonkat et al., 2024).

9.4. Fluroquinolones:

Fluoroquinolones are antibiotics that work by blocking DNA synthesis in bacteria, leading to their death. They are highly effective against many types of bacteria, including those causing UTIs like *E. coli*, *Staphylococcus*, and certain *streptococci*, but less so against anaerobes. Common fluoroquinolones for UTIs are ciprofloxacin, levofloxacin, and norfloxacin, with different dosing schedules and formulations. Ciprofloxacin is particularly effective against *P. aeruginosa*, common in complicated UTIs. They can be given orally or intravenously, with a shift to oral therapy for hospitalized patients (Nickel, 2005). Treatment for uncomplicated UTIs is usually Effective but used only if other oral antimicrobials for acute cystitis are not accessible or possible. Example: Ciprofloxacin 250 mg twice daily for 3 days, while for complicated UTIs it may extend to seven days as Ciprofloxacin 500 mg twice daily for 7 days (Al Lawati et al., 2024).

10. Microorganisms responsible for Urinary tract infection:

Urinary tract infections (UTIs) are mostly caused by Enterobacteriaceae, with *E. coli* accounting for around 80% of cases, followed by *P. mirabilis* and *K. pneumoniae*. Gram-positive cocci, particularly *Staphylococcus* spp., also play an important role in UTIs. These pathogens are known for their propensity to produce biofilms, which aid in infection progression. Enterobacteriaceae are gram-negative bacteria with thin rods and no identifiable cell structures. They do not create endospores. They contain lactose fermenters like *E. coli* and *K. pneumoniae*, with lactose fermentation capabilities varying across different genera and species within the family(Farmer Iii et al., 2010; Vasudevan, 2014).

11. *Klebsiella. pneumoniae*:

11.1. History of *Klebsiella. Pneumoniae*:

Klebsiella has been recognized as a human pathogen since the late 1800s, following its initial isolation by Edwin Klebs. (Ikeda et al., 2018; Prince et al., 1997)**.** *K. pneumoniae*, the Enterobacteriaceae family's second major cause of UTI After *E. coli*, has progressively increased in prevalence over the years. Despite its low prevalence compared to *E. coli*, the pathogenicity of *K. pneumoniae* associated with UTI is substantially higher than that of *E. coli* (Abdallah et al., 2023; Foysal et al., 2018)**.** *K. pneumoniae* is a Gram-negative, non-motile,

encapsulated, lactose-fermenting, facultatively anaerobic, gas-producing, rod-shaped bacteria that colonizes the skin, oropharynx, and urinary tract of humans (Al-Hashimy & Al-Musawy, 2020; Remya et al., 2019).

11.2. Epidemiology of *Klebsiella. pneumoniae:*

Klebsiella spp. are abundant in nature and can be found in soil, water, and on other surfaces. *K. pneumoniae* frequently colonizes mucosal surfaces in humans, including the upper respiratory tract and the gut, with colonization rates varying greatly between individuals depending on their habitat and exposures. According to recent studies, *Klebsiella* colonization rates range from 18.8 to 87.7% in Asia and 5 to 35% in Western countries (Chang et al., 2021). The pooled prevalence of nosocomial multidrug-resistant *K. pneumoniae* was estimated at 32.8% (Asri et al., 2021).

11.3. *Klebsiella. pneumoniae* in Community- and Hospital-Acquired Urinary tract infection:

K. pneumoniae is commonly linked to hospital-acquired infections but can also cause severe infections outside hospitals, contributing to around 6% to 8.6% of community-acquired pneumonia. It's among the top three antibiotic-resistant bacteria of global concern according to the WHO. Typically, it affects individuals with weakened immune systems and is a common cause of hospital-acquired infections, showing resistance to multiple antibiotics. In healthcare settings, *Klebsiella* UTIs, especially in patients with urinary catheters, are significant. The prevalence of UTIs, including catheter-associated ones, is increasing, particularly in long-term care facilities. Factors like weakened immune systems and catheter use increase susceptibility to *Klebsiella* infections (Clegg & Murphy, 2016) (Caneiras et al., 2019).

11.4. Pathogenesis and virulence factors of *Klebsiella. pneumoniae*:

K. pneumoniae employs many surface features to evade the host's immune system. This enables the bacteria to endure the process of being killed by the complement system, the impact of antimicrobial peptides generated by the host, and the engulfment by epithelial cells, macrophages, neutrophils, and DCs (dendritic cells). By doing this, they can avoid the process of neutrophil-mediated killing of bacteria that are taken in by cells, obstruct the production of the proinflammatory cytokine Interleukin-8 (IL-8), as well as antimicrobial peptides Human β-defensins hBD2 and hBD3, by cells in the airway lining, and inhibit the growth of DCs (B. Li et al., 2014).

K. pneumoniae utilizes a wide array of virulent factors, specifically capsule polysaccharides, lipopolysaccharides (LPS), fimbriae, outer membrane proteins, and methods for obtaining iron and using nitrogen sources. These components facilitate the bacterium's ability to persist and elude the immune system while causing infection (B. Li et al., 2014).

K. pneumoniae possesses several virulence traits that facilitate its proliferation and evasion of the human host's immune system, resulting in the development of disease (Saleem et al. 2021). The gene *fimH-1* encodes fimbriae and controls bacterial adhesion, which is a crucial virulence component. Approximately 90% of *K. pneumoniae* bacteria express Type 1 fimbriae, which enables them to adhere to many types of epithelial cells, such as bladder epithelial cells. The *rmpA* gene, also known as the regulator of mucoid phenotype A, functions as a regulator of capsular polysaccharide formation and can be found on either a plasmid or a chromosome. (LPS) protect microorganisms from being destroyed by complement-mediated lysis, and the synthesis of LPS is regulated by the Uridine diphosphate galacturonate 4epimerase (*uge*) gene (Remya et al., 2019). DNA gyrase, regulated by *gyr-B-2*, is an enzyme that relies on ATP to facilitate replication by untwisting the DNA supercoil by an atypical mechanism. The presence of DNA gyrase subunit 2 is essential for the survival of cells and is associated with beta-hemolytic activity, which refers to its ability to break down blood agar. This activity may potentially enhance the virulence of any given strain (Foysal et al., 2018). The *mrkD* gene serves a critical role in the microorganism's ability to attach to collagen molecules (Mahmood & Abdullah, 2015.)

11.5. *Klebsiella. pneumoniae* Phenotypic resistance Types:

The misuse of antibiotics, including in animal feed and over-prescription, along with poor infection control practices, has led to the rise of antibiotic-resistant microorganisms, posing a serious threat to human health. Bacteria, such as *K. pneumoniae*, are becoming resistant to almost all available drugs, causing a range of diseases like pneumonia and septicemia. In some regions, antimicrobial resistance in *Klebsiella* exceeds 50%, especially in Eastern Europe and Latin America. Resistance is categorized into MDR (resistance to three or more antimicrobial categories), XDR (resistance to all but two or fewer categories), and PDR (resistance to all agents in all categories). This escalating resistance is a global health concern, burdening patients, and healthcare providers alike (Shamsuzzaman, 2017) (Usman et al., 2022).

11.6. *Klebsiella. pneumoniae* as ESBL-producer:

The epidemiology of ESBL-producing bacteria is becoming more complex, blurring boundaries between hospitals and communities. ESBL-producing

organisms, particularly *Klebsiella*, pose a significant challenge for therapy, especially with cephalosporins. Over the last 15 years, global cases of infections caused by ESBL-producing microbes have risen. These bacteria compromise the effectiveness of antibiotics, notably cephalosporins. The incidence of ESBL-producing *Klebsiella* strains in clinical isolates has steadily increased, accounting for 6 to 17% of nosocomial UTIs. These bacteria can be classified as sensitive, moderately susceptible, or resistant to antibiotics. The global prevalence of ESBL synthesis by *K. pneumoniae* has increased. The ESBLs are categorized into different groups, with the *bla-*$_{TEM}$ and *bla-*$_{CTXM}$ versions being the most significant (Jazayeri Moghadas et al., 2018)**.**

11.7. *Klebsiella. pneumoniae* as Carbapenemase-prouducer:

Carbapenem-resistant Enterobacteriaceae (CRE) has recently become the primary group of bacterial infections that present a substantial risk to worldwide public health. The increasing incidence of KPCs is a significant public health challenge because *K. pneumoniae* carbapenemases (KPCs) were initially discovered in 1996 in the United States. since, there have been localized instances of *KPC*-producing *K. pneumoniae* in the United States, which have since spread to other countries (Chen et al., 2014). It is worth noting that carbapenem hydrolyzing-lactamases are on the rise. *bla-*$_{KPC}$, *bla-*$_{OXA-48}$, and the Metallo Beta Lactamases as *bla-*$_{NDM}$ are now the most effective carbapenemases in terms of carbapenem hydrolysis and geographical dispersion (Halat & Moubareck, 2020). Furthermore, due to plasmid, encoded -lactamases, and carbapenemases, MDR and XDR *K. pneumoniae* bacteria showed resistance to -lactams such as penicillin, third and fourth-generation carbapenems, cephalosporins, and monobactam (Makhrmash et al., 2022). Unfortunately, *Klebsiella* spp has developed resistance to the final option family of antibiotics, resulting in carbapenem hydrolysis beta-lactamases. In recent years, Carbapenem hydrolysis beta-lactamases have rapidly evolved, with *K. pneumoniae* being the most connected with KPC resistance determinants. KPCs provide a serious public health concern as they can resist numerous antibiotic classes such as β-lactams, fluoroquinolones, and aminoglycosides. *K. pneumoniae* also exhibits simultaneous resistance to structurally unrelated antibiotics such as nalidixic acid, trimethoprim, and chloramphenicol (Makhrmash et al., 2022) (Alebachew Woldu, 2016).

Conclusion:

In conclusion, UTIs continue to be a major global health concern, with women experiencing a higher incidence due to anatomical and clinical reasons. *E. coli* and *K. pneumoniae*, the most common Enterobacteriaceae bacteria, have increased in prevalence, with *K. pneumoniae* offering greater dangers although being less common than *E. coli*. The emergence and dissemination of ESBL-producing bacteria, particularly those carrying *bla-*$_{TEM}$ and *bla-*$_{CTXM}$ genes, point to a troubling trend in antibiotic resistance. Furthermore, the emergence of carbapenemases like *bla-*$_{KPC}$, *bla-*$_{OXA-48}$, and *bla-*$_{NDM}$ highlights an increasing problem in treatment efficacy, posing a global public health risk. Understanding the virulent characteristics of K. pneumoniae is critical for establishing effective measures to mitigate its impact on human health.

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