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ANTIBIOTICS SUSCEPTIBILITY PATTERNS OF UROPATHOGENIC BACTERIA ISOLATED FROM PATIENTS WITH COMMUNITY-ACQUIRED URINARY TRACT INFECTIONS, KANIFING GENERAL HOSPITAL, THE GAMBIA, 2021

SUBMITTED BY

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THIS THESIS IS SUBMITTED TO THE UNIVERSITY OF GHANA, LEGON IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF MASTERS OF PHILOSOPHY DEGREE IN APPLIED EPIDEMIOLOGY AND DISEASE CONTROL

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DECLARATION

I, Abou Kebbeh hereby declare that the work presented in this thesis is my original research work done undertaken in the Department of Epidemiology and Disease Control, School of Public Health, University of Ghana, Legon, under the supervision of Prof. Francis Anto, and Dr. Bismark Y. Sarfo and that this work has neither in whole nor part been presented for another degree in this University or elsewhere. All the references have been duly acknowledged.

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ABSTRACT

Background: Urinary tract infection is a common infection affecting about 150 million people worldwide annually. Currently, the disease is becoming difficult to treat due to the emergence of resistant strains of uropathogenic bacteria. Bacterial resistance to antibiotics is a major public health concern resulting in treatment failure, leading to over 700,000 deaths yearly. The antimicrobial susceptibility pattern among uropathogenic bacteria for empirical decision making in treating UTI is unknown, at Kanifing General Hospital in The Gambia. This study determined the prevalence and risk factors associated with antibiotic susceptibility patterns of uropathogenic bacteria isolated from patients with Community-acquired UTI at Kanifing General Hospital in The Gambia.

Methods: A cross-sectional study was conducted among Out-patients referred by attending clinicians to the laboratory to confirm UTI at the Kanifing General Hospital from March to May 2021. A purposive sampling method was used to recruit 422 study participants. Data on demographic characteristics and risk factors were collected from the patients using a case record form and structured questionnaires. A clean-catch mid-stream sample of urine was collected from study participants and analyzed after culture. The bacterial isolates identification was performed using standard microbiological methods and tested against various antibiotics using the Kirby Bauer disc diffusion method. Data were entered into an Excel sheet exported to the STATA Corp version. 16.1 for analysis. Data were analyzed using descriptive analysis, bivariate and multivariate logistic regression analysis at 95% confidence interval. Associations with p-values <0.05 were considered statistically significant.

Results: The overall prevalence of UTI among patients clinically diagnosed with UTI was 12.8% (54/422) and females were most affected with a frequency of 14.7% (51/348). A total of five bacterial isolates were isolated from urine samples that yielded significant growth of bacteria. The most common bacteria isolated were *E. coli* 74.1% (40/54), followed by *Klebsiella* spp 18.5% (10/54). Resistance was highest for Erythromycin 96.3%(52/54), Ampicillin 87.0%(47/54), Trimethoprim/Sulfamethoxazole 77.8%(42/54) and Tetracycline 75.9%(41/54) antibiotics. Uropathogens sensitivity was 77.8% (42/54) for Nitrofurantoin and 75.9% (41/54) for ceftazidime. Imipenem and Meropenem were the most active antibiotics with a 100% susceptibility rate. The prevalence of multidrug-resistant among the bacteria isolated was 87.0% (47/54). Being female (aOR= 6.9,95% CI: 1.7-28.0), history of UTI (aOR= 2.6, 95% CI: 1.05-6.16), purchasing antibiotic from street vendor/local pharmacy (aOR= 2.0, 95% CI: 1.07-3.74) and having no formal education (aOR= 8.6, 95% CI: 1.1-67.1) were significantly associated with uropathogenic bacteria isolates (p-value < 0.05).

Conclusion: *Escherichia coli* was the most prevalent bacteria and mostly identified among females. Nitrofurantoin, Ceftazidime, cefotaxime, cefoxitin, Imipenem and Meropenem were the most active antibiotics to the isolates. The identified uropathogenic bacteria show a high resistance to ampicillin, trimethoprim/sulfamethoxazole, erythromycin and tetracycline antibiotics. A high prevalence of MDR among the uropathogenic bacteria identified were also observed. Being female, having no formal education, history of UTI and buying antibiotics from street vendors or local pharmacy without medical prescription were significantly associated with uropathogenic bacterial isolates. Continuous AMR surveillance and monitoring are required to update clinical protocol of UTI management. We recommended community health education to reduce inappropriate use of antimicrobials.

Key words: Urinary Tract Infections, Uropathogens, Susceptibility Testing, Antimicrobial Resistance, The Gambia.

DEDICATION

This work is gratefully dedicated to the Almighty God for His guidance and blessings for the completion of this work. It is also dedicated to my Mum, Fatou Saine, my late Father Mbaye Kebbeh, my brother Muhammed Kebbeh, my wife Ramatoulie Gaye, and my son Muhammad A. Kebbeh.

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LIST OF ABBREVIATION

AMC	Amoxicillin
AMR -	Antimicrobial Resistance
AST -	Antimicrobial Susceptibility Testing
CA-UTI-	Community Acquired-Urinary Tract Infections
CAZ -	Ceftazime
CHL -	Chloramphenicol
CIP -	Ciprofloxacin
CLED -	Cysteine Lactose Electrolytes Deficient
CLSI -	Clinical Laboratory Standard Institute
CTX -	Cefotaxime
E -	Erythromycin
FOX -	Cefoxitin
GEN -	Gentamycin
KGH -	Kaninfing General Hospital
KMC -	Kaninfing Municipal Council
LGA -	Local Government Area
NAL -	Nalidixic acid
NIT -	Nitrofurantoin
OPD -	Out Patient Department
SXT -	sulfamethoxazole/trimethoprim
TET -	Tetracycline
UTI -	Urinary tract infections
W HO -	World Health Organization

DEFINITION OF TERMS

Urinary Tract infection: Is the invasion of any part of the urinary tract system by microbial

Community acquired-UTI: This can be defined as an infection of an individual's urinary tract system that occurs at community settings or in the hospital environment with less than 48 hours of admission.

Antimicrobial Resistance: Is the ability of microbial to survive and multiply in the presence of antimicrobial agent (eg. antibiotics, antiparasitic, antiviral)

Susceptibility Testing (S): Is a laboratory method use to directly detect the ability of one or more antimicrobial agents against a bacterial isolate.

Culture: This is a method of multiplying bacteria to help determine the specific type of microorganisms and their quantity in a sample

Antibiotic Resistance: This is when microorganisms (bacteria) develop the ability to survive and defeat the antibiotics designed to kill them.

Resistant (R) – a category defined by a breakpoint that implies that isolates with a zone diameter at or below the resistant breakpoint are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules.

CHAPTER ONE

1.0 INTRODUCTION

1.1. Background

Urinary Tract Infections (UTIs) is the presence of significant bacteria in the urinary tract system. It is one of the most prevalent bacterial infections that leads to patients seeking medical attention in clinics and hospitals (Boye et al., 2012). The Community-Acquired Urinary Tract infections (CA-UTIs) occur when infection of the urinary tract system takes place in community settings, or in the hospital environment with less than 48 hours of admission (Odoki et al., 2019). The disease is mostly caused by Gram-negative bacteria accounting for 80-85% of CA-UTIs (Mohammed et al., 2016). Among these organisms, *Escherichia coli* (*E. coli*) is the leading cause of the infection, which accounts for 75.5-87% of UTI cases, followed by *Klebsiella* spp. (Greenwood, 2012; Mohammed et al., 2016). Other bacteria such as *Proteus mirabilis, Staphylococcus aureus, Pseudomonas aeruginosa, Citrobacter* spp and *Enterococcus faecalis* have also been reported as causative agents by studies in Uganda, Ghana, Senegal and other parts of the world (Akram et al., 2007; Barry et al., 2017; Donkor et al., 2019; Odoki et al., 2019). The disease occurs when pathogenic bacteria multiply significantly within the urinary tract irrespective of the site of infection. Therefore, UTI is classified according to the site of infection in the urinary tract. Cystitis is an infection of the lower urinary system that affects the bladder, urethritis is an infection of the urethra, and pyelonephritis is an infection of the kidney. The prevalence of uropathogens is increased by several factors like age, poor economic status, poor hygiene, catheterization, hospitalization, sexual activities and use of contraceptives like spermicide (Choe et al., 2018; Guclu et al., 2021; Tazebew Emiru, Getenet Beyene, 2013). Besides other clinical conditions such as diabetes mellitus, patients with acquired immunodeficiency disease, urologic abnormalities, pregnancy, recurrent UTI and neurogenic bladder retention contribute to the prevalence of the disease (Betsy Foxman, 2003).

Globally, about 150 million people are diagnosed with UTIs yearly, resulting in global health care expenses of an excess of 6 billion dollars (Moyo et al., 2010). The infections are predominant in young, sexually active women, where UTIs exceed 0.5 episodes per person annually, with about 30% of women experiencing recurrent infections. In comparison to the male urethra, the female urethra is shorter and broader, and it is located near the warm, moist perirectal area, which is densely packed with microorganisms (Greenwood, 2012). In developed countries, like the USA, eight million physician visits occur annually as a result of UTIs. The situation is worse in many developing countries where clinicians initiate antibiotic treatment before urine culture laboratory results are out (Paulo et al., 2012).

In Sub-Saharan African countries, several studies have been conducted to elucidate the burden of UTI. The prevalence of UTI in Uganda among outpatients adults attending the hospital was 39.13% (Kabugo et al., 2016). In Nigeria, the prevalence reported was 89.17% among female patients (Oli et al., 2017). A similar study in Ghana by Donkor et. al also reported a prevalence of 10.1% among adults (Donkor et al., 2019). In Senegal, the prevalence reported was 26.7% among patients aged ≥18 years, of which males constituted 77.3% of the infections (Barry et al., 2017). Unfortunately, few studies have been conducted in The Gambia concerning the prevalence of uropathogenic bacteria and their susceptibility patterns to antibiotics. Okomo *et al*, 2011 found 21.2% urinary isolates among Gambian children with severe acute malnutrition (Okomo et al., 2011). Similarly, Sumareh et al in 2014 found 9% of uropathogenic bacteria among patients seen at the Medical Research Council (MRC) Unit, The Gambia (Sumareh, 2014). Despite these studies, the antibiotic susceptibility patterns of uropathogenic bacteria causing CA-UTI has not been extensively studied in The Gambia. Most health facilities rely on urinalysis and urine microscopes, of which the susceptibility patterns are unattainable with these techniques. As a result, clinicians frequently utilize empirical therapy without knowing the local susceptibility patterns of the bacteria to antibiotics being used.

The treatment of the causative pathogen for UTIs, uropathogenic bacteria, requires the appropriate usage of antimicrobial agents (antibiotics) to reduce morbidity and mortality associated with these pathogens and other related infectious diseases. These antibiotics classes include; cephalosporins, tetracyclines, quinolones, aminoglycosides, trimethoprim and sulphonamides (Greenwood, 2012). Among these antibiotics, trimethoprim-Sulfamethoxazole (TMP-SMX), cefuroxime, amoxicillin/clavulanic acid, and fluoroquinolones are the most common antibiotics used to treat UTI (Gupta et al., 2001). In The Gambia, according to the standard treatment guidelines, Nitrofurantoin and cephalosporin (cefotaxime) are mainly the antibiotics recommended for the treatment of UTI (Gambia, 2017).

However, the misuse of these antibiotics can result in the emergence of Antimicrobial Resistance (AMR). The increasing AMR of bacteria is a global concern (WHO, 2015) and this rising trend also prevails among UTI causative agents (Rahman et al., 2009). This global issue is more apparent in developing countries where the prevalence of infectious diseases is high and cost constraints hinder the use of newer and more expensive antimicrobial agents. The emergence and rapidly increasing resistant strains make the management of all these infectious diseases critical and complicated (Okeke et al., 2005). In developing countries, including The Gambia, empirical treatment for UTIs with antibiotics is usually performed without urine culture and susceptibility testing. Such practices by clinicians and a lack of awareness of uropathogenic bacteria-resistant patterns will greatly contribute to the emergence of antibiotic resistance. It is useful for clinicians to be aware of the local prevalence of uropathogenic bacteria and their sensitivity patterns to decide on their choice of antibiotics. This knowledge will improve antimicrobial resistance stewardship. Henceforth study on the antibiotic susceptibility pattern for uropathogenic bacterial isolates that cause CA-UTI may give chances to obtain insight into local prevalence and risk factors associated with urppathogenic isolates circulating in the community. Therefore, this study determined the antibiotic susceptibility patterns and risk factors of uropathogenic bacterial isolates among patients attending Kanifing General Hospital (KGH), The Gambia.

1.2. Problem Statement

UTI is one of the most prevalent bacterial infections, affecting approximately 150 million people worldwide annually costing the global healthcare system more than $6 billion (Moyo et al., 2010). Complication such as cystitis, urethritis and pyelonephritis affects all human population and frequent recurrence could arise from UTIs (Fihn, 2003). Patients should anticipate being treated within a few days following therapy with routinely accessible antibiotics. However, the misuse of antibiotics can lead to the emergence of bacterial resistance in the world including The Gambia (Sanneh et al., 2018). Drug resistance is estimated to cause 700,000 deaths per year globally, and if present trends continue, AMR might cause over 10 million deaths per year by 2050. In Africa, if actions are not taken research findings estimate 4.1 million people could die as a result of drug treatment failure by 2050 (Africa CDC, 2018).

Unfortunately, few studies have been conducted in The Gambia concerning the prevalence of uropathogenic bacteria and antibiotic susceptibility patterns. Okomo *et al,* 2011 found 21.2% urinary isolates among Gambian children with severe acute malnutrition (Okomo et al., 2011). Similarly, Sumareh et al (2014) found 9% of uropathogenic isolates among patients seen at the Medical Research Council (MRC) unit, The Gambia. However, these studies could not provide data on antibiotic susceptibility patterns among isolated bacteria. Also, data from the Kanifing General Hospital show an increasing number of UTI cases over the past two years. Out-patients UTI cases increased from 5750 in 2019 to 9577 in 2020. Despite this increasing number of UTI cases, there was no data on antibiotic susceptibility patterns among uropathogenic bacterial isolates at the Hospital hence there is a paucity of data on Antimicrobial Resistance (AMR). Therefore, the antimicrobial susceptibility patterns among uropathogenic bacteria are unknown for empirical decision-making in treating UTIs at KGH.

In The Gambia, clinicians start empirical treatment with a broad spectrum of antibiotics with no susceptibility testing. The aim is to alleviate the patients' suffering, but this contributes to antibiotic resistance. Moreover, access to drugs over-the-counter is rampant in the Gambia as a result of numerous local pharmacies (Sumareh et al, 2014). Most patients suspected of UTI, out of frustration, visit these local pharmacies and buy antibiotics with no medical prescriptions, resulting in the emergence of bacterial resistance to antibiotics and treatment failures.

The direct consequences of the infection with resistant microorganisms include increased morbidity and mortality, longer illnesses, prolonged stay in the hospital, increased medical cost, and reduced productivity, which leads to losses to the global economy and the country (WHO, 2015).

Despite the routine urine analysis done at the laboratory, the local resistance pattern of antibiotics used to treat UTIs is unknown. Therefore, this study seeks to add a knowledge base on UTIs ' main causative agent and their antibiotic susceptibility pattern and assess if there is an association between the uropathogenic bacterial isolates with socio-demographic characteristics, risk factors and antibiotics usage.

1.3. Justification

This study provides AMR data on community-acquired UTIs in The Gambia. The identification of antibiotic resistant of uropathogenic bacteria in CA-UTI patients will provide an essential dataset for assessing health (estimating resistant bacterial isolates and associated risk factors) and burden at the community level. Furthermore, information on the antibiotic susceptibility patterns of bacteria that cause CA-UTIs can be utilized to help clinicians choose the right medication. Clinicians at Kanifing General Hospital will have a better understanding of the susceptibility pattern of uropathogenic bacteria to antibiotics available locally for treating community-acquired UTIs.

Overall, it is anticipated that the current study on the antibiotic susceptibility patterns of uropathogenic bacteria among CA-UTI patients would have a significant effect on the health sector and minimize AMR as a result of clinicians' inappropriate antibiotic prescriptions and population overuse.

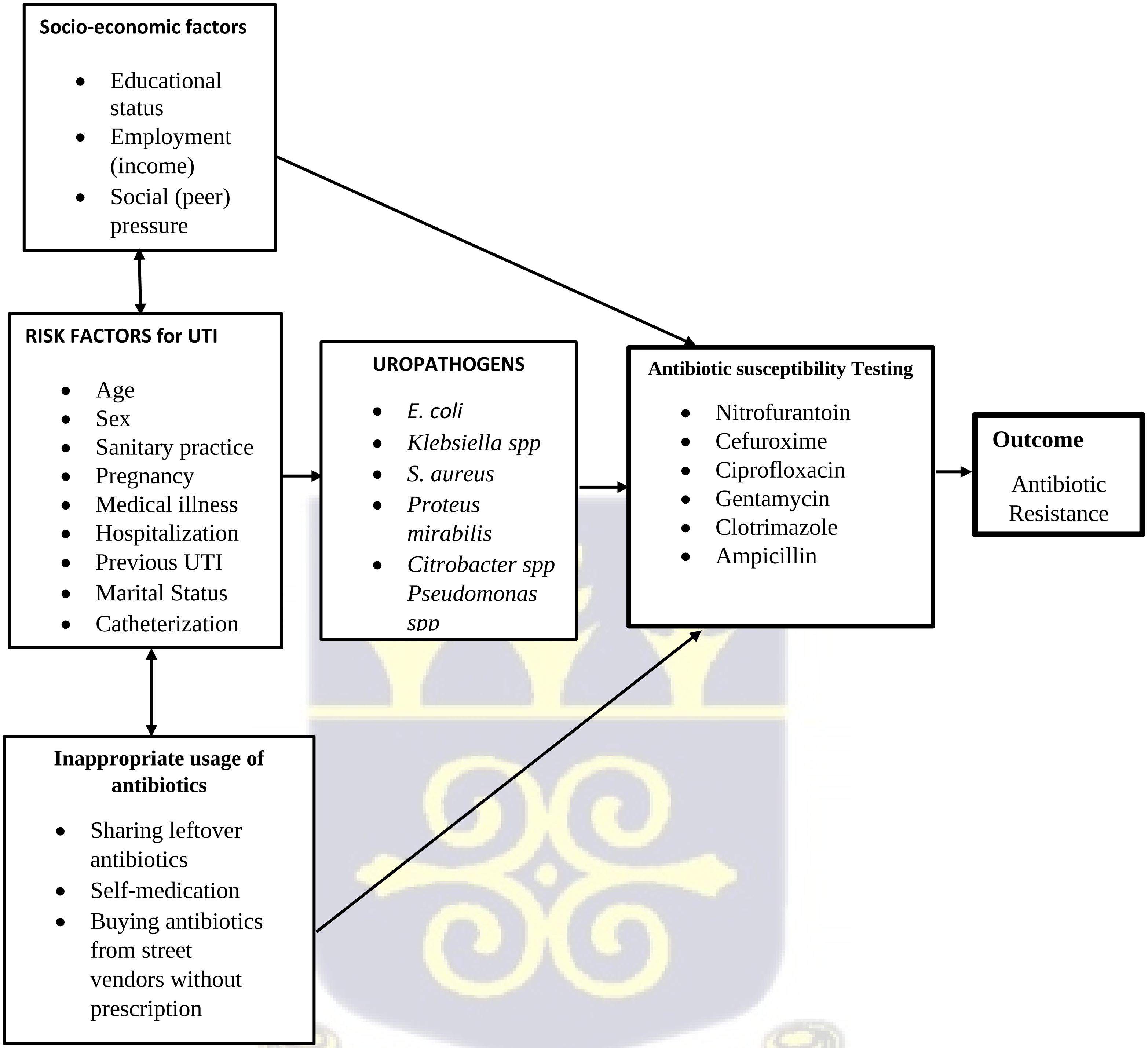

Figure 1. Conceptual framework of uropathogenic bacteria causing CA-UTI and interrelated risk factors leading to AMR

1.4 Narrative of the conceptual framework

Figure 1 is a conceptual framework of uropathogenic bacteria causing community-acquired UTI and some of the risk factors leading to antibiotic resistance in which the study aims to determine. The risk factors resulting in the acquisition of uropathogens and the subsequent emergence of antibiotic resistance can be grouped into several categories; demography characteristics, behavioral risk factors and socioeconomic factors.

The occurrence of UTI is influenced by several risk factors such as; sex, age, pregnancy, sexual activity, marital status (demography characteristic), poor hygiene, hospitalization and exposure to some clinical procedures such as catheterization (Betsy Foxman, 2003). The incidence of UTI is higher in females compared to males across all age groups. This can be attributed to the short and wider urethra in females. Age is a known predisposing factor to UTI. Besides that, urological abnormalities, chronic diseases and immunocompromised (medical illness) are other predisposing factors. These risk factors expose people to certain Uropathogens that cause UTIs. (Betsy Foxman, 2002).

Besides, UTI during pregnancy enhances the possibility of infection. UTI incidence is at its peak during pregnancy due to several features of pregnancy that act as predisposing factors. Such factors include; urinary stasis in ureters, increased progesterone, uterine growth, bladder displacement and increased volume of residual urine.

Catheterization is another factor that can lead to the acquisition of uropathogenic bacteria. Failure in infection prevention and control like poor hand hygiene, poor aseptic technique, and poor catheter placement predispose patients to UTI (Storme et al., 2019).

UTIs occur when there is a presence of uropathogenic bacteria within the urinary tract system. Such pathogens include *E. coli, Klebsiella, S. aureus*, *Pseudomonas.* spp, *Citrobacter*. spp etc.

Many studies have been reported that these organisms are the causative agent of community-acquired UTI(Betsy Foxman, 2003; Lee et al., 2013). Depending on the infection site, uropathogens can cause cystitis (bladder infections), pyelonephritis (kidney infections), and urethritis(Betsy Foxman, 2002).

When the disease ensues, out of frustration, an individual will have the urge to seek medical attention or buy antibiotics to treat the illness using various antibiotics like trimethoprim-sulfamethoxazole, ceftriaxone, Nitrofurantoin, Cefotaxime, and Gentamycin, Ciprofloxacin, Ampicillin etc. The inappropriate usage of such antibiotics results in antibiotic resistance emergence (Pietrucha-Dilanchian & Hooton, 2016).

The inappropriate usage of antimicrobial agents greatly influences uropathogenic bacteria's sensitivity pattern to various antibiotics. Many studies have reported several risk factors that influence the development of antimicrobial resistance. However, it is crucial to note that some studies showed conflicting findings. Therefore, a risk factor that shows significant association with uropathogenic bacteria resistant to antibiotics might differ in another study. Factors that facilitate the development of antibiotic resistance within the community can be categorized as demography characteristics, behavioral and socioeconomic factors.

Furthermore, the behavioral factors that have been reported to be associated with the development of resistant uropathogenic bacteria include the inappropriate usage of antibiotics over the counter (buying antibiotics from a local pharmacy/street vendors without a medical prescription) (Sanneh et al., 2018), sharing of left-over antibiotics and antibiotics consume in the last three months. Self-medication without a medical prescription is also another important driver for the overuse and misuse of antibiotics. (Larson, 2007; Okeke et al., 1999, 2005). These behavioral factors predispose for the inappropriate usage of antibiotics and thus leading to antimicrobial resistance.

Moreover, other risk factors identified to be associated with antibiotic resistance include catheterization, age, previous UTI episodes, medical illness, and educational status. These factors (demography characteristics) influence an individual to inappropriately misuse antibiotics, like buying antibiotics from street vendors (behavioral risk factors), thereby resulting in the development of antibiotic resistance (Mar et al., 2015). Furthermore, it has been proven that socioeconomic factors such as employment and educational status, peer pressure are also vital drivers for the misuse of antibiotics (Okeke et al., 1999).

The conceptual framework also further shows the outcome, antibiotic resistance. Antibiotic resistance poses some consequences, like treatment failures, longer hospital stays, prolonged illness, and increased cost to individuals and society. Although other drugs may be available, they are often more expensive. Many developing countries, like The Gambia, are disproportionately affected because such drugs may not be available.

These factors' interrelationship greatly affects the susceptibility pattern of various antibiotics currently used to treat UTI, leading to AMR.

However, the highly effective antibiotics used to treat UTIs are becoming ineffective as bacteria develop resistance against them. Thus, it is very crucial to research and be up-to-date with the rapidly changing causative agent and their antibiotic sensitivity patterns. This will add knowledge to determine the etiology profile, antibiotic susceptibility pattern and risk factors to the uropathogenic bacterial isolates for empirical treatment in UTI cases.

1.5 Research Questions

1. What is the burden of uropathogenic bacteria among patients diagnosed with CA-UTIs visiting the hospital?
2. What is the susceptibility pattern of the isolates to various antibiotics?
3. What are the risk factors associated with the isolates?
4. What antibiotic usage factors are associated with the bacterial isolates?

1.6 Objectives

1.6.1 General objective:

To determine the antibiotic susceptibility patterns of uropathogenic bacteria causing community-acquired Urinary Tract Infection at Kanifing Municipal Council (KMC).

1.6.2 Specific Objectives

1. To identify isolates of uropathogenic bacteria causing community-acquired UTIs among patients attending Kanifing General Hospital
2. To determine the susceptibility pattern of uropathogenic bacteria isolates to the antibiotics that are currently used to treat UTIs in KGH
3. To assess risk factors associated with the isolates among patients with community-acquired UTI.
4. To determine the association between antibiotic usage and uropathogenic bacterial isolates.

CHAPTER TWO

2.0. LITERATURE REVIEW

2.1. Urinary Tract infection

Urinary Tract Infections (UTIs) can be described as the presence of microbial pathogens in the urinary tract, which is categorized into the upper (kidney and ureter) and the lower urinary tract (urethra and bladder). Infections by microbial pathogens may affect both the upper and lower tracts, and the infection is classified depending on the site of the infections. The infection of the upper tract, such as the kidney, is known as pyelonephritis and that of the lower tract like the bladder (cystitis), urethra (urethritis), or the prostate in males (prostatitis). Bacteria, viruses, parasites, and fungi can all cause such infections. Lower abdomen discomfort, dysuria, urgency, fever, and chills are some of the symptoms of a UTI (Betsy Foxman, 2003; Tan & Chlebicki, 2016).

UTI is one of the commonest bacterial infections diagnosed at primary care (Tan & Chlebicki, 2016). The disease is among the major causes of morbidity and mortality in all human populations, including infants (Betsy Foxman, 2003; Soiza et al., 2018). Various factors such as age, gender, sexual behavior, personnel hygiene, hospitalization and abnormality of the urinary tract are the main determinants factors of the infections (Tan & Chlebicki, 2016).

2.2. Causative agents of UTI

Bacteria are by far the most frequent group of microbial organisms causing UTI. Most of these bacteria are gram-negative, accounting for about 80-85% of infections, and the leading cause is *E. coli*, which accounts for about 75.5-87% infections, followed by *Klebsiella* spp (Mohammed *et al.*, 2016). The other gram-negative *Enterobacteriaceae* causative includes *Enterobacter* spp, *Citrobacter* spp, *Serratia* spp, *Acitenobacter* spp, *Pseudomonas* spp and *Proteus* spp. Examples of other gram-positive causative bacteria include *Staphylococcus* and *Enterococcus* spp (Akram et al., 2007; Betsy Foxman, 2002; Mohammed et al., 2016).

Several studies have been conducted, which showed *E. coli* as the main cause of CA-UTI. A study conducted in Nigeria to determine UTI incidence among children and adolescents revealed *E. coli* and *Klebsiella* spp were the most isolated organisms (Okoh, 2007). In addition, Kashef et al investigated the sensitivity pattern of uropathogenic bacteria to routinely used antibiotics and discovered that *E. coli* (68.8%), Proteus spp (12.4%), *Klebsiella* spp (9.6%), Pseudomonas spp (3.3%), and *Streptococcus* spp (2.3%) are the most prevalent pathogens causing UTI (Kashef *et al*., 2010).

2.3. Pathogenesis of UTI

The urinary tract infection starts when the periurethral is contaminated with uropathogenic bacteria and then colonized the urethra. For successful colonization, uropathogens require appendages such as flagella or pili that are attached to the host receptors. This process is usually dictated by complex host-pathogen interaction. After colonization, uropathogenic bacteria travel to the bladder. During this interaction and pili attachment to receptors on the uroepithelium (bladder epithelium), it produces toxins and proteases to survive. After attachment, uropathogens multiply and overcome the host immune response. It then ascends to the kidney and is attached through pili, thus colonizing the renal epithelium (Ana L. Flores-Mireles, Jennifer N. Walker, Michael Caparon, 2015; McLellan & Hunstad, 2016).

However, *E. coli* has been reported to be a major causative of UTIs. This is because uropathogenic *E. coli* has a virulence factor that enhances it to colonize and invade the urinary tract. Examples of these virulence factors include pili, multiple types of fimbriae, cytotoxic necrotizing factors and alpha-hemolysin production (Subashchandrabose et al., 2014; Tille, 2014). *Klebsiella* spp and other strains such as *Proteus mirabilis* adheres to the uroepithelial cells and often hydrolyzed urea, increasing the urine pH which is directly toxic to kidney cells (Tille, 2014).

2.4. Classification and Types of UTIs

UTIs are composed of a wide range of clinical units that differ in terms of clinical manifestation, epidemiologic setting and requirements for antibiotics therapy. Base on the clinical presentation, Uncomplicated and complicated UTIs are the two types of UTIs. Persons who are otherwise healthy and do not have any urological abnormalities are usually affected by uncomplicated infections. Uncomplicated UTIs affect more females and occasionally in male infants and male adolescents. Lower urinary tract infections (cystitis) and upper urinary tract infections (pyelonephritis) are two types of infections. Most of the uncomplicated UTIs respond readily to antibiotic agents to which the causative agent is susceptible. Female gender, vaginal infection, sexual activity, diabetes, obesity, previous urinary tract infection, and genetic predisposition are all risk factors for cystitis. The clinical signs and symptoms of uncomplicated cystitis include dysuria, frequency or urgency of urination. Pyelonephritis is usually shown by fever and back pain/costovertebral angle tenderness (Gupta et al., 2001; Paulo et al., 2012).

Complicated UTIs may affect both men and women at any time in their lives, and they can have terrible consequences, even death may occur in extreme cases. The infections can lead to other outcomes like structure anomalies that affect the urinary tract capacity to flush out the urine. This provides a suitable environment for the growth of bacteria as urine is considered a suitable growth medium (Vasudevan, 2014). Furthermore, complicated UTIs are usually connected to conditions that impair the urinary tract or the host's defense system. Urinary retention caused by neurological disease, immunosuppression, renal failure, urinary obstruction, renal transplant, and the presence of foreign bodies such as calculi, indwelling catheters, or other drainage devices are some of the conditions (Ana L. Flores-Mireles, Jennifer N. Walker, Michael Caparon, 2015).

Moreover, there are several types of UTIs; cystitis, pyelonephritis, urethritis, asymptomatic bacteriuria and urethral syndrome.

2.4.1. Cystitis

Generally called the lower urinary traction or bladder infection, which is common in females. It causes various symptoms dysuria, polyuria (frequent urination), urinary urgency, nocturia (urination during night) and hematuria. Affected individuals may note urine cloudiness and bad a odor. These symptoms are a result of bacterial multiplication and inflammation of the bladder (Vasudevan, 2014).

2.4.2. Pyelonephritis

Pyelonephritis is commonly referred to as the upper urinary tract infection and affects the kidneys, and is usually caused by bacteria. Inflammation of the kidney parenchyma commonly called urinary tract infections that affect the kidney. It may appear as an acute or chronic condition. Acute pyelonephritis presents with enlarged kidneys that contain surface abscesses. A chronic condition, it presents with scarring on one or both kidneys. The typical upper urinary tract infection includes fever, flank pain and some of the lower tract symptoms like frequency, urgency and dysuria. Affected individuals may also exhibit systemic signs of infection like vomiting, lower abdominal pain chills and increased heart rate (Tille, 2014; Vasudevan, 2014).

2.5. Epidemiology of UTI

UTIs are one of the most prevalent bacterial illnesses that lead to medical attention. Globally, an estimated 150 million people have been affected by the disease annually. The disease affects everyone, but traditionally it is thought of as a disease for women of which 50% will experience it in their lifespan (McLellan & Hunstad, 2016). Adult women are mostly affected who are 30 times more likely to develop UTI than men. It has been reported that one in three women will have had their first episode of UTI before the age of 24yrs (Tan & Chlebicki, 2016). The incidence of bacteriuria (the presence of bacteria in urine) in females rises consistently with time, reaching as high as 10% to 20% in older females. In addition, almost 50 % of women who have had UTIs between the ages of 30 and 40 are likely to get infections again (Tille, 2014). Furthermore, sexual activity increases the risk of bacterial contamination of the female urethra, which might explain why females have a higher rate of infection. Moreover, because of the hormonal and anatomic changes during pregnancy, the incidence of bacteriuria increases which favors the development of UTIs.

Despite that everyone is susceptible to UTIs, there are specific subpopulations at increased risk of developing the disease. Such groups include the elderly, infants, patients with diabetes, patients with urologic abnormalities, immunocompromised individuals, renal disease and patients with structural and neurologic abnormalities (Betsy Foxman, 2002; Tille, 2014).

2.6. Treatment of UTI

Presently, antibiotics are recommended for the treatment of uropathogenic bacteria causing UTI. Some of the class of antibiotics commonly prescribed to treat UTI includes penicillin, cephalosporins, Carbapenems, Nitrofurantoin, monobactams, Aminoglycosides, quinolones, etc. The susceptibility test of urine culture mainly guides the choice of antibiotic therapy. Since susceptibility testing takes a long time before results are issued, clinicians usually initiate empirical treatment (Ana L. Flores-Mireles, Jennifer N. Walker, Michael Caparon, 2015; Tan & Chlebicki, 2016). This may result in the development of resistant bacterial strains thereby, making the treatment very difficult. A study by Lee *et al.* showed that the isolated organisms from urine samples of UTI patients were susceptible to amikacin, amoxicillin-clavulanic acid and aztreonam etc (Lee *et al.*, 2013). In the Gambia, the main recommended choice of antibiotics to treat complicated or uncomplicated UTI include; ciprofloxacin, ceftriaxone, doxycycline, nitrofurantoin (Gambia, 2017). However, the increasing trend of antibiotic resistance greatly threatens the treatment of these bacterial infections. Bacterial resistance to antibiotics poses a major public health concern and contributes to increasing the cost of healthcare in developing countries, including sub-Saharan Africa (Mohammed *et al.*, 2016).

2.7. Antimicrobial Resistance Mechanism

Antimicrobial resistance results when microbe (bacteria, fungi, viruses and parasites) develop the ability to survive in the presence of antimicrobial agents (such as antibiotic, antifungal, antiviral etc) (CDC, 2019). Standard therapies are rendered ineffective, and the sickness may be extended and spread to others.

Antibiotics are one of the most effective weapons in the battle against life-threatening diseases. Their discovery began in 1928 when Sir Alexander Fleming discovered penicillin. Antibiotics have saved millions of lives and changed modern medical practice since then. It also plays a critical part in key medical and surgical breakthroughs (Ventola, 2015). Since that time, numerous new antimicrobials have been developed, and many have found their way into clinical practice. Since the first antibiotic was discovered, other classes of antibiotics have been developed. These antibiotics classes that have been used to treat various infections include; cephalosporins, sulfonamides, quinolones, tetracyclines, carbapenems, etc (Jeffrey *et al*, 2011). However, in less than a century, the evolution of antibiotic resistance has been recorded in almost all antibiotic classes. The threat poses by antibiotic resistance undermines the progress of the health care system, life expectancy and food production (CDC, 2019).

Antibiotic resistance develops in bacteria through a variety of mechanisms. The major mechanisms by which bacteria develop resistance to antibiotics include; efflux pumps (pumping of the antimicrobial agent from the bacterial cell), inactivation of an antibiotic by an enzyme and an altered-antibiotic target.

An effective antimicrobial must enter the bacterial cell act on the target with its sufficient concentration. Gram-negative bacteria, for example, have a protective membrane (cell wall and cell membranes) that shields them from the outside environment. These protective membranes serve as a formidable barrier for access to the interior of the cell. These openings like the protein porins can be selectively adjusted to prevent antibiotic traverses, thereby rendering the antibiotic ineffective. Besides, some bacterial species have an energy-dependent efflux mechanism that pumps antibiotics that entered the cell back out. For example, *Pseudomonas aeruginosa* develops resistance to beta-lactams, fluoroquinolones and carbapenems using this mechanism. However, some bacteria are intrinsically resistant. For example, *Streptococci, Enterococci*, anaerobes lack the metabolic pathways required for the transport of aminoglycosides across the cytoplasmic membrane (Ryan, 2018).

Once the antibiotic entered the bacterial cell, it acts by binding and inhibiting its target for destruction. If the target is altered to decrease its affinity for the antibiotic, the inhibitory and destruction effect will be reduced. These target site changes enable some bacteria to avoid destruction, thereby making them resistant to the antibiotic. For example, an alteration of penicillin-binding proteins are the prime reason for the emergence of penicillin-resistant pneumococci.

Another mechanism in which bacteria develop resistance to an antibiotic is enzymatic inactivation. The bacterium produces an enzyme, such as the beta-lactamase enzyme, which destroys the antibiotic beta-lactam ring and inactivates it. For example, *Staphylococcus aureus* beta-lactamases may hydrolyze penicillin or first-generation cephalosporins. Also, *K. pneumonia* carbapenemases, which are ESBL type enzymes, use this mechanism to confer resistance to third and fourth-generation cephalosporins (Pommerville, 2011; Ryan, 2018).

2.8. Global Prevalence of AMR

Antimicrobial resistance is a global problem and threatens the very core of modern medicine. To mitigate this impact, in 2015, the WHO constituted the Global Antimicrobial Resistance Surveillance System (GLASS), one of the first global collaborative efforts to foster AMR surveillance in bacteria causing infections. Following this global collective effort, as of December 2018, 71 countries were enrolled in GLASS to provide annual AMR surveillance data. According to the GLASS report 2017-2018, a total of 3097 hospitals and 2358 outpatients clinics reported AMR data. Furthermore, 45 (94%) nations submitted blood specimen results, 24 (50%) urine specimen results, 21 (44%) stool specimen results, and 20 (42%) cervical and urethral specimen results. The most frequently reported pathogens were *E. coli, K. pneumoniae, Salmonella* spp., *Acinetobacter* spp., *S aureus, S pneumoniae, N gonorrhoea*, and *Shigella* spp (WHO, 2017). Similarly, thirty European union countries reported data to European Antimicrobial Resistance Surveillance Network (ECDC, 2020). Among these countries, twenty-nine countries reported data on the bacteria species under surveillance (*E. coli, K. pneumoniae, P. aeruginosa, Acinetobacter species, S. pneumoniae, S. aureus, E. faecalis and E. faecium*). The most commonly reported bacterial species were *E. coli* (44.2%) followed by *S. aureus* (20.6%), *K. pnueumoniae* (11.3%), *E. faecalis* (6.8%), *P. aeruginosa* (5.6%), *S. pnumoniae* (5.3%) *E. faecium* (4.5%) and *Acinetobacter*. spp (1.7%) (EARS-Net, 2020). Moreover, an estimate of 400,000 and 25000 infections and deaths, respectively, due to the most frequent multidrug-resistant bacteria (*S.*

aureus, E. coli, Enterococcus faecium, Streptococcus pneumoniae, Klebsiella pneumoniae and *Pseudomonas aeruginosa*) occurs yearly (Prestinaci et al., 2015).

2.9. Regional prevalence of AMR

In Africa, several studies on AMR have been conducted, with the results suggesting a rising trend. A systematic review by Tadesse *et al* describes the AMR situation in Africa of published data from 2013-2016 antibiotic drug sensitivity. They observed a huge data gap on AMR in Africa, whereby no suitable reports were identified in 42.6% (23/54) countries. The same study observed that amoxicillin and sulfamethoxazole/trimethoprim were mostly reported resistance, recording 72.9% and 75.0%, respectively. The study also further revealed a lower resistance level of *S. aureus*, *Klebsiella* spp and *E. coli* to carbapenems and fluoroquinolones. In all regions, resistance to trimethoprim (33.9 % -100 %), ampicillin (7.9% -100 %), and penicillin (zero -75 %) was high. In the same study, *Klebsiella* spp resistance to ciprofloxacin in West Africa was higher than in other regions (Tadesse et al., 2017). Similarly, a study by Stije J. Leopold et al, a systematic review of antimicrobial drug resistance in sub-Sharan Africa from 1990-2013, found 61% of the reviewed papers studies were done in East sub-Sharan Africa (Leopold et al., 2014).

In West Africa, a systematic review and meta-analysis study was conducted to estimate AMR prevalence that could compromise first-line empirical treatment by Bernabe et al (2017). The study found commonly used antibiotics (gentamicin, ampicillin, penicillin, ciprofloxacin, chloramphenicol and trimethoprim) to treat UTI infections, bloodstream infections, meningitis, diarrhea and pneumonia have demonstrated some degree of resistance. In the same study, the majority of the review studies were from Nigeria (70; 58.3%), Ghana (15; 12.5%) and Senegal (15; 12.5%). Among the studies conducted on UTI originated from Nigeria (n = 31), Senegal (n = 4), Ghana (n = 4), Benin (n = 2), Burkina Faso (n = 1) and Ivory Coast (n = 1). Moreover, UTI studies conducted in outpatients setting showed *E. coli* and *Klebsiella* spp. were resistant to ampicillin was reported in 75.4% and 97% of strains, respectively (Bernabé et al., 2017)

2.10. National prevalence of AMR

In The Gambia, Numerous studies have reported antibiotic resistance; antibiotic-resistant pattern for ESBL producing Enterobacteriaceae among food handlers (Sanneh et al., 2018), *Salmonella* spp infection in The Gambia (Kwambana-Adams et al., 2015), antibiotic susceptibility of *Streptococcus pneumonia* and *Staphylococcus aureus* among infants (Bojang et al., 2018). However, few studies focus on UTI and antimicrobial resistance of its etiology. A study by Okomo et al determines bacterial isolates from severe acute malnourished children found 17 urinary isolates. Among which all the 13 isolates of *E. coli* were susceptible to gentamicin, nitrofurantoin, ciprofloxacin, cefotaxime and ceftriaxone (Okomo et al., 2011). Despite these studies conducted in The Gambia, the current national AMR surveillance system recorded zero reports, according to GLASS report 2017-2018 (WHO, 2017).

2.11. Factors responsible for the emergence of Antimicrobial Resistance

The development of antimicrobial resistance is a complex problem fueled by several interconnected predisposing factors. Many of these factors can be categorized into demographic characteristics, behavioral and socioeconomic factors. Several of these factors have been linked to antimicrobial usage to both humans, plants, and animals, including environmental factors. It has now been accepted that antimicrobial usage is the main driver for bacterial resistance emergence (Ayukekbong, 2017; Byarugaba, 2004).

2.11.1 Age, Sex

Several studies have found an association between demographic factors and uropathogenic bacteria resistance to an antibiotic in UTI patients

In a Canadian study by Karlowsky *et al*, a total of 2,943 urine samples were tested for culture and sensitivity over three years. The study found a significant association between an increased age with resistance to ciprofloxacin and other commonly prescribed antibiotics (nitrofurantoin, amoxicillin-clavulanate). It also revealed gender differences among isolates' resistance to amoxicillin (AMC), ciprofloxacin (CIP), nitrofurantoin (NIT), and trimethoprim-sulfamethoxazole (SXT). The percentage resistance to various antibiotics for females was AMC (4.3%), NIT(2.9%), CIP(17.%), SXT(20.8), while that of males was AMC (3.3%), NIT(7.9%), CIP(27.2%), SXT(26.3) (Karlowsky et al., 2011). A similar study conducted in Senegal by Dromigny *et al.* shows consistent findings on sex variation and age with resistant strains. They found that *E. coli* resistant strains to ampicillin were significantly associated amongst men than women. *E. coli* resistance to nalidixic acid and fluoroquinolones was also associated with persons above 45 years old (Dromigny et al., 2005).

2.11.2. Hospitalization

Hospitalization status can be referred to as an individual visiting the Outpatient department or being an In-patient (admission within 24 hrs). This is known to impact disease patterns and the emergence of resistant isolates among diverse uropathogens. Some infectious diseases, such as UTIs, have been reported to be acquired both in the community and in hospitals as a result of medical operations such as catheterization (Sasikala *et al.*, 2019). Several studies have shown a significant association between hospitalization status and resistant uropathogenic bacteria to antibiotics. A study by Moore *et al.*(2008) showed recent admission and hospitalization (in the preceding year) were significantly associated with extended-spectrum beta-lactamase-producing (ESBL) bacterial infection isolated from clinical specimens with urine as the commonest source (Moor *et al.*, 2008).

2.11.3. Overuse of antibiotics

The overuse of antibiotics clearly defines the emergence of antibiotic resistance. Several Epidemiological studies have demonstrated a direct association between antibiotic consumption and the emergence and dissemination of bacterial resistance isolates. In many countries like developing countries, antibiotics are unregulated and easily accessible over the counter, hawkers/street vendors without medical prescription and are usually dispensed on streets by untrained personnel (Ayukekbong *et al*., 2017). This lack of regulation results in easily accessible, plentiful and cheap antibiotics, thereby promoting overuse and contributing to antibiotic resistance. Also, purchasing such products online promotes self-medication (Larson, 2007; Planta, 2007).

2.11.4. Sanitation

Aside from the inappropriate usage of antibiotics, other factors such as poor hygiene, crowding fueled the transmission and spread of resistant bacteria. Such transmission is aided by contaminated water, food, or vectors (Ayukekbong *et al.*, 2017).

2.11.5. Inappropriate Prescribing

Incorrectly prescribed antibiotics also promote the emergence of antibiotic resistance. This exposes patients to potential complications of antibiotic therapy (Gbadago, 2011). Antibiotic concentrations that are subinhibitory and subtherapeutic can potentially aid in the development of antibiotic resistance by promoting genetic changes. Low levels of antibiotics have also been demonstrated to aid in strain diversity in organisms like *Pseudomonas aeruginosa* (Viswanathan, 2014). Additionally, in developing countries, the patient-clinician ratio is very high, clinicians are usually overwhelmed, and there is often limited time for meaningful health education and communication with the patient on adherence to treatment guidelines, resulting in nonadherence to treatment guidelines. Besides, due to insufficient surveillance on AMR, clinicians often lack up-to-date knowledge of AMR patterns in the population for reference purposes in treating infections.

Moreover, in some settings where there is no capacity for susceptibility testing, clinicians often rely on blind treatment using a broad spectrum of antibiotics to treat infections. These practices make a significant contribution to the development of antibiotic resistance (Ayukekbong et al., 2017).

Furthermore, clinicians' knowledge and practices on AMR are other critical factors contributing to antibiotic resistance development. A study by Garcia *et al* with a sample size of 256 participants, that evaluates the knowledge, attitude and practice of doctors on AMR and antimicrobial prescribing, revealed the lack of knowledge and bad practices on antimicrobial among doctors. The study also shows that 78 (31%) participants responded with difficulty to select the correct antimicrobial. A quarter of the respondents 58 (23%) agreed that prescribing antimicrobials when they are not required does not cause harm (García et al., 2011). In a similar study in The Gambia by Sanneh et al among 225 respondents, 23.08% were not aware that antibiotics are not effective against viral infections such as the common cold (Bakary Sanneh et al., 2020). These practices and lack of awareness of antimicrobial resistance considerably led to the emergence of AMR.

2.11.6 Income (Employment)

Poverty is the most important underlying factor in developing countries, including The Gambia. The lack of money combined with other factors like lack of awareness on antibiotic resistance, lack of education, cultural beliefs, inaccessible proper health, and diagnostic facilities precipitate the emergence of antibiotic resistance. Also, the lack of income contributes to a poor diet to keep a healthy and fit body to fight off infections. This makes individuals vulnerable to certain infections in developing countries. Economic hardship results in premature cessation of treatment even though the infection does not heal or share one single dose of antibiotic with the whole family, resulting in misuse of antibiotics (Byarugaba, 2004; Planta, 2007). Another factor that leads to antibiotic resistance is the restraining of the usage of new antibiotics advised by microbiologists and infectious-diseases specialists. Once new antibiotics are developed, physicians, rather than prescribing them immediately, usually hold this new agent in reserve for only the worst cases due to fear of developing resistance. This urges them to continue to use older agents that have shown comparable efficacy resulting in over-usage. Such practice has led to reduced usage of new antibiotics and diminishing return on investment, which is no longer considered a wise investment by many pharmaceutical companies (Ventola, 2015).

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1. Study Design

A cross-sectional study was conducted among Out-Patients referred by attending clinicians to the laboratory for confirmation of urinary tract infection at the Kanifing General Hospital from March to May 2021. Mid-stream urine samples were received from patients and culture and sensitivity tests were performed. Data on demographic characteristics (age, sex, occupation, education), risk factors, and antibiotic usage were collected from the patients using a case record form and structured questionnaires.

3.2 Study site

Kanifing General Hospital is located in Kanifing Municipal Area Council (KMC), which is one of the eight Local Government Areas (LGAs) in The Gambia (GBoS, 2013). The municipality is one of the most densely populated areas and lies at the West of Banjul, the main capital. The municipality includes Serekunda, which is the largest urban area in Gambia. Kanifing LGA has a land size of 75.6 km^2. According to the Gambia Bureau of Statistics, the population of Kanifing LGA is 382,096 (GBoS, 2013). The climatic condition is mainly tropical, with only one rainy season, which starts in July through October. Trading is the main occupation of the inhabitants at Kanifing LGA.

The Hospital is among the main tertiary healthcare center in the country. The hospital received patients mainly from the urban area and is the second major point of referral within the urban areas. It is manned by a team of medical professionals responsible for the management of clients both admission and at the outpatient department (OPD). The hospital has seven main clinical departments (Outpatients Department, Laboratory Department, Gynae Department, Dental Department, Accident and Emergency department, Surgical department, and Pharmaceutical

Department) with an admission capacity of 340 beds. The laboratory department of the hospital has three main sub-units, including the hematology, microbiology, and serology units.

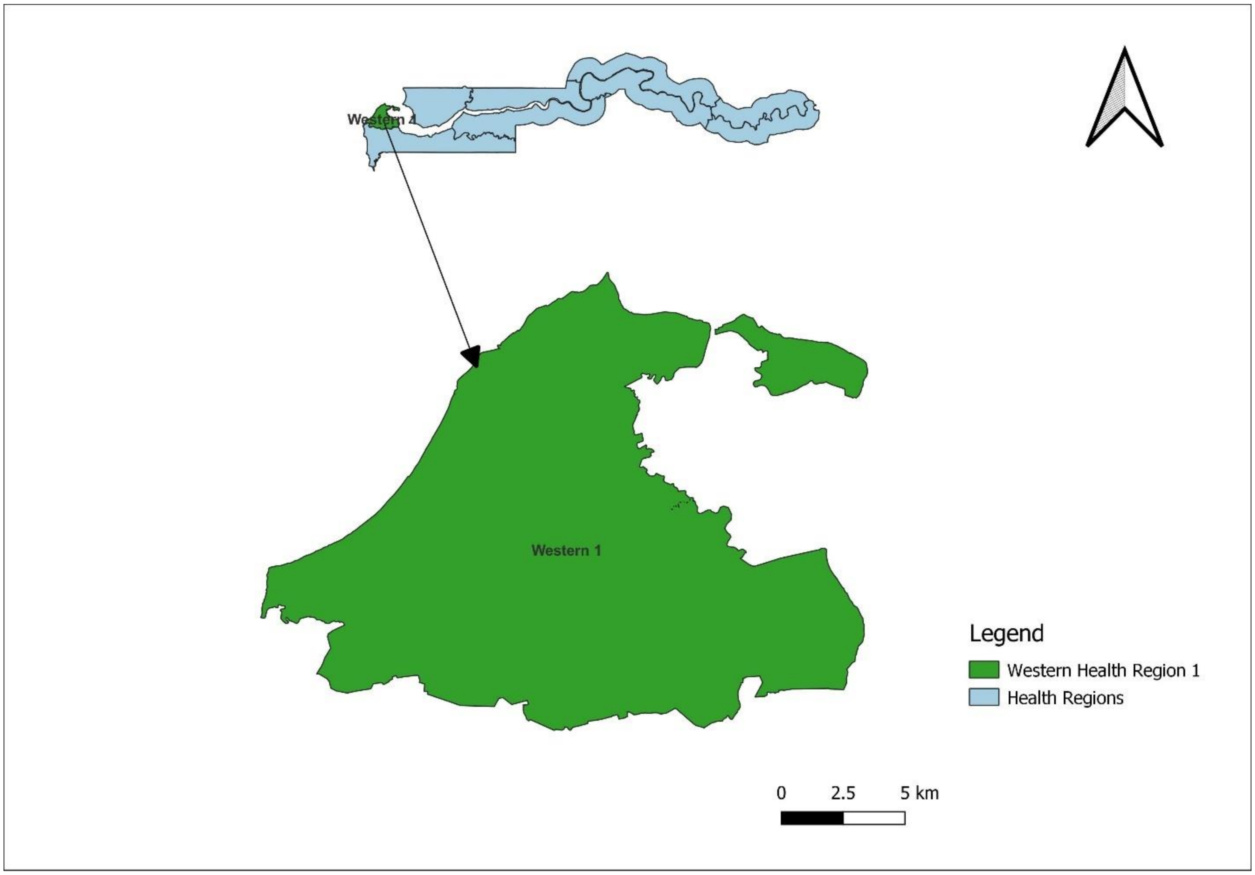

Figure 2. Map of Western Region 1 highlighting Kanifing Municipal Council

3.3 Study population

Study participants were any persons from the community who have clinical signs and symptoms of UTI attending the Out-Patients Department (OPD) of the hospital.

3.4 Sample Size Calculation

The following Cochran formula was used to determine the sample size of the study.

$\mathbf{n = Z^2 \frac{p(1-p)}{d^2}}$, Where n = required sample size, Z normal deviation = 1.96 which correspond to 95% confidence interval, *P* = the estimated attribute that is present in the targeted population, 0.5= 50% (an assumed estimation due to lack of data on CA-UTI in The Gambia), d = desired level of precision, 0.05 (Kasiulevičius et al., 2006). Assuming the prevalence of UTI is 50%, the minimum sample size therefore was obtained using the formula below. An assumption of 50% prevalence is used to compute the study sample size, because of a paucity of data on UTI in The Gambia.

$n = 1.96^2 * \frac{0.5(1-0.5)}{0.05^2}$ = 3.8416(0.5*0.5)/0.0025 = 384

Consequently, a total of 422 study participants were enrolled in the study including the 10% dropout (Fofana, 2016).

3.5 Sampling methods.

A purposive sampling method was used in the study to enroll study participants. The study protocol was explained to clinicians at the OPD before starting the study. Clinically suspected UTI patients were identified in the hospital's OPD with the assistance of clinicians and referred to the laboratory for confirmation. Clinicians selected study participants who had clinical symptoms of CA-UTI and met the inclusion and exclusion criteria. Patients with a clinical diagnosis of CA-UTI were given consent to participate. After administering the informed written consent form, questionnaires were administered by the principal investigator and research assistants. Patients were guided on the correct way of urine collection for culture. The inclusion and exclusion criteria to include study participants were strictly followed to select participants. The selection of the study participants was followed until the sample size was obtained.

3.6 Study Criteria

3.6.1 Inclusion Criteria

All OPD patients with a clinical diagnosis of suspected UTI, with or without signs and symptoms of the infection.

3.6.2 Exclusion Criteria

Among the OPD patients suspected of UTI pregnant mothers who were in labour or persons already on antibiotic treatment were excluded from the study (Priyadharshana *et al.*, 2019).

3.7 Specimen Collection Techniques

The sample collection for this study was done with the support of clinicians stationed at the OPD. For suspected patients who met the inclusion criteria, a clean, sterile screw-cap labeled container was given to patients to collect clean-catch midstream urine. The container was marked on the graduate measure to collect the right volume of a urine sample. A volume of 10-20 ml of urine specimen was requested from each patient. Handwashing and cleaning the region surrounding the urethral opening with clean water, drying with sterile gauze, and collecting the urine with the labia kept apart were described to female patients. For male patients, wash hands before collection and collect urine in the middle of the urine flow. The midstream is collected to ensure that the sample collected is not contaminated with the skin flora, which may lead to misleading results. For children younger than two years and who cannot produce urine under with parents/guardian help, urine samples were collected by transurethral catheterization performed by a qualified clinician. For children who were more than two years old, the procedure of collecting mid-stream samples of urine was thoroughly explained to their parents or escort for guidance, to ensure the correct collection of a urine sample (Pouladfar et al., 2017). The collected samples were analyzed within one hour after collection (Pietrucha-Dilanchian & Hooton, 2016).

3.8 Data collection Tool and Quality Assurance

A structured questionnaire was used to obtain data from consented patients on; socio-demographic characteristics, history of UTI in the last month, catheterization, hospitalization, self-medication, antibiotic consumption in the last month, buying antibiotics from street vendors/local pharmacy without medical prescription, finishing dosage of the antibiotics, and many more as shown in the appendix. The questionnaires were pre-tested from the hospital prior to the start of the study. In this process, 10% of the sample was selected to represent the population for the piloting. This was conducted to ensure the questions are standardized and can be modified if the necessary before data collection.

3.9 Study Variables

The dependent variable is the presence of significant uropathogenic bacterial isolates among patients diagnosed with CA-UTI. The independent variables were; the age of the patient, sex of the patient, educational level, history of UTI, antibiotic consumed in the last three months, buying antibiotics from street vendors/local stores, self-medication, sharing of unfinished antibiotics with someone, catheterization, diabetes status and history of hospitalization in the last three months (Table 1).

Table 1. Variables description that was used in the study

Variables		Indicators	Types of variables
Dependent Variable	Uropathogenic isolates	Bacterial Isolates with significant growth of $\geq 10^5$CFU	categorical
Independent Variables	Age	Age of participant at last birthday	continuous
	Sex	Male or female	categorical
	Employment (income)	Working	categorical
	Educational status	Formal education	categorical
	Marital status	Married or single	categorical
	Pregnancy status	Pregnant or not pregnant for female participants	categorical
	Medical Illness (diabetes)	Diabetic	categorical
	History of hospitalization	Hospitalized in the last three months	categorical
	History of UTI	UTI in the last three months	categorical
	History of Catheterization	Catheterization in the last month	categorical
	Wash hands with water and soap after visiting the toilet	Sanitation	Categorical
	Complete dosage of prescribed antibiotics	Antibiotic usage	categorical
	Antibiotics consumed in the last three months	Antibiotic usage	categorical
	Buying antibiotics from street vendors/local pharmacy	Antibiotics usage	categorical
	Self-medication	Antibiotic usage	categorical
	Sharing of left-over antibiotics	Antibiotics usage	categorical

3.10. Laboratory analysis of Urine sample

3.10.1. Isolation of Uropathogenic Bacterial Isolates

The collected sample of urine was mixed thoroughly and the lid of the container was removed before inoculation. A calibrated loop designed to deliver a known volume of 0.01mL was used to inoculate the collected urine sample on Cysteine Lactose Electrolytes Deficient (CLED) agar plates and incubated at 37°C for 18-24 hours within one hour after sample collection. After incubation, the number of isolated bacterial colonies was counted and multiplied by 1000 for the estimation of bacterial load per milliliter of the urine sample (Bailley and Scotts, 2014.). A specimen was considered positive for UTI if the isolates cultivated are a concentration of $\geq 10^5$cfu/ml. Colony morphology on CLED was observed for the identification of the uropathogenic bacteria. After 24hrs, bacterial colonies with pure and significant growth were further confirmed using standard biochemical tests (Muray, 2007; Pietrucha-Dilanchian & Hooton, 2016)

3.10.2. Biochemical Reaction

Presumptive isolates were confirmed following their biochemical reaction, such as Analytical Profile Index 20E (API 20E), indole production, Simmons Citrate, Urease, catalase, oxidase and Voges-Proskauer(Sharif *et al.*, 2016).

For API 20E, commercial biochemical test kits (bioMerieux API) were used. The API test strips consist of cupules containing dehydrated substrates to detect the enzymatic activity by inoculation of organisms. A bacterial suspension isolated from the urine samples was used to rehydrate each of the wells and the strips were incubated at 37^0C for 24 hours. During incubation, metabolism produced color changes that are either spontaneous or revealed by the addition of reagents. All positive and negative test results were compiled to obtain a profile number. The test results are entered into an online database to determine the bacterial identity (The Global Health Network, 2013).

3.10.3. Antimicrobial Susceptibility Testing

Antimicrobial Susceptibility Testing (AST) was performed on each of the confirmed isolates using Kirby Bauer's disc diffusion technique according to Clinical Standard Institute (CLSI) guidelines (Bauer et al., 1978; CLSI, 2020). A few well-isolated colonies from an overnight culture were selected, transferred to a tube with 5ml of sterile saline solution and emulsified inside the tube. The organism suspension was compared with a turbidity standard, McFarland turbidity standard 0.5. A sterile cotton swab was placed in the inoculum suspension and swirled several times to absorb it. To avoid too much fluid content from the swab, the swab was placed against the side of the tube wall and applied moderate pressure. The standard inoculum was swabbed on Mueller Hinton (Oxoid) agar plates and allowed to soak for 2 to 5 minutes. Antibiotics disc was aseptically placed on the media surface and press gently with sterile forceps, then incubated at 37^0C for 24 hours. The discs that were used for the disc diffusion assay contain a standardized known concentration of antimicrobial agents. On incubation, the bacteria grow on the plate areas except those around the drugs to which they show sensitivity. A zone of inhibition was created around the disc as a result of the antimicrobial agent diffusion and inhibits the growth of isolates. These zone of inhibition were measured using a ruler and results were interpreted as Resistance, Intermediate and Sensitive using standardized guidelines as in (Table 2) (CLSI, 2020). The isolates were tested for their resistance using the following antibiotics that are locally available; Ampicillin (AMP 10µg), Cefotaxime (CTX 30µg), Cefotaxizime (CAZ 30µg), Cefoxitin (FOX30µg), Gentamycin (GEN) (10 µg), Nitrofurantoin (300 µg) Tetracycline (TET 15µg), Chloramphenicol (CHL 10µg), Nalidixic acid (NAL 30µg), Ciprofloxacin (CIP 5µg), sulfamethoxazole/trimethoprim (SXT 25µg), Erythromycin (E 15µg), Imipenem (I 10 µg) and Meropenem (MEM 10 µg) (Sanneh *et al*., 2018). In this study, we define multidrug resistance to be bacterial resistant to three or more antimicrobial classes (Magiorakos et al., 2012).

Table 2. Antimicrobial agents and interpretive criteria; Adopted from CLSI 2020

Antibiotic class	Group	Antibiotics	Disk concentration	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm		
				S	I	R
PENICILLIN	A	Ampicillin	10 µg	≥ 17	14-16	≤ 13
B-LACTAM AGENT	B	Amoxicillin-clavulanate	10 µg	≥ 18	14-17	≤ 13
CEPHALOSPORINS	B	Cefotaxime[2nd]	30 µg	≥ 26	23-25	≤ 22
	B	Cefoxitin[2nd]	30 µg	≥ 18	15-17	≤ 14
	C	Ceftazidime[3rd]	30 µg	≥ 21	18–20	≤17
CARBAPENEMS	B	Imipenem	10 µg	≥ 23	20–22	≤ 19
	B	Meropenem	10 µg	≥ 23	20–22	≤ 19
AMINOGLYCOSIDES	A	Gentamicin	10 µg	≥ 15	13–14	≤ 12
TETRACYCLINES	C	Tetracycline	30 µg	≥ 15	12–14	≤ 11
FLUOROQUINOLONE	B	Ciprofloxacin	5 µg	≥ 26	22–25	≤ 21
	O	Nalidixic acid	30 µg	≥ 19	14–18	≤ 13
PHENICOLS	C	Chloramphenicol	30 µg	≥18	13–17	≤12
NITROFURANS	U	Nitrofurantoin	300 µg	≥ 17	15–16	≤ 14
MACROLIDES		Erythromycin	10 µg	≥23	14-22	≤13
SULFONAMIDES AND TRIMETHOPRIM	B	Trimethoprim sulfamethoxazole	1.25/23.75 µg	≥16	11–15	≤10

3.11 Quality control

For quality control purposes the following standard isolates were used in the study; *Escherichia coli* American Type Culture Collection (ATCC) 25922, *Klebsiella pneumoniae* ATCC 700603. All the culture media were prepared following the manufacturer's guidelines. After preparation of CLED and Mueller Hinton media plates, sterility and performance were conducted. Control strains were run alongside every batch of AST being worked on to ensure the accuracy of tests done.

3.12 Data Processing and Analysis

The generated data were entered into a spreadsheet of Microsoft Excel, cleaned, coded and transferred to the STATA Corp version. 16.1. Dependent variable categories like "Negative" and "Positive" was coded as "0" and "1" whereas independent variables that have two categories for example "Yes" and "No" was coded as "1" and "2", while variables with more than two categories were coded as 1, 2, 3…

3.12.1 Descriptive Analysis

In the descriptive analysis continuous variable was analyzed into Inter Quartile Ranges (IQR), and median after checking for normal distribution of the data using both graphical and numerical methods. Categorical variables like culture result, demographic characteristic, risk factors and antibiotic usage was analyzed into percentages and frequencies. The susceptibility patterns from the AST result were also analyzed in proportion.

3.12.2 Inferential Analysis

A chi-square test and Fisher exact were used to compare the difference in the demographic characteristic, risk factors, antibiotic usage to culture results positive and negative. Bivariate logistic regression analysis was conducted to estimate the association between each of the independent variables and dependent variable (uropathogenic bacterial isolates) at 95% confidence interval. Multiple logistic regression models were used to further estimate the true association of variables that were statistically significant at bivariate analysis. Results were reported in odds ratios with its associated p-value and 95% confidence interval.

3.13. Ethical Consideration

Ethical approval was sought from the University of The Gambia, Research and Publication Committee (RePubliC) and obtained from The Gambia Government and Medical Research Council Joint ethical committee with a reference number **R021011**.

Permission to conduct the study at KGH was granted by the Chief Executive Officer and Head of the Laboratory department before the commencement of data collection. The study protocols were explained to the clinicians and laboratory technicians before the commencement of the study.

The objectives and benefits of the study were also explained to the participants before seeking consent. An oral presentation was conducted to brief participants about the type of data to be collected. The procedures for sample collection, which is non-invasive was also thoroughly explained to participants. Participants have the option to decline participation in the study, which is voluntary. For adult participants, a signed or thump stamp consent form was obtained. For children, parents' consent/assent for the child to participate was obtained. The signed or thump stamp consent forms obtained from consented patients were documented and strictly guarded.

CHAPTER FOUR

4.0 RESULTS

4.1 Background characteristics of study participants

A total of 422 patients with a median age of 30 years, (IQR= 30 to 40 years) participated in the study. Most of the study participants 82.5% (348/422) were females, and 67.5% (285/422) were married. Almost, half of the study participants had no formal education 46.2% (195/422) with 52.84% (223/422) being unemployed (Table 3).

Table 3. Demographic Characteristics of the study participants visiting Kanifing General Hospital, 2021.

Characteristics	Frequency	Percentage
Age groups		
≤10	7	1.7
11-20	67	15.9
21-30	157	37.2
31-40	89	21.1
41-50	46	10.9
51-60	28	6.6
61-70	17	4.0
≥71	11	2.6
Sex		
Male	74	17.5
Female	348	82.5
Marital status		
Single	123	29.2
Married	285	67.5
Divorce	14	3.3
Pregnancy Status		
Pregnant	67	19.3
Not pregnant	281	80.8
Level of Education		
No formal education	195	46.2
Primary	40	9.5
Secondary	123	29.2
Tertiary	64	15.2
Occupation		
Not employed	223	52.8
Self-employed	83	19.7
Civil servant	46	10.9
Student	70	16.6

4.2 Frequency Distribution of Risk factors

Among the 422 study participants, 67.3% (284/422) had experienced UTI in the previous month, and 58.1% (245/422) had used antibiotics for the previous UTI episode. More than half 57.8% (244/422) of the participants indicated that they completed the full course of antibiotics prescribed for them. Concerning sanitation, 76.8% (324/422) of the participants indicated that they practice basic hand hygiene with water and soap. One Hundred and sixty-one (38.15%) of the respondents said they purchase antibiotics from street vendors, 33.2% (140/422) had used antibiotics in the last three months and 32.2% (136/422) usually consumed antibiotics without a medical practitioner prescribing it. Table 4. illustrates the frequency distribution of risk factors among study participants.

Table 4. Frequency distribution of risk factors among study participants, Kanifing General Hospital, 2021. (n=422)

Variables	Frequency	Percentage
Medical illness (diabetes)		
Diabetic	70	16.6
Non-diabetic	352	83.4
Hospitalization Status		
Yes	43	10.2
No	379	89.8
Catheterization in the last month		
Yes	25	5.9
No	397	94.08
History of UTI		
Yes	284	67.3
No	177	32.7
Antibiotic consumed during last UTI episode		
Yes	245	58.1
No	177	41.9
Antibiotic used in the past three months without medical prescription		
Yes	140	33.2
No	282	66.8
Bought antibiotics from local pharmacy/street vendors		
Yes	161	38.2
No	261	61.8
Usually take antibiotics without medical prescription		
Yes	136	32.2
No	286	67.8
Complete taking your prescribed antibiotics		
Yes	244	57.8
No	178	42.2
Share antibiotics with family members or friends		
Yes	79	18.7
No	343	81.3
Handwashing with water and soap		
Yes	324	76.8
No	98	23.2

4.3 Bacterial Isolates

A total of 54 samples yielded significant positive growth of uropathogenic bacterial isolates. Thus, the overall prevalence of uropathogenic bacterial infection was 12.8% (54/422). The isolates consisted of five different bacteria; *Escherichia coli*, *Klebsiella* spp, *Pseudomonas aeruginosa*, *Proteus* spp and *Citrobacter* spp. The predominant bacterial isolates were *E. coli* 74.1% (40/54), followed by *Klebsiella* spp 18.5% (10/54) (Fig.3).

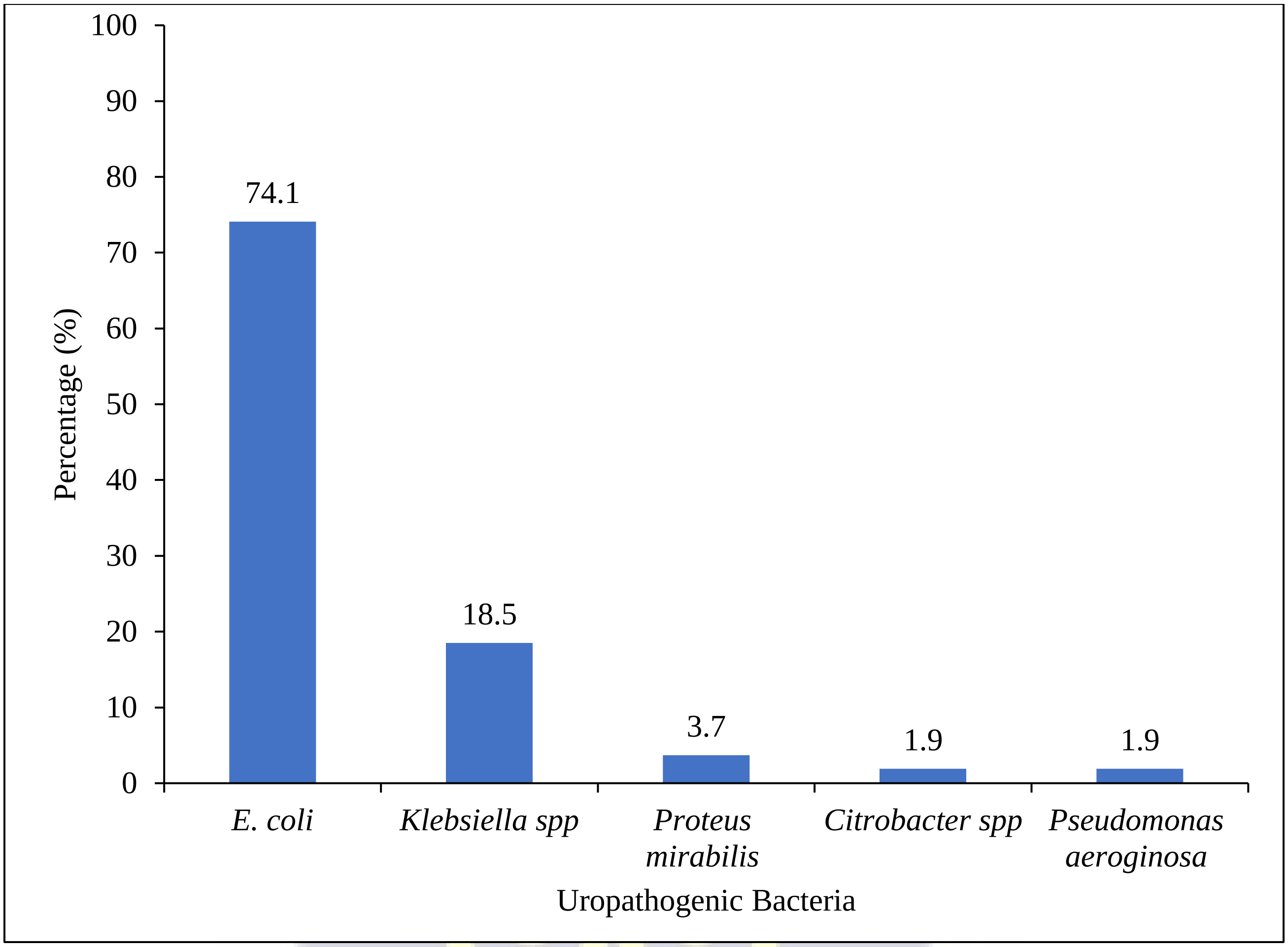

Figure 3. Isolates of uropathogenic bacteria isolated from study participants diagnosed with UTI, KGH, 2021

4.4 Distribution of Uropathogenic bacteria among tested patients by gender and age group.
As indicated earlier, 54 (12.8%) samples were positive for the presence of uropathogenic bacteria. These were distributed among all the age groups above 10 years. The highest occurrence, 25.93% (14/54) was found among the age groups (21-30 years) and (31-40 years) respectively. Followed by those in the age category (11-20 years), 20.37% (11/54). The lowest incidence occurred among those in the age category (51-60 years), 1.85% (1/54). Concerning the distribution of isolated bacteria to patients' sex, the majority of the isolates were from females, 94.44% (51/54) Fig.4.

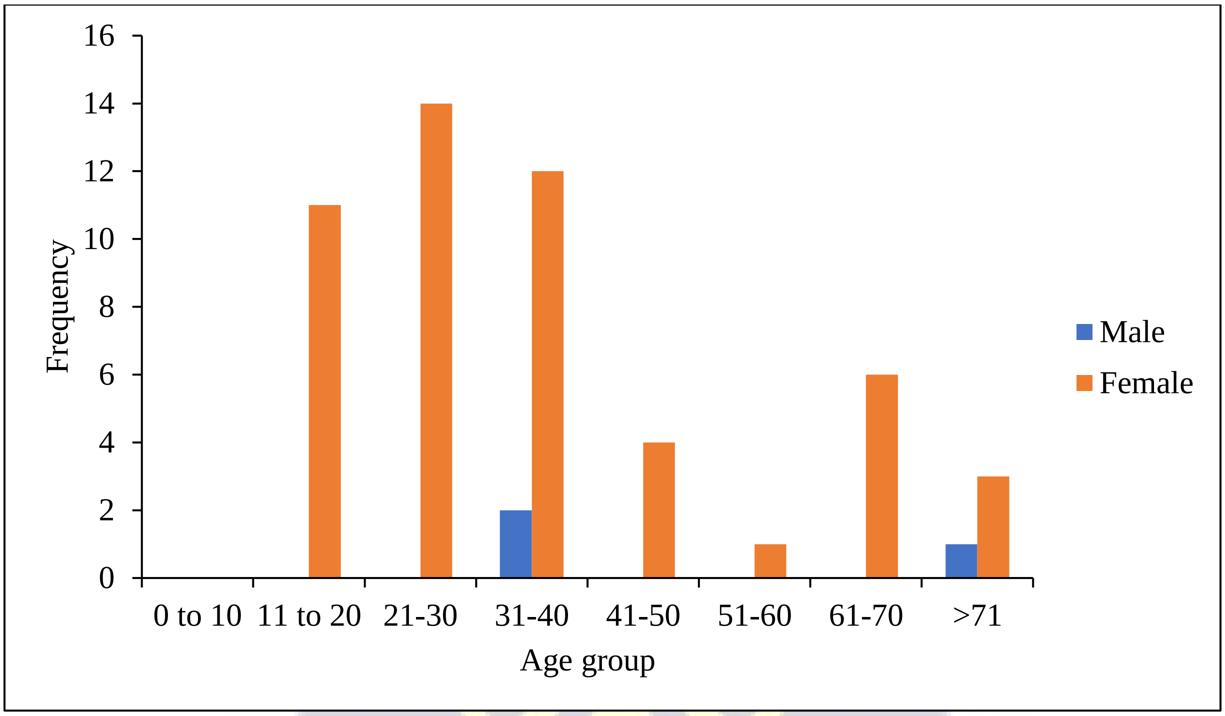

Figure 4. Distribution of uropathogenic bacteria isolates by sex and Age group at KGH, 2021.

4.5 Association between Demographic characteristics and Uropathogenic bacterial isolates
Females had a significantly greater incidence of uropathogenic bacterial isolates 14.7 % (51/348) than men 4.1% (3/74) (p= 0.012). Regarding marital status, 8.1%(10/123) of single people and 15.4%(44/285) of married people tested positive for uropathogenic bacteria. A high proportion of the isolates were observed for persons having no formal education, 15.9% (31/164) followed by having secondary education 15.4% (19/123). The observed difference for positive bacteria was

statistically significant (p= 0.005). However, there were no significant differences when positive culture and pregnancy status were compared (Table 5).

Table 5. Association between Demographic characteristics and uropathogenic bacteria isolates, KGH, 2021

Variable	Total n (%)	Culture Result: Negative Frequency (%)	Culture Result: Positive Frequency (%)	χ^2	P-value
Sex					0.012*
Male	74(17.5)	71(95.9)	3(4.1)		
Female	348(82.5)	297(85.3)	51(14.7)		
Marital status				6.23	0.044
Single	123(29.2)	113(91.9)	10(8.1)		
Married	285(67.5)	241(84.6)	44(15.4)		
Divorce	14(3.32)	14(100)	0		
Pregnancy Status				0.32	0.945
Pregnant	67(19.3)	57(85.1)	10(14.9)		
Not pregnant	281(80.7)	240(85.4)	41(14.6)		
Level of Education					0.005*
No formal education	164(84.1)	164(84.1)	31(15.9)		
Primary	40(9.5)	37(92.5)	3(7.5)		
Secondary	123(29.2)	104(84.6)	19(15.4)		
Tertiary	64(15.2)	63(98.4)	1(1.6)		
Occupation					0.014*
Not employed	223(52.8)	183(82.1)	40(17.9)		
Self-employed	83(19.7)	77(92.8)	6(7.2)		
Civil servant	46(10.9)	43(93.5)	3(6.5)		
Student	70(16.6)	65(92.9)	5(7.1)		

Note; *Fisher's exact p-value

4.6 Association between risk factors and Uropathogenic bacterial isolates

The prevalence of uropathogenic bacteria among patients who had a UTI within the previous month was 15.1% (43/284), (p = 0.039). Additionally, 17.4% (28/161), (p = 0.026) of the respondents who said they bought antibiotics from a local pharmacy or street vendor without a medical prescription had the infection. However, there were no significant differences between culture-positive and medical illness(diabetes), hospitalization in the last month, catheterization and sharing of antibiotics with family relations (Table 6a & 6b).

Table 6a. Association between risk factors and uropathogenic bacteria

		Culture result			
		negative	positive		
Variables	**Total n (%)**	**Frequency (%)**	**frequency**	χ^2	**P-value**
Medical illness (Diabetes)				0.6404	0.424
Diabetic	70(16.6)	59(84.3)	11(15.7)		
Non diabetic	352(83.4)	309(87.8)	43(12.2)		
Hospitalization in the last month				0.5205	0.471
Yes	43(10.2)	36(83.7)	7(16.3)		
No	379(89.8)	332(87.6)	47(12.4)		
Catheterization in the last month				2.9893	0.084
Yes	25(5.9)	19(76.0)	6(24.0)		
No	397(94.1)	349(87.9)	48(12.1)		
History of UTI in the past month				4.2784	**0.039**
Yes	284(67.3)	241(84.9)	43(15.1)		
No	138(32.7)	127(92.0)	11(8.0)		

Table 6b. Association between risk factors and uropathogenic bacteria

Variables	Total n (%)	Culture result: negative Frequency (%)	Culture result: positive Frequency (%)	χ^2	P-value
Antibiotic consumed during last UTI episode				1.8851	0.170
Yes	245(58.1)	209(85.3)	36(14.7)		
No	177(41.9)	159(89.8)	18(10.2)		
Had antibiotic in the past three months without medical prescription				0.8138	0.367
Yes	140(33.2)	125(89.3)	15(10.7)		
No	282(66.8)	243(86.2)	39(13.8)		
Bought and used antibiotics from local pharmacy/street vendors				4.9257	0.026
Yes	161(38.2)	133(82.6)	28(17.4)		
No	261(61.8)	235(90.0)	26(10.0)		
Usually take antibiotic without medical prescription				2.0548	0.152
Yes	136(32.2)	114(83.8)	22(16.2)		
No	286(67.8)	254(88.8)	32(11.2)		
Complete taking your prescribed antibiotics				0.6716	0.412
Yes	244(57.8)	210(86.1)	34(13.9)		
No	178(42.2)	158(88.8)	20(11.2)		
Share antibiotics with family members or friends				3.3386	0.068
Yes	79(18.7)	64(81.0)	15(19.0)		
No	343(81.3)	304(88.6)	39(11.4)		
Handwashing with water and soap				0.0348	0.852
Yes	324(76.8)	282(87.0)	42(13.0)		
No	98(23.2)	86(87.8)	12(12.2)		

4.7 Overall Resistance patterns of uropathogenic bacterial isolates to antibiotics

All the 54 uropathogenic bacterial isolates were subjected to AST with eleven different classes of antibiotics (penicillin, cephalosporins, β-lactams, fluoroquinolones, carbapenems, aminoglycosides, tetracycline, macrolides, Nitrofurans, phenicol and sulfonamides/trimethoprim) making a total of 15 different antibiotics. Among the isolates tested against various antibiotics, 96.3% (52/54) were resistant to Erythromycin and 87.0% (47/54) were resistant to Ampicillin. A greater proportion of the bacteria isolated were observed to be resistant to Tetracycline and Trimethoprim/Sulfamethoxazole, 75.9% (41/54) and 77.8% (42/54) respectively. In addition, 61.1% (33/54) and 53.9% (29/54) of the isolates were also found to be resistant to Ciprofloxacin and Nalidixic acid respectively. None of the isolates were resistant to Imipenem and Meropenem (Table.7).

Table 7. Overall Susceptibility Pattern of uropathogenic bacteria isolated from study participants with positive CA-UTI, Kanifing General Hospital, 2021 (N=54)

Antibiotics	Sensitive n(%)	Resistance n(%)	Intermediate n(%)
Amoxicillin-clavulanic acid (AMC 30µg)	37 (68.5)	8 (14.8)	9 (16.7)
Cefotaxime (CTX 30µg)	39 (72.2)	14 (25.9)	1 (1.9)
Ceftazidime (CAZ 30µg)	41 (75.9)	11 (20.4)	2 (3.7)
Cefoxitin (FOX 30µg)	52 (96.3)	0 (0.0)	2 (3.7)
Ampicillin (AMP 10µg)	4 (7.4)	47 (87.0)	3 (5.6)
Nitrofurantoin (F 300µg)	42 (77.8)	11 (20.4)	1 (1.9)
Gentamycin (GEN 30µg)	39 (72.2)	15 (27.8)	0
Ciprofloxacin (CIP 5µg)	33 (61.1)	21 (38.9)	0
Tetracycline (TET 15µg),	11 (20.4)	41 (75.9)	2 (3.7)
Chloramphenicol (CHL 10µg)	42 (77.8)	8 (14.8)	4 (7.4)
Trimethoprim/Sulfamethoxazole (SXT1.25/23.75µg)	12 (22.2)	42 (77.8)	0
Nalidixic (NA 30 µg)	23 (42.6)	29 (53.7)	2 (3.7)
Erythromycin (E 15µg)	0	52 (96.3)	2 (3.7)
Meropenem (MEM 10µg)	54 (100)	0	0
Imipenem (I 10µg)	54 (100)	0	0

4.8 Resistance patterns among uropathogenic bacteria by isolate

E. coli isolates were resistance to Erythromycin 95% (36/40) followed by Ampicillin 90% (36/40), sulphamethoxazole/trimethoprim 80% (32/40), Tetracycline 77.50% (31/40) and Nalidixic acid 52.5% (21/40). Similarly, isolates of *Klebsiella* spp exhibited resistance to Erythromycin 100% (10/10), Ampicillin 90% (9/10), Tetracycline 80% (8/10), Trimethoprim/sulphamethoxazole 70% (7/10), Cefotaxime 60% (6/10). Ciprofloxacin, Nitrofurantoin and Gentamycin, a resistance of 50% (5/50) was observed respectively. For *Proteus mirabilis*, 50% (1/2) of the isolates were resistant to sulphamethoxazole/trimethoprim, Nitrofurantoin, Gentamycin, Ciprofloxacin and Tetracycline respectively. Moreover, for *Citrobacter* spp and *Pseudomonas* spp isolates, 100% (1/1) resistance was observed in Ampicillin, Erythromycin and Trimethoprim/sulphamethoxazole (Table 8).

Table 8. Antimicrobial resistance Patterns among uropathogenic bacteria per isolate, Kanifing General Hospital, 2021

Antimicrobial agent	***E. coli*** **n = 40, (%)**	***Klebsiella*** **spp n = 10, (%)**	***Proteus mirabilis*** **n = 2, (%)**	***Citrobacter*** **spp n = 1, (%)**	***Pseudomonas aeruginosa*** **n = 1, (%)**
Amoxicillin-clavulanic acid (AMC 30µg)	6(15)	3(30)	1(50)	0(0)	0(0)
Cefotaxime (CTX 30µg)	8(20)	6(60)	0(0)	0(0)	0(0)
Ceftazidime (CAZ 30µg)	6(15)	5(50)	0(0)	0(0)	0(0)
Cefoxitin (FOX 30µg)	0	0	0(0)	0(0)	0(0)
Ampicillin (AMP 10µg)	36(90.0)	9(90)	1(50)	1(100)	1(100)
Nitrofurantoin (F 300µg)	5(12.5)	5(50)	1(50)	0(0)	0(0)
Gentamycin (GEN 30µg)	9(22.5)	5(50)	1(50)	0(0)	0(0)
Ciprofloxacin (CIP 5µg)	15(37.5)	5(50)	1(50)	0(0)	0(0)
Tetracycline (TET 15µg),	31(77.5)	8(80)	1(50.0)	1(100)	0
Chloramphenicol (CHL 10µg)	5(12.5)	2(20.0)	1(50)	0(0)	0(0)
Trimethoprim/Sulfamethoxazole (SXT1.25/23.75µg)	32(80)	7(70)	1(50)	1(100)	1(100)
Nalidixic (NA 30 µg)	21(52.5)	6(60)	1(50)	1(100)	0(0)
Erythromycin (E 15µg)	38(95.0)	10(100)	2(100)	1(100)	1(100)
Meropenem (MEM 10µg)	0(0)	0(0)	0(0)	0(0)	0(0)
Imipenem (I 10µg)	0(0)	0(0)	0(0)	0(0)	0(0)

N= number of uropathogenic isolates

4.9 Multidrug resistance rates of uropathogenic bacteria by isolates

Of the 54 uropathogenic bacterial isolates tested, 88.9% (48/54) showed resistance to at least one of the fifteen antimicrobial agents used. Of this number, 1.9% (1/54) showed resistance primarily to one antibiotic only, 11.1% (6/54) were resistant to two antibiotics, 13.0% (7/54) were resistant to three antibiotics, 16.7% (9/54) were resistant to four antibiotics and 57.4% (31/54) were resistant to five or more antibiotics. Overall, 87.0% (47/54) of the isolates were multidrug-resistant (MDR) as they were resistant to three or more antimicrobial classes. The highest frequency of MDR was observed in *Klebsiella* spp (9 isolates) *E. coli* (35 isolates). For *Pseudomonas aeruginosa* no MDR was found (Table 9).

Table 9 Distribution of multidrug resistance among uropathogenic bacteria by isolate type, Kanifing General Hospital, 2021

Isolates	Degree of Resistance					Total MDR (≥R3)
	R1 n (%)	R2 n (%)	R3 n (%)	R4 n (%)	≥R5 n (%)	
E. coli **(N= 40)**	1(2.5)	4(10.0)	5(12.5)	7(17.5)	23(57.5)	35(87.5)
Klebsiella **spp (N= 10)**	0(0)	1(10.0)	1(10.0)	2(20.0)	6(60.0)	9(90.0)
Proteus mirabilis **(N=2)**	0(0)	0(0)	1(50.0)	0(0)	1(50.0)	2(100)
Citrobacter **spp (N= 1)**	0(0)	0(0)	0(0)	0(0)	1(100)	1(100)
Pseudomonas aeruginosa **(N= 1)**	0(0)	1(100)	0(0)	0(0)	0(0)	0(0)
Total (N=54)	1(1.9)	6(11.1)	7(13.0)	9(16.67)	31(57.4)	47(87.0)

Note: R1-5: Resistance to 1, 2, 3, 4 and ≥5 antibiotics, ≥R3 resistance to 3 or more antibiotics classes

4.10 Risk factors for Uropathogenic Bacteria

The result shows that 14.7% (51/348) of females and 4% (3/74) of males had significant growth of uropathogenic bacteria. In the bivariate logistic analysis, females had a 4.1 times larger chance of having uropathogenic bacterial infection compared to males (95% CI 1.23-13.30) (Table 10). This association was statistically significant at 95% confidence interval (p=0.021). For the Occupational status of study participants recruited, it was observed that 17.9% (40/223) of those not employed were affected, while 7.2% (6/83), 6.5% (3/46) and 7.1% (5/70) of those with a self-employed, civil servant and student categories were affected respectively. The results in the bivariate analysis showed that unemployed individuals had 3.1 times greater odds of developing UTI as compared to those who were employed or being a student. This, however, is not statistically significant at 95% confidence interval OR= 3.13 (95% CI 0.93-10.61). Out of the 422 study participants, 195 had no formal education, of which 15.9% (31/195) were infected with uropathogenic bacteria. Also, those who had a formal education; primary 7.5% (3/40) and secondary 15.5% (19/123) had urine culture positive for UTI. The bivariate logistic analysis showed that, individuals who had no formal education have 11.90 times increased odds of having UTI as compared to those who had formal education, primary or tertiary, OR= 11.90 (95% CI 1.59-89.09). This association was statistically significant (p=0.016). Analysis of our results showed that 15.1% (43/284) of the participants who had a history of UTI were affected with uropathogenic bacteria. It was observed that in the bivariate logistic regression analysis individuals who had a history of UTI have 2.06 times greater odds of developing uropathogenic bacteria compared to individuals who did not report having a history of UTI, OR=2.06 (95% CI 1.03-4.13). This association was statistically significant at 95% confidence interval (p=0.042). For catheterization, 24.0% (6/25) had a positive significant culture for uropathogenic isolates of the participants who responded of been catheterized in previous months. The bivariate logistic regression shows that individuals who were catheterized had 2.29 times increased odds of acquiring uropathogenic bacterial isolates as compared to participants who were not catheterized OR = 2.29 (95% CI 0.87-6.03). This association is not statistically significant at 95% confidence interval ($p=0.092$) (Table 10).

Table 10 Association between risk factors and urinary tract infections, Kanifing General Hospital, 2021

		Uropathogenic Bacteria			
Variables	**Total n (%)**	**Negative Frequency (%)**	**Positive Frequency (%)**	**cOR(95% CI)**	**p-value**
Sex					
Male	74(17.5)	71(96.0)	3(4.0)	1	
Female	348(82.5)	297(85.3)	51(14.7)	4.1(1.23-13.30)	0.021
Occupation					
Not employed	223(52.8)	183(82.1)	40(17.9)	3.1(0.93-10.61)	0.066
Self-employed	83(19.7)	77(92.8)	6(7.2)	1.11(0.26-4.70)	0.880
Civil servant	46(10.9)	43(93.5)	3(6.5)	1	
Student	70(16.6)	65(92.9)	5(7.1)	1.10(0.25-4.85)	0.897
Level of education					
No formal education	164(84.1)	164(84.1)	31(15.9)	11.91(1.59-89.09)	0.016
Primary	40(9.5)	37(92.5)	3(7.5)	5.1(0.51-50.91)	0.164
Secondary	123(29.2)	104(84.5)	19(15.5)	11.5(1.50-88.08)	0.019
Tertiary	64(15.2)	63(98.4)	1(1.6)	1	
Marital status					
Married	285(67.5)	241(84.6)	44(15.4)	2.06(1.00-4.24)	0.049
Single	123(29.2)	113(91.9)	10(8.1)	1	
Divorce	14(3.32)	14(100)	0(0)		
Medical illness (Diabetes)					
Diabetic	70(16.6)	59(84.3)	11(15.7)	1.34 (0.63-2.74)	
Non-Diabetic	352(83.4)	309(87.8)	43(12.2)	1	0.425
Hospitalization in the last month					
Yes	43(10.2)	36(83.7)	7(16.3)	1.37 (0.58-3.26)	0.472
No	379(89.8)	332(87.6)	47(12.4)	1	
Catheterization in the last month					
Yes	25(5.9)	19(76.0)	6(24.0)	2.29(0.87-6.03)	0.092
No	397(94.1)	349(87.9)	48(12.1)	1	
UTI history					
Yes	284(67.3)	241(84.9)	43(15.1)	2.05(1.03-4.13)	0.042
No	138(32.7)	127(92.0)	11(8.0)	1	

cOR= crude odds ratio, CI = Confidence Interval, p-value ≤0.05 is statistically significant, 1 reference group

4.11 Antibiotics Usage

Out of the 422 study participants, 245 had consumed antibiotics during their last UTI episode. Of which 14.7% (36/245) were positive for urine culture. The bivariate logistic regression analysis observed was OR= 1.52 (95% CI 0.83-2.77). This indicates that individuals who used antibiotics in their last UTI episode have 1.52 times increased odds of acquiring uropathogenic bacteria isolates compared to individuals who did not use antibiotics. This association was not statistically significant at 95% confidence interval (p=0.172).

In a bivariate logistic regression analysis, antibiotic use in the previous three months was found to be protective against uropathogenic bacteria OR = 0.74 (95% CI 0.40-1.41). The results showed that participants who were on antibiotics in the last three months have 26% lesser odds of developing uropathogenic bacterial isolates compare to participants who did not consume antibiotics in the past three months. This was not statistically significant at 95% CI (p=0.368).

Among the study participants, 161 individuals responded to buying antibiotics from street vendors/local pharmacies without medical prescriptions. Among which 17.4% (28/161) were positive for uropathogenic bacteria. Results from the bivariate logistic analysis indicate that respondents who purchased antibiotics from street vendors/local pharmacies have 1.9 times greater odds of developing uropathogenic bacterial isolates compared to individuals who did not buy antibiotics from street vendors/local pharmacies without medical prescription, OR= 1.9 (95% CI 1.07-3.38). This association was statistically significant at 95% confidence interval level (p=0.028) (Table 11)

Table 11 Antibiotics usage factors associated with Uropathogenic among UTI patients, Kanifing General Hospital, 2021

Uropathogenic Bacteria					
Variable	**Total n (%)**	**Negative Frequency (%)**	**Positive Frequency (%)**	**cOR(95% CI)**	**p-value**
Antibiotic consumption during that UTI					
Yes	245(58.1)	209(85.3)	36(14.7)	1.52 (0.83-2.78)	0.172
No	177(41.9)	159(89.8)	18(10.2)	1	
Had antibiotics in the past three months without a medical prescription					
Yes	140(33.2)	125(89.3)	15(10.7)	0.74 (0.39-1.41)	0.368
No	282(66.8)	243(86.2)	39(13.8)	1	
Bought and used antibiotics from local pharmacy/street vendors					
Yes	161(38.2)	133(82.6)	28(17.4)	1.90 (1.07-3.38)	0.028
No	261(61.8)	235(90.0)	26(10.0)	1	
Usually take antibiotics without medical prescription					
Yes	136(32.2)	114(83.8)	22(16.2)	1.53 (0.85-2.75)	0.154
No	286(67.8)	254(88.8)	32(11.2)	1	
Finished dosage prescribed antibiotics					
Yes	244(57.8)	210(86.1)	34(13.9)	1.27 (0.71-2.30)	0.413
No	178(42.2)	158(88.8)	20(11.2)	1	
Share antibiotic with family members or friends					
Yes	79(18.7)	64(81.0)	15(19.0)	1.83 (0.95-3.51)	0.064
No	343(81.3)	304(88.6)	39(11.27)	1	
Handwashing with soap and water					
Yes	324(76.8)	282(87.0)	42(13.0)	1.07 (0.54-2.12)	0.852
No	98(23.2)	86(87.8)	12(12.2)	1	

Note: cOR= crude odds ratio, CI = Confidence Interval, p-value ≤0.05 is statistically significant, 1 reference group

4.12 Multiple Logistic Regression results for associations of Uropathogenic bacteria among participants

A stepwise forward elimination was conducted to select a variable for the Multiple logistic regression analysis. The variables that remain in the final model after using the stepwise forward elimination include; sex, educational status, history of UTI and purchasing of antibiotic from street vendor/local pharmacy without medical prescription. Four variables were statistically significant and strongly associated with the development of uropathogenic bacteria at 95% CI ($p \leq 0.05$) (Table 12). These variables include; female gender, educational status, history of UTI and purchasing antibiotics from street vendors/local pharmacies without medical prescription.

Table 12. Risk factors and antibiotics usage factors associated with UTI among participants attending Kanifing General Hospital, 2021

Variables	Uropathogenic Bacteria		Adjusted odds (95% CI)	P-value
	Negative Frequency (%)	Positive Frequency (%)		
Sex				
Male	71 (96.0)	3 (4.0)	Reference	
Female	297 (85.3)	51 (14.7)	6.87 (1.7-28.0)	0.007
Level of education				
No formal education	164 (84.1)	31 (15.9)	8.58 (1.1-67.1)	0.041
Primary	37 (92.5)	3 (7.5)	5.95 (0.6-62.7)	0.138
Secondary	104 (84.5)	19 (15.5)	10.69 (1.35-84.82)	0.025
Tertiary	63 (98.4)	1 (1.6)	Reference	
UTI history				
Yes	241(84.9)	43 (15.1)	2.62 (1.05-5.16)	0.037
No	127 (92.0)	11 (8.0)	Reference	
Bought and used antibiotics from local pharmacy/street vendors				
Yes	133 (82.6)	28 (17.4)	2.0 (1.07-3.74)	0.031
No	235 (90.0)	26 (10.0)	reference	

aOR= adjsuted odds ratio, CI = Confidence Interval, p-value ≤0.05 is statistically significant

CHAPTER FIVE

5.0 DISCUSSION

The study determined the prevalence, etiology, antibiotic susceptibility patterns of uropathogenic bacterial isolates and associated factors among outpatients attending the Kanifing General Hospital in The Gambia. This current study provides valuable laboratory data that assists clinicians to determine which antibiotics to employ in the treatment of urinary tract infections and related diseases. The prevalence of Uropathogenic bacteria among patients attending Kanifing General Hospital was 12.8% similar to findings reported in Madagascar, 12.9% by Randrianirina et al., (2007). However, the prevalence in our current study was observed to be higher than was reported in an earlier study in The Gambia which recorded, 9% and in Ghana 10% (Sumareh et al 2014; Donkor et al., 2019). Our study recorded prevalence two times lower than was found in a study in Senegal, 26.7% by Barry et al., (2017) and in Ethiopia (21.1%) by Gebremariam et al., (2019). This lower prevalence observed in our study compared to the one done in Senegal could be a result of the study duration and methodology used. Also, the low prevalence in the study could be attributed to the patients' tradition of going to local pharmacies for medical checkups and self-medication due to the easy accessibility of over-the-counter antibiotics in The Gambia. This could affect the interpretation of urine culture results as the antibiotic may inhibit bacterial growth. Moreover, the disparity between studies could be as a result of the difference in sample size, study population, methodology and traditional practice of the study population (Gebremariam et al., 2019; Tesfa et al., 2021).

In this study, the majority of uropathogenic bacterial were isolated from female patients, as UTIs are common in females due to the shorter nature of the female urethra. These findings are in accordance with those of prior studies enrolling outpatients (Odoki et al., 2019; Randrianirina et al., 2007; Tesfa et al., 2021). Also, among the isolated uropathogenic bacteria, all *E. coli* isolates were from female patients. This high prevalence of *E. coli* among females may be due to the shorter urinary tract and proximity of the vagina to the anus (Greenwood, 2012). The other factor that can contribute to the high prevalence of *E. coli* among the female gender could be as a result of the intrinsic virulence of *E. coli* for urinary tract colonization. Whereby, it has abilities to attach to the urinary tract using pili, multiple types of fimbriae and cytotoxic necrotizing factors and colonize the urinary tract (Brady et al., 2018).

About the distribution of isolated bacteria among patients' age groups, sexually active adults had a higher incidence followed by young children than elderly. Our findings are in agreement with a study conducted in Libya that reported 35% in sexually active individuals and 10.6% in the elderly (Mohammed et al., 2016). However, UTI was found in 16.55% of elderly women (Paulo et al., 2012). The possible causes of the high incidence of UTI among young adults and elderly may be attributed to sexual activity in young adults and urinary tract anomalies, recurrent UTI, urinary incontinence, and decline in immune system in the elderly (Foxman, 1990; Martha et al., 2018; Vasudevan, 2014).

Regarding the causative agents in this study, all the isolates were Gram-negative bacteria and mostly *Enterobacteriaceae*. Our study found *E. coli* as the main causative uropathogenic bacterial isolates with 74.07% (40/54). This result is in agreement with other studies in Africa; Uganda 41.9% (Odoki et al., 2019), Ghana 48.39% (Donkor et al., 2019) and Madagascar 67.2% (Randrianirina et al., 2007). *Klebsiella* spp was the second-highest prevalence causative organism for UTI with 18.5% (10/54). The high frequency of *Klebsiella* spp is not exceptional to this study. Previous studies in Accra (Ghana) 2019, Isfahan (Iran) 2021 and Asian Global Prevalence Study of Infection in Urology (GPIU) data 2018 reported high rates of *Klebsiella* spp of 16.1%, 8% and 14.1% respectively (Choe et al., 2018; Donkor et al., 2019; Mostafavi et al., 2021). The other uropathogenic bacterial isolates found in this study; *Proteus mirabilis* 3.7% (2/54), *Citrobacter* spp 1.8% and *Pseudomonas aeruginosa* 1.8% had low prevalence which is comparable with other studies done by Magliano in Italy, Atul in India and Barry in Senegal (Barry et al., 2017; Kothari & Sagar, 2008; Magliano et al., 2012). The differences and similarities in the type and distribution of uropathogenic bacterial isolates from country to country may be due to different factors such as; laboratory procedures, health practices, patient wellbeing, personal hygiene and environmental conditions.

5.1 Overall Antimicrobial Susceptibility patterns of uropathogenic isolates

The most active antibiotics in the study were carbapenems (imipenem and meropenem) and cephalosporin (ceftazidime, cefoxitin and cefotaxime). In addition, Nitrofurantoin, which is among the recommended antibiotics to treat uncomplicated UTI in The Gambia shows moderate sensitivity. This finding could suggest the review and readjustment of the treatment guidelines for the empiric treatment of uncomplicated UTI and patients with severe symptoms. However, carbapenems are effective drugs for the treatment of MDR isolates especially among *Enterobacteriaceae*, resistance to this class of antimicrobial could be found in The Gambia as reported by Sanneh et al., (2018). Hence, it should be saved for severely ill patients to avoid its increasing resistance.

Ciprofloxacin and other fluoroquinolones are among the recommended and broadly prescribed antibiotics for the therapeutic of UTI (Ana L. Flores-Mireles, Jennifer N. Walker, Michael

Caparon, 2015). This current study found a moderate sensitivity rate to ciprofloxacin 61.11% and Nalidixic acid 42.59%. Therefore, this agent should be reserved and only be used after confirmation of susceptibility patterns of the bacteria causing the infection. These findings are consistent with other reports previously conducted in Ethiopia (Tesfa et al., 2021) and in contrast with a study from Madagascar (Randrianirina et al., 2007)

Amongst the aminoglycosides, the sensitivity pattern of isolates to Gentamicin was 72.22% (39/54). This finding concords with a study in Nigeria, 85.5% sensitive (Uwaezuoke & Ogbulie, 2006) but contrast to a previous study in Ghana that reported about 32.26% susceptible (Donkor et al., 2019).

The analysis found that the isolated bacteria were highly resistant to ampicillin, tetracycline and trimethoprim/sulfamethoxazole. Therefore, making these antibiotics unsuitable to treat UTI empirically. In our study, the majority of the isolates 87.0% (47/54) showed resistance to ampicillin, as reported in previous studies in Ghana 97.6% and 95.2% bacterial resistance to ampicillin and Co-trimoxazole respectively (Fofana, 2016) and India (Akram et al., 2007). The international clinical practice guidelines suggested that TMP-SMX should not be used empirically for the treatment of uncomplicated UTI in women if the resistance prevalence is known to exceed 20% (Colgan et al., 2011). In developing countries including the Gambia, antibiotics can be purchased without medical prescription. Also, these drugs are readily available and inexpensive (Okeke et al., 1999). The misuse of antibiotics by the public can be attributed to this high resistance.

Amongst the isolated uropathogens, 87.04%(47/54) were MDR, our findings were similar to a study in Ethiopia (Tesfa et al., 2021), but showed a higher prevalence as compared to a study in Turkey, 53.8%(Guclu et al., 2021).

5.2 Antimicrobial Resistant of Uropathogenic bacteria Per isolate

The majority of the isolates of *E. coli* were found to be resistant to Ampicillin, Tetracycline, Trimethoprim/Sulfamethoxazole and Erythromycin (Table 7). Similar findings were reported in a study in Libya, where resistance to Ampicillin was 85.4% (Mohammed et al., 2016), The Gambia where resistance to Ampicillin and Tetracycline was 100% (Sanneh et al., 2018) and in Pakistan where resistance to Trimethoprim/Sulfamethoxazole was 74.1%. This high prevalence could be due to the inappropriate usage of antibiotics and they are readily available over the counter. For Nitrofurantoin, fluoroquinolones, chloramphenicol and cephalosporin, *E. coli* isolates showed a lower resistance rate. Comparably, our findings were concordance in previous studies done by Magliano et al., (2012) which reported 76.8% CIP and 90.0% Ceftazidime susceptible respectively, Khan et al., (2014) reported 72.6% Nitrofurantoin sensitivity. However, the Carbapenems (Imipenem and Meropenem) were the most active drug, which show zero resistance. This finding is consistent with a study reported in Senegal (Barry et al., 2017).

Overall, resistance data for *Klebsiella* spp isolates indicate that the first-line drugs like ampicillin, Trimethoprim/Sulfamethoxazole and tetracycline exhibited high resistance. In general, Trimethoprim/sulfamethoxazole, tetracycline, ampicillin, Erythromycin and nalidixic acid were the most inactive drugs as they showed a resistance rate of more than 50% (Table 7). The figure changes with resistance rates of 50% and less, except for meropenem and imipenem which were effective against *Klebsiella* spp isolates with a susceptibility rate of 100%. For the isolates of *Citrobacter* spp, *Proteus Mirabilis* and *Pseudomonas aeruginosa* similar trend of resistance rate was observed. This finding is in agreement with that reported in other African studies (Barry et al., 2017; Donkor et al., 2019; Sanneh et al., 2018). In west African countries including The Gambia, clinicians usually start antibiotic therapy with inexpensive and well-known antibiotics, such as ampicillin, Trimethoprim/sulfamethoxazole and tetracycline. This could explain why the high resistance level among these antibiotics.

5.3 Risk factors Associated with Uropathogenic bacteria

Our study revealed female participants had six-fold increased odds of acquiring uropathogenic isolates. This finding is in line with previously documented results by Gebremariam et al. (2019) and Paulo et al., (2012) in elderly women. This significant association might be due to females' short, wider and moist urethra which could be supportive for the growth of bacteria compared to males. The present study showed the percentage of pregnant females with UTI was higher than nonpregnant females. Our finding is similar to a study by Shaifali et al., (2012), where 50% of pregnant women were found to be infected with bacteria. Pregnancy causes a series of changes in the physiology of a woman. The hormonal and physical changes increase urine stasis. Such changes along with the short and wider urethra increase the likelihood of a pregnant woman acquiring uropathogens. These changes increase the chances of infections which could be either symptomatic or asymptomatic (Boye et al., 2012; Vasudevan, 2014). In the present study, a married individual has a higher prevalence of UTI compared to single and divorced participants. Our findings were similar to a study in Nigeria, 90.9% of married individuals had significant bacteria (Oli et al., 2017) and also in Uganda, where married individuals had 2 times increased odds of acquiring uropathogens compare to single and others (Odoki et al., 2019). Analysis in our study revealed a low prevalence of UTI among individuals who had been admitted to a hospital in the previous month. Our findings were in contrast with other results documented in Ethiopia where hospitalization was significantly associated with UTI (Tesfa et al., 2021).

Our findings showed that level of education (taking tertiary as a reference) individuals who had no formal education have 11 times increased odds of acquiring uropathogenic bacteria and are statically significant. This finding was in contrast to a study reported in Ethiopia by Emiru, (2013). This may be due to the high-level treatment-seeking behaviors of infected literates compared to illiterates (no formal education). In line with other documented results (Gebremariam et al., 2019; Tesfa et al., 2021), medical illness (diabetes) showed no association with uropathogenic isolates. However, diabetes was found to be associated with UTI in a study by Odoki et al., (2019). The statistical association between diabetes and UTI could be the high-level presence of glucose in the urine which may serve as the culture medium for uropathogenic microorganisms in diabetic patients which could lead to UTI.

The current study found participants with a history of UTI having significant association with uropathogenic isolates compared to those without a history of UTI (p=0.042). This result concords with a cross-sectional study conducted in Ethiopia by Gebremariam et al., (2019), found out that the history of UTI was a risk factor for uropathogenic isolates. The possible explanation for this association could be due to the presence of resistant strains from earlier uropathogenic isolates. The present study revealed the history of catheterization with uropathogenic isolates was not significantly associated. Similar findings were observed in Ethiopia by Tesfa et al., (2021), whereas Gebremariam et al., (2019) reported a significant association. The catheter serves as a portal for bacteria entry into the urinary tract due to frequent and long-term catheterization.

5.4 Antibiotic usage

The findings of the study showed antibiotic use in previous UTI, antibiotic use in the last three months and taking antibiotics without medical prescription were not significantly associated with uropathogenic resistant isolates. Similar findings were documented in Mulago (Uganda) (Kabugo et al., 2016) and Sri Lanka (Fernando et al., 2017), whereas in Turkey antibiotic use in the preceding three months showed significant association. The use of antibiotics as prophylactic in recurrent UTIs is not recommended as this could enhance the emergence of resistant strains. Analysis in our study showed purchasing antibiotics from street vendors or local pharmacy were significantly associated with uropathogenic resistant bacterial isolates. Our findings contrast the findings by Sanneh et al which showed buying and use of antibiotics from street vendors were not associated (Sanneh et al., 2018). The possible explanation could be as a result of numerous pharmacies available and the lack of control on the inappropriate sales of antibiotics over-the-counter. This may result in the development of antimicrobial-resistant strain which is evidenced in (Kebbeh et al., 2017; Kwambana-Adams et al., 2015; Okomo et al., 2011; Sanneh et al., 2018).

CHAPTER SIX

6.1 Conclusions

The study showed the presence of uropathogenic bacteria among patients diagnosed with CA-UTI at KGH. The study revealed low prevalent of uropathogenic bacteria among outpatients with UTIs in KGH. The study also revealed that females were mostly affected with uropathogenic bacteria.

E. coli was the most prevalent bacteria followed by *Klebsiella* spp of the causal agent identified among patients attending Kanifing General Hospital.

Nitrofurantoin, Ceftazidime, cefotaxime, cefoxitin, Imipenem and Meropenem were the most active antibiotics to the isolates. The identified uropathogenic bacteria show a high resistance to ampicillin, trimethoprim/sulfamethoxazole, erythromycin and tetracycline antibiotics. A high prevalence of MDR among the uropathogenic bacteria identified were also observed.

Being female, having no formal education, history of UTI and buying antibiotics from street vendors or local pharmacy without medical prescription were significantly associated with uropathogenic bacterial isolates.

However, no significant association was observed for hospitalization, catheterization, antibiotic consumption in the last three months, marital status, pregnancy status, finished dosage of antibiotics prescribed and sharing of antibiotics with others, even though studies conducted elsewhere reported significant association to some of these risk factors.

6.2 Recommendations

Based on the findings of this study, the following recommendations were made;

The Ministry of Health;

1. Should establish antimicrobial surveillance to monitor the resistance strain of microbials.
2. Must ensure continuous capacity building for laboratory staff and provisions of resources (laboratory consumables and equipment) for the proper delivery of effective and efficient AMR surveillance.
3. Should develop antimicrobial stewardship program to reduce inappropriate use of antimicrobials in The Gambia
4. And Medicine Control Agency should establish and implement policy to curb over-the-counter sale of antibiotics to clients without medical prescription.
5. Should conduct periodic community health education to avoid indiscriminate usage of antibiotics by patients suffering from UTI.

The National Public Health Laboratory

1. Under the Ministry of Health should establish a national registry to accumulate isolates of uropathogens from different hospitals to set up diagnostic and update treatment guidelines.
2. Must ensure that susceptibility testing is conducted at various health facilities before empirical treatment of patients with CA-UTI by clinicians.

The hospital management

1. Should consider reviewing the treatment guidelines for empiric UTI therapy based on our findings on various antibiotics, ampicillin, trimethoprim/sulfamethoxazole, erythromycin, and tetracycline.

2. Must ensure that Ciprofloxacin, Chloramphenicol, Gentamycin and Augmentin antibiotics should be used based on the susceptibility tests of the isolated bacteria.
3. Must ensure the laboratory conduct continuous AMR surveillance and monitoring to update clinical protocol of UTI management.
4. Should ensure that clinicians enforce health education to patients to adhere to the treatment and thereby reducing drug resistance.
5. Must ensure that clinicians health educate their patients (especially female patients) to practice good personnel hygiene in order to avoid been infected with uropathogens.

6.3 Limitations of the study

One of the study's major limitations is that majority of the urine samples yielded negative growth bacterial growth, which limited the number of isolates for AST. This could have affected the identification of some of the risk factors of UTI in the study. The other major limitation of the study is the lack of the facility and resources to do genotyping of the resistance genes. Due to a lack of resources, the study was unable to identify ESBL-producing organisms.

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APPENDIX

INFORMED CONSENT FORM

Research Title: Antibiotics Susceptibility Patterns of Uropathogenic Bacteria Isolated from Patients with Community-Acquired Urinary Tract Infections at Kanifing General Hospital, The Gambia.

Principal Investigator: (ABOU KEBBEH: University of Ghana, School of Public Health, Department of Epidemiology and Disease Control. Email: kebbehabou@yahoo.com/Tel: +2203656691**)**

SCC Number: R021011

Background

Dear Patient,

I wish to invite you to participate in academic research involving individuals from Kanifing Municipal council suspected of Urinary Tract Infections (UTIs) in Kanifing General Hospital. My name is Abou Kebbeh, at the University of Ghana, School of Public Health. As mentioned above, I am undertaking a research on the subject. The objective of this study is to determine antibiotics susceptibility patterns of community-acquired uropathogens and the potential risk factors associated with the resistant isolates. The findings of this study will help to influence policy-makers decision on antimicrobial resistance surveillance and early treatment of UTIs and related diseases. This research would form part of my work for the award of a Master's degree in Epidemiology and Disease Control.

Methods

The study seeks to interview and collect demographic data and a sample of urine for culture and sensitivity testing. The procedure for sample collection will be non-invasive and it will be thoroughly explained to the participant. The data will be collected via a face-to-face interview of the participants. The participants will be briefed about the purpose of the study before the commencement of the interview. Questionnaires on antibiotic use would be administered, which will take approximately 10 minutes of your time. The information will be collected by the researcher or a research assistant.

Risks and Benefits

There is little or no harm in collecting a sample of urine. The information you provide will help the researcher understand factors that influence antibiotic resistance. The specimen you provide will enable the researcher to determine the type of uropathogens infection that affect people in this area and help to guide the right choice of drug to be prescribed. Moreover, the conduct of this study will greatly help clinicians at Kanifing General Hospital to better understand the susceptibility pattern of antimicrobial locally available for treating community-acquired UTI care. It will also reduce cost and duration of hospitalization of patients, thus reduce the economic burden on patients. The information you provide will be handled with confidentiality.

Right to refuse

Your participation in this study would be on voluntary basis. The questionnaire will be administered to the participant that volunteers and they can opt-out of the survey anytime if they decline to continue. This will not affect the medical care that you would normally receive. In case you decide to withdraw your participation during the study, any information already generated from the samples until the time of withdrawal will not be used and samples already collected, for which you have given consent, will also not be analyzed and data used. However, I will encourage your full participation since your participation is important.

Consent form

Participant Identification Number: |__|__|__|__|__|__|__|__|__|__|__|__|

____
(Printed name of participant)

☐ I have read the written information **OR**

☐ I have had the information explained to me by study personnel in a language that I understand,

and I

- confirm that my choice to participate is entirely voluntarily,
- confirm that I have had the opportunity to ask questions about this study and I am satisfied with the answers and explanations that have been provided,
- understand that I grant access to data about me to authorized persons described in the information sheet,
- have received sufficient time to consider to take part in this study,
- agree to take part in this study.

I agree to further research on my samples as explained Yes ☐ No ☐

Participant's signature/ thumbprint* ☐ _______________________________________
Date (dd/mmm/yyyy) Time (24hr)

Printed name of witness* _______________________________________

Printed name of person obtaining consent _______________________________________

I attest that I have explained the study information accurately in ______________________ to, and was understood to the best of my knowledge by, the participant. He/she has freely given consent to participate *in the presence of the above-named witness (where applicable).

Signature of person obtaining consent _______________________________________
Date (dd/mmm/yyyy) Time (24hr)

** Only required if the participant is unable to read or write.*

QUESTIONNAIRE

Study Title: Antibiotics Susceptibility Patterns of Uropathogenic Bacteria Isolated from Patients with Community-Acquired Urinary Tract Infections at Kanifing General Hospital, The Gambia

QUESTIONNAIRE

Identification Number…………………………..

AGE……….. SEX……… DATE_____/____/____

1. Home/address of respondent.……………………. Tribe………….
2. Level of education: ☐ Primary ☐ Secondary ☐ Tertiary ☐ No formal education…………
3. Marital status: ☐ Single ☐ Married ☐ Divorce
4. Occupation: ☐ Student ☐ Civil servant ☐ Self-employed ☐ Not employed
5. Pregnancy status for female participants: Pregnant ☐ Not pregnant ☐
6. Are you suffering from any chronic disease (Medical illness)? ☐ Yes ☐ No, if yes specify…………….
7. Have you been hospitalized in the past month? Yes ☐ No ☐
8. In the last month, were you put on any catheterization? Yes ☐ No ☐
9. Any history of UTI episodes over the last month? Yes ☐ No ☐
10. During those UTI episodes, did you use any antibiotics? Yes ☐ No ☐
11. Do you wash your hands with soap and water after visiting the toilet? ☐ Yes ☐ No
12. In the last three months, have you taken any antibiotics? ☐ Yes ☐ No ☐
13. Do you frequently purchase antibiotics from street vendors without medical practitioners prescribing them? ☐ Yes ☐ No

14. Do you usually take antibiotics without medical prescription? ☐ Yes ☐ No

15. Do you usually finish taking the antibiotics you have been prescribed? ☐ Yes ☐ No

16. Do you share unfinished antibiotics with family relationships or others? ☐ Yes ☐ No

LABORATORY FORM

CLINICAL LABORATORY SERVICES KGH							**MICROBIOLOGY**			
SURNAME							**CLINICAL DATE**			
			AGE		**SEX**		**LABORATORY RESULT**			
FORENAMES							**NAME OF ISOLATE**			
ADDRESS								**Interpretation**		
STUDY ID							**ANTIBIOTIC SENSITIVITY**	**R**	**S**	**I**
CULTURE RESULTS							Amoxicillin/clav			
							Ceftazidime			
							Cefotaxime			
							Cefoxitin			
							Ciprofloxacin			
							Augmentin			
							Sulphamethoxazole/trimethoprim			
GROWTH	**N^{O} OF COLONIES**	**CFUX1000**	**>10^5CFU**	**<10^5CFU**	**NO GROWTH**		Chloramphenicol			
			☐	☐	☐		Erythromycin			
BIOCHEMICAL REACTION	INDOLE	SIMON	UREA	CATALASE	OXIDASE	TSI	Ampicillin			
POSITIVE							Gentamycin			
NEGATIVE							Nalidixic acid			
API 20E IDENTIFICATION:							Nitrofurantoin			
							Tetracycline			

STANDARD OPERATING PROCEDURE (SOP) FOR MEDIA PREPARATION
Research Title: Antibiotics Susceptibility Patterns of Uropathogenic Bacteria Isolated from Patients with Community-Acquired Urinary Tract Infections at Kanifing General Hospital, The Gambia

	compiled by	Examined by	Approved by	Replaced version	New version
Name	Abou Kebbeh	Dr. Adam Zakaria	Prof. Francis Anto and Dr. Adam Zakaria	non	001
Date	30/03/21				
Signature					

1.0 Introduction

This is a comprehensive Standard Operating Procedure (SOP) manual for preparation of Cysteine Lactose Electrolytes Deficient (CLED), Mueller Hinton and MacConkey agar in a clinical diagnostic laboratory at Kanifing General Hospital. The manual has been compiled by referring to international protocols customized to the needs and the infrastructure already available in The Gambia, National Public Health Laboratories (NPHL) or infrastructure that can be achieved by upgradation. Both conventional and automated procedural alternatives are included. It is intended that all laboratory personnel will strictly adhere to the procedures. The manual has been organized to place each part of the procedure together, including media preparation, supplies, and step-by-step testing procedure. This will allow the user to see an overview of the entire procedure together.

2.0 Purpose

The objective of this SOP is to describe the method of media preparation and quality control (QC) of prepared media to use for isolation of uropathogenic bacteria among patients suspected of CA-UTI visiting the OPD at Kanifing General Hospital.

3.0 Scope

One Laboratory scientist and two Laboratory technicians will be trained on this protocol and will be responsible for the media preparation to be use for isolation and identification of uropathogens from patients visiting the OPD of the hospital.

4.0 Safety

Universal precautions should be followed when handling controls and samples. Disinfect and clean all spills of specimens or controls, and other potentially contaminated materials using a suitable disinfection method such as applying 70% alcohol on the spillage.

5.0 ABBREVIATIONS

ATCC - American Type Culture Control

CA-UTI - Community Acquired Urinary Tract Infections

CLED - Cysteine Lactose Electrolytes Deficient

UTI - Urinary Tract Infections

OPD - Outpatient Department

6.0 Materials/ Supplies

6.1 Materials

Gloves

Reagent Bottles

Autoclave Tape

Autoclave Machine

Pasteur pipettes

Measuring Cylinder

Disposable loops

Timer

Electrical Burner

Lamp

Wax pencils

Markers

Petri dishes (Double and Single compartment)

Swab sticks/ cotton swabs

0.5 McFarland Standard

6.2 Supplies

Media

1) Cysteine Lactose Electrolytes Deficient (CLED) agar
2) Mueller Hinton Agar
3) MacConkey Agar

7.0 Quality Control Samples

E. coli ATCC 25922 control strain and ***Streptococcus pneumoniae***

8.0 MEDIA PREPARATION

8.1.0 Cysteine Lactose Electrolytes Deficient (CLED) agar

Principle: CLED agar is non inhibitory medium use in the isolation and identification of bacteria that causes UTIs.

8.1.1 Procedure for Preparation: To make 1L

1. Dispense 32.2g of medium in 1L of distilled water (**NB:** concentration may change depending on manufacturer)
2. Mix well to dissolve completely
3. Sterilize by autoclaving at 121^0C for 15 minutes
4. Cool to 45^0C preferably in water bath
5. Dispense aseptically in 15ml in sterile petri dishes
6. Date the medium and give a batch number
7. Stack in plastic bag, label and store at 2-8˚C.

8.1.2 QC of CLED agar - sterility differential and inhibitory (performance) characteristics

- No inoculation on sterility plate
- Using a double compartment plate, inoculate one half of the plate with the *Escherichia coli* and the other with ***Streptococcus pneumoniae*** and incubate both plates at 37^0C.

8.1.1 Result:

- ✓ The colonies of ***Escherichia coli* should appear yellow indicating** it's a lactose fermenter.
- ✓ The portion with the *S. pneumoniae* should be inhibited as ***S. pneumoniae*** doesn't grow on CLED agar.
- ✓ The plate for sterility should have no growth on it.

8.1.3 Shelf life: Up to **16 weeks** provided there is no change in the appearance of the medium to suggest contamination or deterioration.

8.2 Muller Hinton Agar

8.2.1 Principle: It is the medium of choice for antibiotics sensitivity testing for fastidious bacteria like facultative anaerobic or aerobic, members of Enterobacteriaceae and aerobic gram-negative rods. However, Streptococci do not grow well on Mueller Hinton.

8.2.2 Procedure for preparation: To make 1L

1. Dispense 38g of medium in 1L of distilled water
2. Soak for 10 minutes
3. Mix well and heat for 1 minute whilst shaking frequently to completely dissolve powder, sterilize by autoclaving at 121^0C for 15 minutes
4. Cool to 47^0C and mix before dispensing into the petri dishes and then dry the agar surface and leave to solidify for 30 minutes
5. Store the culture media plates upside down at 2-8^0C sealed in plastic bags to reduce chances of contamination.

8.2.3 QC of Mueller Hinton agar - sterility

- Incubate one uninoculated plate at 37°C.

8.2.1 Result:

✓ The plate should be sterile after overnight incubation with no bacterial growth.

8.2.4 Shelf life: up to ***16 weeks*** provided there is no change in the appearance of the medium to suggest contamination or deterioration.

8.3 MacConkey Agar

8.3.1 Principle

This is a differential and low selective medium for the isolation of Coliforms. It differentiates Coliforms into lactose-non fermenting, gram-negative enteric bacteria from lactose-fermenting organisms. Lactose fermenters are coloured pink, while non-lactose fermenters are pale/colourless.

8.3.2 Procedure for preparation: To make 1L

1. Suspend 52g in 1 litre of distilled water.
2. Mix well to dissolve completely.
3. Sterilize by autoclaving at 121˚C for 15 minutes.
4. Cool to 45˚C preferably in a water bath.
5. Aseptically dispense about 20 ml of base medium in sterile Petri dishes.
6. Carefully flame the surface of the agar plate to remove bubbles.
7. Allow medium to set.
8. Stack in plastic bag, label and store at 2-8˚C.

8.3.3 QC of MacConkey agar - sterility differential and inhibitory (performance) characteristics

- No inoculation on sterility plate
- Using a double compartment plate, inoculate one half of the plate with the *Escherichia coli* and the other with *Streptococcus pneumoniae* and incubate both plates at 37^{o}C.

8.3.3.1 Results:

- ✓ The colonies of ***Escherichia coli*** should appear **pink to red** indicating it's a lactose fermenter.
- ✓ The portion with the *S. pneumoniae* should be inhibited as *S. pneumoniae* doesn't grow on MacConkey agar.

✓ The plate for sterility should have no growth on it.

8.3.4 Shelf life: up to ***16 weeks*** provided there is no change in the appearance of the medium to suggest contamination or deterioration.

9.0 References

1. Cheesbrough. M (2009) *District Laboratory Practice in Tropical Countries part* 1 (2nd ed) Cambridge University press.
2. Cheesbrough. M (2006) *District Laboratory Practice in Tropical Countries part* 2 (2nd ed) Cambridge University press.
3. Global Salm-Surv, A global Salmonella surveillance and lab support project of the World Health Organiztion, Laboratory Protocols. 2003.
4. David Greenwood M. B (2012) Medical Microbiology (8th Edition) Elsevier.

Ethical Approval Letter

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The Gambia Government/MRCG Joint
ETHICS COMMITTEE

29 April 2022

Mr Abou Kebbeh
C/o University of Ghana

Dear Mr Kebbeh

Project ID/Ethics ref: R021011

Project Title: Antibiotics susceptibility patterns of uropathogenic bacteria isolated from patients with community-acquired urinary tract infections at Kanifing General Hospital, The Gambia.

Thank you for responding to the queries raised by The Gambia Government/MRCG Joint Ethics Committee at its meeting held on 3 March 2022.

Confirmation of Ethical Opinion
On behalf of the committee, I am pleased to confirm a favourable ethical opinion on the basis of the application and supporting documents.

Documents reviewed were

Document Type/Name	Version Number	Date
Ethics Application Form	1.1	1 April 2022
Informed Consent Document	1.1	1 April 2022
Questionnaire	1.2	22 April 2022
RePubliC Approval		15 July 2021
Letter from Supervisor		14 July 202
Ethics Committee Reply		22 April 2022
CV		

After Ethical Review

The Principal Investigator (PI) or delegate is responsible for informing the Ethics Committee of any subsequent changes to the application. These must be submitted to the Committee for review using an Amendment form. Amendments must not be initiated before receipt of written favourable opinion from the Committee.

With best wishes

Yours sincerely

Dr Mohammadou Kabir Cham
Chairperson, Gambia Government/MRCG Joint Ethics Committee