CHAPTER 1- INTRODUCTION

Urinary tract infections (UTI) are one of most frequently encountered diseases in clinical medicine with an estimated 150 million cases per annum worldwide (Karlowsky, et al., 2002). It is an inflammatory disorder that is caused by microbial invasion of the tissues in the urinary tract (Mobley, 2000). UTIs are most commonly caused by bacteria, however, infections by fungi, viruses and parasites can also occur (Sheerin, 2011). The pathogens may affect the entire tract or may be limited to a specific portion of the tract. Depending upon the presence of functional or anatomical abnormalities of the urinary tract, UTI can be classified as complicated or uncomplicated. Uncomplicated UTIs are the commonest type where no functional or anatomical abnormality is found. On the other hand, complicated UTIs usually involve presence of abnormal urinary tract or presence of factors (such as urinary catheter, ureteral stents, BPH, etc.) that increase susceptibility to UTI (Sheerin, 2011).

The most common type of UTI is cystitis and a significant number of risk factors such as female gender, a prior UTI, sexual activity, vaginal infection, diabetes, obesity and genetic susceptibility are associated with this (Foxman, 2013). The clinical symptoms of UTIs are not extensive but burning sensations while urinating, lower abdominal pain, itching, formation of blisters and ulcers in the genital area, genital and suprapubic pain, and pyuria have been observed in different studies (Hooton, 2012; Sheerin, 2011). Symptoms vary depending on the gender and the anatomy of the affected part of urinary tract (Amali, et al., 2009).

On epidemiological investigations, it has been revealed that UTI can either be acquired from the community or through nosocomial route. In community-acquired urinary tract infections (CA-UTIs), clinical manifestations occur within the community or in the hospital environment within 48 hours of admission (Moyo, et al., 2010). In contrast, nosocomial urinary tract infections (N-UTIs) are the infection of the urinary tract that are encountered after 48 hours of hospital admission, or within 3 days after discharge

(Iacovelli, et al., 2014; Dias, et al., 2010). In the general population, CA-UTIs are the most common types of bacterial infections (Öztürk & Murt, 2020) and major risk factors are age, previous history of UTI, sexual activity and diabetes mellitus (Tandogdu & Wagenlehner, 2016). As for N-UTIs, these make up between 25 to 50% of all hospital acquired infections (Hooton, et al., 2010). In case of recurrences in UTIs, several factors such as gender, age, race, circumcision (Conway, et al., 2007), HIV (Banu & Jyothi, 2013), diabetes, urinary catheter, genitourinary tract abnormalities (Yuyun, et al., 2004), pregnancy, infants, elderly (Nicolle, 2008; Nelson & Good, 2015), and hospitalization status (Adukauskiene, et al., 2006) bear significant risk.

Globally, UTIs are the third most common type of infection after respiratory tract and gastrointestinal tract infection. (Flores-Mireles, et al., 2015). In Asia, the prevalence is around 9.8% (Choe, et al., 2018) with crude incidence rates rising steadily in some countries (Yuan, et al., 2021). Also, variations in prevalence were observed within different areas of the same country (Dash, et al., 2013; Mehta, et al., 2013; Sahay, 2020). UTI remains an important cause of morbidity and mortality in Bangladesh with women and children being the most vulnerable (Rahman , et al., 2014; Rustom, et al., 2020). Apart from gender and age; factors such as seasonal variations have also been reported with higher incidences in summer months (Yolbas, et al., 2013; Rustom, et al., 2020).

The causative organisms for UTI are usually bacterial, and the spectrum of bacteria that cause complicated UTI is much broader than those causing uncomplicated UTI. One common pathogen that leads to both complicated and uncomplicated UTI is *Escherichia coli*. This micro-organism alone is the sole cause in around 85% of all UTI cases (Dimitrov, et al., 2004). In Europe, over 50% of urine cultures come back positive for *E. coli* in Europe (Fluit, et al., 2000), while in Asia, the frequency is around 38.7%. Although multiple studies have showed that UTI prevalence in Bangladesh varies based upon the geographical location (Ahmmed, et al., 2021; Mazed, et al., 2008; Moue, et al., 2015; Parveen & Rahim, 2017; Saha, et al., 2015) all of these studies reported *Escherichia coli* to be the most frequent causative organism.

The choice of antibiotics to successfully treat UTIs vary across different regions of the world. This is due to the emergence of resistant strains owing to decades of mis-prescribing

and over utilization of these drugs (Habte, et al., 2009). Even now in many places, empirical treatment of uncomplicated UTIs is based on national recommended guidelines rather than culture and sensitivity testing (Haslund, et al., 2013). As a result, antibiotics that once were used broadly to treat UTIs are now resistant to most strains of UTI causing organisms (Nickel, 2005). In Bangladesh, antibiotics such as amoxicillin, cotrimoxazole, nalidixic acid and ciprofloxacin are still used empirically to treat UTIs (Parveen & Rahim, 2017).

Since most UTIs are treated empirically the selection of antimicrobial agent should be determined not only by the most likely pathogen but also by its expected susceptibility pattern. Hence, proper knowledge regarding antimicrobial therapy and their susceptibility patterns regarding the uropathogens is an essential and important factor to minimize drug resistance in UTIs (Erdem, et al., 2018).Like other countries in Asia, and the world, E. *coli* is the most commonly isolated uropathogen in Bangladesh (Moue, et al., 2015). The *E. coli* found here is resistant to ampicillin, penicillin and gentamycin (Moue, et al., 2015). Very high microbial resistances have also been observed against nalidixic acid, ciprofloxacin as well as antibiotics of the third generation cephalosporins such as cefixime and ceftriaxone (Hossain, et al., 2020).

In recent times, owing to varying antimicrobial resistance patterns, further analysis is necessary to identify the widespread resistance patterns of *E. coli* in different regions of Bangladesh. Hence, the current study was undertaken to depict the overall prevalence of the most frequent pathogen responsible for UTI and its antimicrobial resistance pattern among the residents of Chattogram city.

RATIONALE

Urinary tract infections are a one of the most common infectious diseases diagnosed in the community with *E. coli* being the most frequently isolated organism causing this. While empirical therapy is commonly used to treat uncomplicated UTI, emergence of resistant strains has led to decreased efficacy of the drugs used. The sensitivity patterns of *E. coli* are different based on geographical locations, with differences sometimes among different regions or different healthcare centers of the same city. As such, the overall susceptibility pattern of the organism and its drug sensitivity must be studied for an effective treatment against the contagion. Since there isn't much information on the resistance pattern of *E. coli* among UTI cases in Chattogram, this retrospective study aims to compare the frequency and drug resistance pattern of this causative organism.

OBJECTIVES:

- To isolate and identify *E. coli* from patients with urinary tract infection.
- To identify the pattern of antimicrobial resistance of *E coli*
- To detect the multidrug resistance of *E. coli* and the associated risk factors.

CHAPTER 2- LITERATURE REVIEW

2.1 History of Urinary tract infections

Urinary tract infections (UTI) have been known since antiquity. It had plagued humans long before bacteria were recognized as the main cause of the disease, and before urology became an established medical specialty. The Ancient Egyptians mentioned UTI in Ebers Papyrus dated to 1550 BC., and they dealt with them by using medicated herbs, and describing it as "sending forth heat from the bladder" (Topley, 1990). The Greeks thought UTI was the result of disharmony; while the Roman physicians recommended bed rest, herbs, diets and narcotics in managing this disease (Al-Achi, 2008).

Early in the ninth century, an Arabic physician named Ar Rhazi was the first person to diagnose pyelonephritis in a patient from Baghdad with a febrile illness and necrotizing papillitis (Asscher, 1980). Later on, in the year1881, the presence of bacteria in urine of patients with urinary symptoms was noted by Roberts, followed by Wagener; who described focal histologic changes in women with recurrent UTI, just a year later (Asscher, 1980; Ronald & Pattullo, 1991). Twelve years later, 'bacillus coli' was cultured in the urine of children with UTI by Escherich who then labeled 'pyelitis' as a disease of childhood. In 1917, Lohlein recognized a connection between recurrent UTI, progressive pyelonephritis with renal impairment; and end-stage renal disease. Before the chemotherapeutic era, cranberry juice, methenamine mandelate and ketogenic diets were prescribed to modify urinary pH and thus prevent and treat recurring UTI. Since ancients never understood the true cause of UTI, their treatment was palliative in nature. Effective treatment for UTI was developed only after the availability of antibiotics in 1930s (Al-Achi, 2008).

During this time, UTI recurrence and outcome in patients were further described. In an article by Longcope and Winkenwerder (1933) hypertension and atrophic pyelonephritis were characterized as complications of recurrent renal infection. Further clarification on the entity of pyelonephritis was given by Weiss and Parker (1939) which included radiographic changes, focal nature in the pathology, presence of acute interstitial

inflammation and observation of abscesses within the renal parenchyma. The authors also described a silent subclinical pyelonephritis known as "pyelonephritis lenta ", a progressive disease predominantly in young adult women associated usually with hypertension and leading to end stage renal disease. These investigators presented an era in which recurrent bacterial infections of the urinary tract were presumed to put the patient at risk of chronic terminal renal disease, and they concluded that chronic pyelonephritis was more common cause of end stage renal disease than glomerulonephritis. In 1940 another article was published describing the outcome of a cohort of 45 women who presented with pyelonephritis during pregnancy. Over 10 years, five of them developed renal stones and three progressed to significant renal impairment (Crabtree EC & Reid, 1940). Prior to the development of antimicrobial drugs, experiences derived from studying adult patients upheld the hypothesis that progressive destruction of renal tissue could gradually lead to continued pathological increases in blood pressure or renal damage. By 1940, sulfonamides were used to treat patients with renal infections and as a result recurrent destructive infection became less common. Over the next half century, a plethora of studies identified various antimicrobial regimens to treat acute and asymptomatic infections, and prevent recurrence as each new therapeutic agent was introduced into clinical practice. Following the introduction of antimicrobials, natural history of UTIs were rarely followed without the use of therapeutic interventions (Ronald & Pattullo, 1991).

2.2 Background of Urinary tract infection

A urinary tract infection (UTI) is an infection in any part of the urinary system that involves the kidneys, ureters, bladder and urethra (Foxman, 2010). In fact, one study describes this as an infection, usually of bacterial origin, that can occur anywhere along the urinary tract, from the urethral meatus to the perinephric fascia (Barnett & Stephens, 1997). When it affects the lower urinary tract, it is known as a bladder infection (cystitis) and when it affects the upper urinary tract it is known as a kidney infection (pyelonephritis). The most common infectious agent is *Escherichia coli*, though other bacteria or fungi may also cause infection. Females are more prone to UTI than males due to their anatomical features i.e., they have a shorter urethra than men.

2.2.1 Classification of urinary tract infections

UTI can be classified according to their location within the urinary tract but the different parts of the urinary tract, however, communicate with each other to some degree. As a result, bacteria in one area are probably also present elsewhere. Infection in different parts of the urinary tract includes;

- Urethritis – infection of the urethra
- Cystitis – infection of the bladder
- Pyelonephritis – more extensive infection involving the upper urinary tract

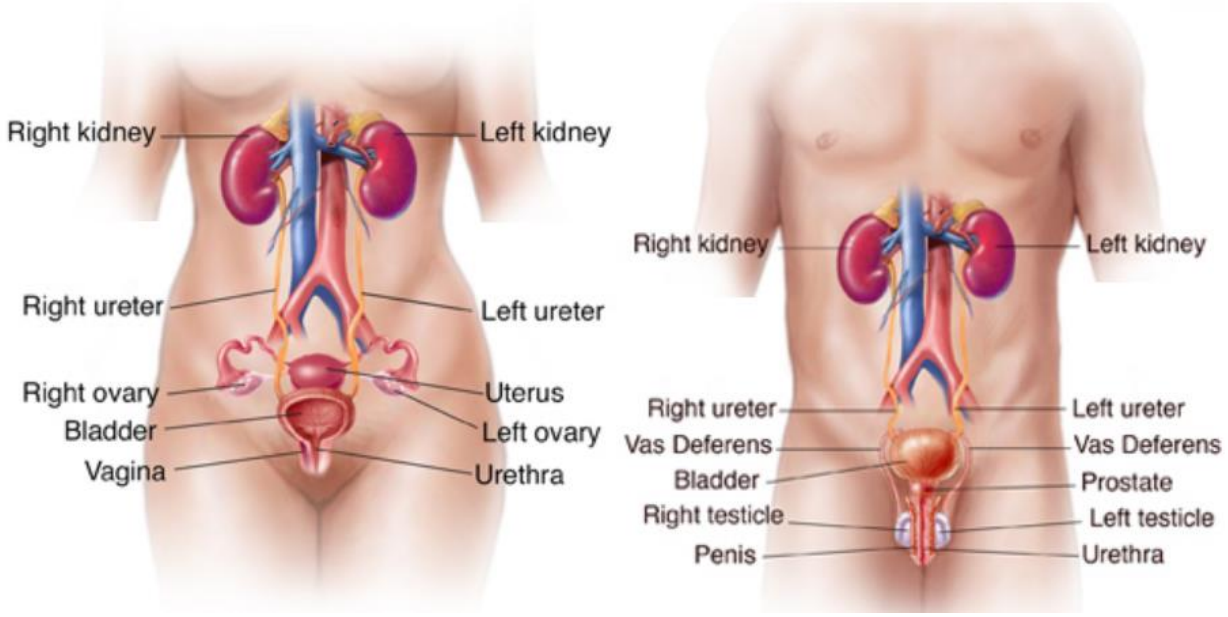

Figure2.1: Male and Female Urinary Tracts

Source **(Urology care foundation, 2021)**

Although these definitions are anatomically described, for clinical use the terms 'uncomplicated' and 'complicated' UTI are more useful. While uncomplicated UTI occurs in patients with normal urinary tracts and resolve with a short course of antibiotics having minimal effects on long term renal function; complicated UTI occurs in patients who have a structurally or functionally abnormal urinary tract and is often caused by bacteria that is resistant to antibiotics. Since these abnormalities are difficult to cure without surgery or

other methods to resolve to normal functioning of the urinary tract, UTI of this type can have long term damage to renal function (Barnett & Stephens, 1997). The predominant clinical symptoms of UTIs are shown in the table below.

2.2.2 Epidemiology

Urinary tract infections (UTIs) are one of the most common outpatient bacterial infections, with a lifetime incidence. Worldwide, UTIs' prevalence was estimated to be around 150 million persons per year (Gupta, et al., 2001). Nearly 1 in 3 women will have had at least one episode of UTI requiring antimicrobial therapy by the age of 24 years. Almost half of all women will experience one UTI during their lifetime. The infection usually occurs between the ages of 16 and 35 years, with 10% of women getting an infection yearly and more than 50% to 60% having an infection at least once in their life time. It is very common for recurrences with nearly half of them getting infected for the second time within the same year (Sakamoto, et al., 2018; Alperin, et al., 2019). UTI occurs 4 times more frequently in females than males (Salvatore, et al., 2011). In the US, there were 10.5 million ambulatory visits for UTIs in 2007, accounting for 0.9% of all ambulatory visits, and 21.3% of these visits were to hospitals. Emergency departments. The annual cost of treatment was $1.6 billion in 1997, and the estimated annual direct treatment cost was $659 million in the US in 1995 (Schappert & Rechtsteiner , 2011). Sweden and other parts of Europe have also seen an exceeding worldwide problem with UTI where 1 in 5 adult women experiences (Salvatore, et al., 2011). In China, UTIs are the second most common infections and hospital acquired UTIs made up 11.5% of hospital acquired infections here. (Yuan, et al., 2021) UTIs may affect around 7.8% of people during childhood (Shaikh, et al., 2008). Among children, urinary tract infections are most common in uncircumcised males less than three months of age with circumcision significantly reducing the risk (Barnett & Stephens, 1997), followed by females less than one year (Bhat, et al., 2011).

In Bangladesh, the prevalence of UTI was around 42% (Rustom, et al., 2020; Haque, et al., 2015). The incidences are higher in adult female, especially women in their reproductive age who are married and have a low level of education (Saber, et al., 2021). In case of children the prevalence increases with increasing age. Among school going girls the prevalence was found to be 9% (Asaduzzaman, et al., 2018). Although UTIs in

Bangladesh are more common in summer months, the prevalence in women is equally raised in winter months unlike men and children. Even though many international studies have shown men to develop higher incidences of UTI at an older age due to prostate enlargement, studies in Bangladesh found no evidence to back this claim (Rustom, et al., 2020). As for hospital admissions, complicated UTIs and UTIs involving the upper urinary tract are more common in hospitalized patients (Ahmmed, et al., 2021). One of the most common causes of recurrent UTIs among hospitalized patients is the presence of a urinary catheter. One study showed that 30% of hospitalized patients with indwelling catheters developed bacteriuria or UTIs, here gender and age did not play any significant role (Akter, et al., 2018).

2.2.3 Risk factors of urinary tract infections

Urine is sterile and free from pathogens such as bacteria, virus, and fungi but contains fluid, salts and waste products that provides a good medium for bacterial proliferation. However, infectious micro-organisms from digestive tract can enter the urethra where they multiply and creates an infectious state. Risk factors for UTI includes history of previous UTI, lack of personal hygiene, sexual activity, urinary retention, indwelling urinary catheters (Akter, et al., 2018), narrowing of the urethra due to prostate enlargement or any other condition that blocks urine flow, use of spermicides, pregnancy, menopause, reduced mobility (i.e., after surgery or bed rest), kidney stones, urinary and bowel incontinence. Females are at high risk of UTI compared to male due to shorter urethra length and proximity of urethra to anus increasing the risk of bacteria entering the urinary tract (Nicolle, 2016; Matthews & Lancaster, 2011). In Bangladesh, improper toilet training, using unhygienic sanitary cloth and wearing tight pants are also additional risks for developing UTI among young women (Asaduzzaman, et al., 2018). In case of elderly women, aging leads to a lack of oestrogen that allows for thinning and deficiency of the tissue in the vagina and urethra thus increasing susceptibility to UTIs. Genetics is yet another factor that play a role in increasing risk for UTIs. Certain cells on the vaginal mucosa and the urethra can express receptors that actually allow some specific bacteria to attach and pull themselves into the bladder causing an increased risk of a UTI (Minardi, et al., 2011). Prolonged use of antibiotics is another risk factor for UTIs since periurethral flora can be damaged by this

allowing uropathogens to colonize and infect urinary tract (Tanagho & Jack, 2004). Diabetes is an important risk factor for UTI since persistently high blood sugar levels can not only lead to immunosuppression, but also raised sugar levels in urine can attract micro-organisms to grow abundantly. Furthermore, new class of drugs Sodium-glucose co-transpoters 2 (SGLT2) inhibitors used in Type 2 diabetes treatment has shown an increase in UTI cases as these drugs increase the amount of glucose in urine (US Food and Drug Administration, 2016).

2.2.4 Symptoms of urinary tract infections

There are many people who do not exhibit any symptoms, but their urine culture shows significant numbers of bacteria. Such people are called asymptomatic cases of UTI (Nicolle, 2000). This usually occurs after sexual activity and with increasing age. Although such cases can progress to symptomatic UTI in the future, prophylactic treatment for asymptomatic bacteriuria beforehand is not advised expect for pregnant women and patients who need to undergo genitourinary procedures (Nicolle, 2005). This is because such treatments can adversely affect the individual's microbiota and increase resistance of organisms to antibiotics (Dethlefsen, et al., 2008). With regards to symptomatic UTI, the most common symptoms are increase in urinary frequency and urgency, burning sensation on micturition, cloudy urine, strong unpleasant smell of urine, dark/ bloody urine, flank or back pain, fevers and chills. Additional symptoms in women include pelvic pain, bloating or vaginal discharge. In male, penile, testicular and abdominal pain, with penile discharge and sometimes rectal pain may also indicate UTI. In newborns and infants, symptoms may also include hypothermia, diarrhea, jaundice, poor feeding and in some children, bedwetting (Komala & Kumar, 2013).

2.2.5 Urinary Pathogens

UTI is a severe public health concern that are caused by a range of urinary pathogens. Uropathogens are defined as organisms isolated from urine that can cause disease. Generally, *Escherichia coli* alone accounts for 85% of community acquired and 50% of hospital acquired urinary tract infections. Gram negative bacteria such as *Proteus mirabilis and Klebsiella pneumonia, and gram-positive bacteria such as Staphylococcus*

saprophyticus and Enterococcus faecalis are causes for the remainder of community acquired infections (Kennedy , et al., 1965). Colonization with *Klebsiella, Enterobacter, Citrobacter, Serratia, Pseudomonas aeruginosa, Providencia, E. faecalis,* or *S. epidermidis* are the causes for hospital acquired infections. The common causes of complicated and uncomplicated UTI are summarized in the table below.

Table 2.1: Commonly isolated uropathogens in complicated and uncomplicated UTI ***Source- (Ronald, 2003)***

Pathogens in uncomplicated UTIs	Pathogens in complicated UTIs
	Escherichia coli
	Klebsiella
Escherichia coli	*Enterobacter cloacae*
Staphylococcus saprophyticus	*Serratia marcescens*
Klebsiella	*Proteus mirabilis*
Enterococcus faecalis	*Pseudomonas aeruginosa*
	Enterococcus faecalis
	Group B streptococci

Multiple studies across the world have been conducted to understand the prevalence of various micro-organisms in causing UTI. In a study from Nepal, the most common organisms found were *E. coli,* followed by *S. aureus* and *Klebsiella* (Jha & Bapat, 2005). In another study in South Africa, again *E. coli,* was the most common causative organism accounting for almost 80% of the bacterial isolates. This was followed by *P. mirabilis* (5%), *E. faecalis* (4%), *S. agalactiae* (3.5%), and others (Lewis, et al., 2013). In India, *E. coli* (48%) was the most common pathogen followed by *K. pneumoniae* (20.8%), *S. aureus* (11.30%), Coagulase negative *Staphylococcus* (7.83%), *Enterococcus* species (6.96%) and *P. aeruginosa* (5.2%) (Vohra, et al., 2015). In case of HIV positive patients, *P. aeruginosa* is the most prevalent micro-organism isolated (Xavier, et al., 2015). In Japan and Indonesia, *E. coli* once again was the most frequent cause of UTI. Apart from this, *E. faecalis* was more common in Japan, while *Klebsiella spp* was more common in Indonesia (Kitagawa, et al., 2018).

2.3 *E. coli* and urinary tract infections

E. coli is the most common cause of urinary tract infections across the world. Apart from this *E. coli* also causes 'traveler's diarrhea' and is one of the two important organisms causing neonatal meningitis.

E. coli belongs to the Enterobacteriaceae group of micro-organisms which are enteric gram-negative rods. Their natural habitat are the intestinal tracts of animals and humans. This family includes many genera some of which are Escherichia, Salmonella, Shigella, Klebsiella, Enterobacter, Proteus, Serratia, and others. While *E. coli* are part of the normal flora which incidentally cause disease, others like salmonellae and shigellae, are pathogenic for humans.

Features that are common to all members of this family are their anatomic location in the intestinal tract and the following four metabolic processes:

- all are facultative anaerobes
- all of them ferment glucose
- none of them have cytochrome oxidase and
- they reduce nitrates to nitrites in order to generate energy.

These four reactions help distinguish enterobacteriaceae from non-fermenting gram negative rods such as Pseudomonas aeruginosa.

2.3.1 Structure of *E. coli*

E. coli is a gram-negative rod that is present abundantly in the colon and feces as a facultative anaerobe. It ferments lactose and this property distinguishes it from the two major intestinal pathogens *Shigella* and *Salmonella.* There are three antigens on *E. coli* that are used to identify this organism in epidemiological investigations: the O or cell wall antigen, the H or flagellar antigen and the K or capsular antigen. Because there are over 150 O, 50 H and 90 K antigens, the various combinations result in more than 1000 antigenic types of *E. coli*. Specific serotypes are usually associated with certain diseases.

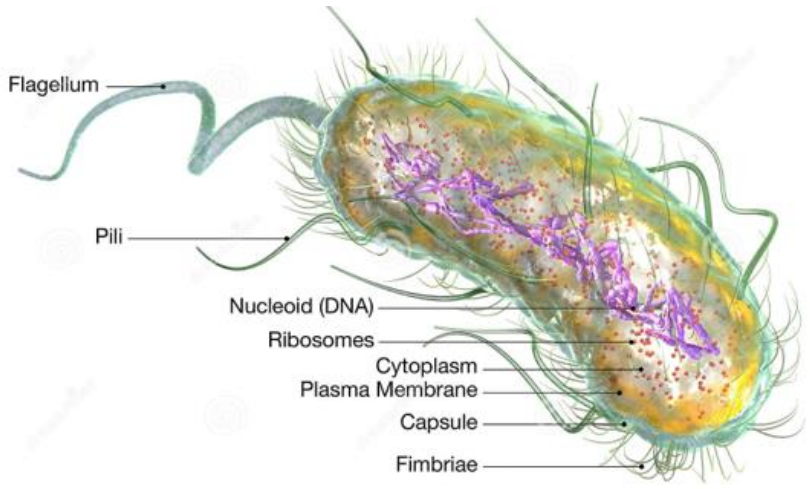

Figure 2.2: Structure of *E. coli*

2.3.2 Pathogenesis of *E. coli*

Under normal circumstances, urine is sterile. However, it is an excellent culture medium for bacteria. Certain O serotypes of *E. coli* preferentially cause urinary tract infections. These uropathic strains are characterized by pili with adhesion proteins that bind to specific receptors on the urinary tract epithelium. The binding site on these receptors, consists of dimers of galactose and the pili are also referred to as P fimbria or pyelonephritis associated pili (PAP). The motility of *E. coli* may help it to ascend the urethra in to the bladder continuing through the ureter and into the kidney. Additionally, urothelium of susceptible persons may have more receptors to which virulent strains of *E. coli* can easily adhere to. Uropathogens are specially adapted to the urinary tract and have features that help them grow and form large colonies within this environment. Although a variety of species can cause UTI, majority of infections is caused by the facultative anaerobic, gram-negative, uropathogenic *E. coli* (UPEC). About 80% of UTI among women of reproductive age is caused by this *E. coli*. (Stamm, 2002) .

2.3.3 Transmission of *E. coli*

The reservoir of *E. coli* includes both humans and animals. The source of *E. coli* that causes urinary tract infections is the patient's own colonic flora that colonizes the urogenital area. Similarly, the *E. coli* that causes neonatal meningitis comes from the mother's birth canal

with vertical transmission to the neonate. In contrast to this, *E. coli* that causes traveler's diarrhea is acquired by the intake of food or water that is contaminated by human feces. As for enterohemorrhagic *E. coli* O157, the main reservoir is cattle and the organism is acquired in undercooked beef.

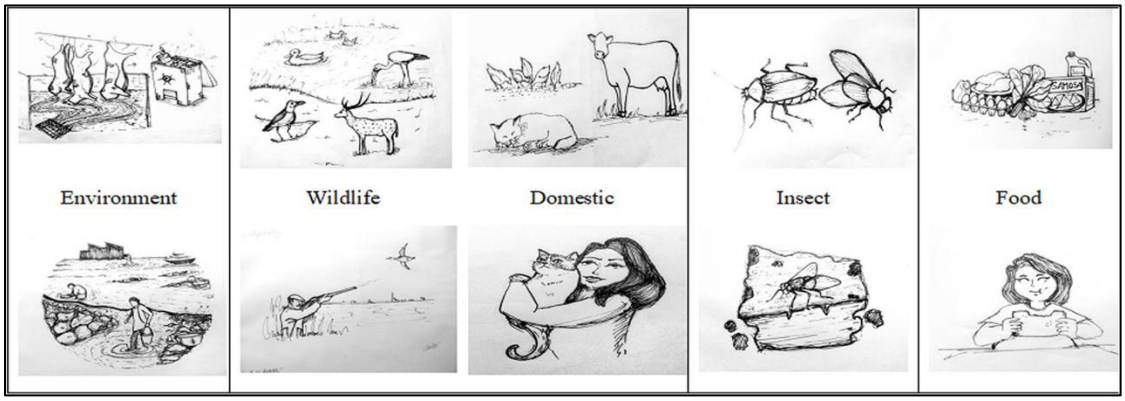

Figure 2.3: Transmission of antimicrobial resistant micro-organisms to humans

Source (Khan, et al., 2020)

E. coli has several clearly identified components that contribute to its ability to cause disease: pili, a capsule, endotoxin, and three exotoxins; two of which cause watery diarrhea and the third causes bloody diarrhea and hemolytic- uremic syndrome. Sometimes, extra intestinal pathogenic E. coli (ExPEC) that show extra intestinal manifestations like UTIs can also colonize the intestine. Nevertheless, they are incapable of causing gastrointestinal manifestations in humans and hence remain asymptomatic (Johnson & Russo, 2002). Due to lack of symptoms, they can establish prolonged colonization of the host intestinal tract and in some cases, may be more effective intestinal colonizers than the typical fecal commensal strains (Wold, et al., 1992). In some patients, colonized sexual partners or other household members may act as a reservoir from which a virulent strain of ExPEC can be reestablished into the patient resulting in recurrent infection (Foxman, et al., 1997).

2.3.4 Laboratory diagnosis

Specimens suspected of containing enteric gram-negative rods, such as *E. coli* are grown initially on a blood agar plate and on a differential medium such as EMB agar or MacConkey's agar. *Escherichia coli* which ferments lactose form pink colonies while

lactose negative organisms remain colorless. On EMB agar, *E. coli* colonies have a characteristic green sheen. Some important features that help distinguish *E. coli* from other lactose fermenting gram negative rods are

- it produces indole from tryptophan
- it decarboxylates lysine
- it uses acetate as it's only source of carbon
- it is motile.

2.4 Treatment of UTI

Antibiotics are used to treat UTI and this is one of the most common infection in a community where antibiotics are prescribed. The massive uncontrolled and inappropriate use of antibiotics have led to the development of antibiotic resistance. The World Health Organization has estimated 80% usage of antibiotics in communities where about 20-50% is used inappropriately. This has caused a serious alarming threat to the public health all throughout the world. It significantly impacts patient treatment and outcomes, increasing health care costs, morbidity, and mortality. Antibiotic therapy is the core treatment for UTIs, so the selected antibiotic should be an efficacious, safe, and cost-effective. In Saudi Arabia, one study estimated the prevalence of community-acquired urinary tract infections (CA-UTIs) as 25% of all infections seen in the Emergency department (Alanazi, 2018).

2.4.1 The aminopenicillins

Agents in this group of antibiotics show broad spectrum of activity and can be destroyed by β-lactamase that is produced by both gram-positive and gram-negative bacteria. (Petri, 2006) The aminopenicillins are bactericidal for both gram-positive and gram-negative bacteria. Although most strains of *N.gonorrhoeae*, *E.coli*, *P.mirabilis*, *Salmonella* and *Shigella* were highly sensitive when ampicillin was first introduced in the 1960s, an increasing percentage of these species are now resistant to the drug (Dahal & Chaudhary, 2018). From 30% to 50% of *E. coli*, practically all species of *Enterobacter*, and a significant number of *P.mirabilis* are currently insensitive to Ampicillin. Resistant strains of *Salmonella* that were plasmid mediated, have been recovered in various parts of the world with increasing frequency (Carattoli, 2003). Most strains of *Shigella* are now

resistant along with many strains of *Pseudomonas*, *Klebsiella*, *Serratia*, *Acinetobacter*, and indole-positive *Proteus*. Concurrent administration of a β-lactamase inhibitor such as clavulanate or sulbactam markedly expands the spectrum of activity of these drugs (Wright, 1999). The drugs in this class are ampicillin, amoxicillin and their congeners.

Ampicillin

This drug is the prototype of the group and its structural formula is shown below. Ampicillin is stable in acid and is well absorbed after oral administration. Intake of food prior to ingestion of ampicillin diminishes absorption. An oral dose of 0.5 g produces peak concentrations in plasma of about 3μg/ml at 2 hours. However, an intramuscular injection of 0.5 to 1g of sodium ampicillin yields peak plasma concentrations of about 7 or 10 μg/ml respectively at 1 hour which decline exponentially with a half-life of 80 minutes (William & Petri, 2006). In severe renal impairment, the persistence of this drug in plasma is prolonged, and peritoneal dialysis is ineffective in removing the drug from the blood. Instead, hemodialysis can help remove about 40% of the body stores in around 7 hours. Hence dose adjustment is required in presence of renal dysfunction. Ampicillin is also released in bile from where it undergoes enterohepatic circulation following which a considerable amount of the drug is excreted in feces (William & Petri, 2006).

Amoxicillin/Clavulanic Acid

Amoxicillin

This drug is semi synthetic penicillin and is susceptible to penicillinase. Pharmacologically and chemically, it is closely related to ampicillin. Amoxicillin is stable in acid and is designed for oral use. In comparison to ampicillin, this drug is absorbed more rapidly and completely from the gastrointestinal tract. The antimicrobial spectrum of amoxicillin is similar to that of ampicillin, with an exception that amoxicillin is less effective than ampicillin in treating shigellosis (William & Petri, 2006). After oral administration of the same dose, peak plasma concentrations appear to be 2 to 2.5 times greater with amoxicillin as compared to ampicillin. On administration of 250mg, the drug reaches its peak of about 4μg/ml at 2 hours. As compared to ampicillin, food does not interfere with its absorption and due to complete absorption of the drug within the gut, adverse effects such as diarrhea

are less following administration of amoxicillin. Apart from this, the incidences of other adverse effects appear to be similar. Even though the half-life of amoxicillin is similar to that of ampicillin, effective concentrations of orally administered amoxicillin are detectable in plasma for twice as long as with ampicillin again owing to more complete absorption. About 20% of amoxicillin is protein-bound in plasma, and most of the dose of antibiotic is secreted in its active form in the urine. Probenecid delays excretion of the drug (William & Petri, 2006). Most uncomplicated urinary tract infections are caused by Enterobacteriacea with *E. coli* being the most common species. Ampicillin often is an effective agent although resistance is increasingly common. Enterococcal urinary tract infections are treated effectively with ampicillin alone (Kristich, et al., 2014).

Clavulanic acid

These are certain molecules that can inactivate β-lactamases, thus preventing the destruction of β-lactam antibiotics which are substrates for this enzyme. β-lactamase inhibitors are most active against plasmid encoded β-lactamases (Saudagar, et al., 2008). Clavulanic acid is produced by *Streptomyces clavuligerus*. It has poor intrinsic antimicrobial activity; however, it can irreversibly bind β-lactamases that are produced by a wide range of gram-positive and gram-negative micro-organisms. Clavulanic acid is well absorbed orally and can also be given parenterally. Combined with amoxicillin it is given as an oral preparation while when combined with ticarcillin it forms a parenteral preparation (Saudagar, et al., 2008).

Amoxicillin plus clavulanate is effective in vitro and in vivo for β-lactamase producing strains of staphylococci, *H. Influenzae*, gonococci and *E. coli* (Rolinson, 1991). Amoxicillin-clavulanate plus ciprofloxacin has been shown to be effective in treating febrile patients with neutropenia from cancer therapy (Freifeld, et al., 1999; Kern, et al., 1999). It is also effective in the treatment of acute otitis media in children, sinusitis, animal or human bite wounds, cellulitis and diabetic foot infections.

2.4.2 Piperacillin/ Tazobactam

In the group of antipseudomonal penicillin, there are two subgroups: the Carboxypenicillins and the Ureidopenicillins. Piperacillin is one of the ureidopenicillins

with mezlocillin being the only other one. Both these ureidopenicillins have superior activity against *P. aeruginosa* as compared with carbenicillin and ticarcillin that belong to the carboxypenicillin subgroup. Both of these are sensitive to destruction by β-lactamases (William & Petri, 2006). Piperacillin has a broader spectrum as compare to ampicillin and includes most strains of *P. aeruginosa*, Enterobacteriaceae (non- β-lactamase producing), many *Bacteroides* species and *E. faecalis*. In combination with a β-lactamase inhibitor, it has the broadest antibacterial spectrum of the penicillins (Schoonover, et al., 1995). This drug is important for the treatment of patients with serious infections caused by gram-negative bacteria. These patients frequently have impaired immunological defenses, and their infections are often acquired in the hospital. Hence this penicillin is used commonly in treating bacteremia, pneumonia, infection following burns, and urinary tract infections due to micro-organisms that are resistant to penicillin G and ampicillin. Tazobactam is a penicillanic acid sulfone β-lactamase inhibitor and has good activity against many of the plasmid β-lactamases, including some of the extended spectrum class. It is combined with piperacillin as a parental combination (Bryson & Brogden, 1994).

2.4.3 Cephalosporins

Cephalosporins are a group pf β-lactam antibiotics that are derived from a fungus called cephalosporium. Although natural cephalosporins have low antibacterial activity, the attachment of various R- side groups have resulted in a wide range of drugs with varying pharmacologic properties and antimicrobial spectra and activity. The mechanism of action of cephalosporins is similar to that of penicillin. They bind to specific penicillin binding proteins (PBP) on the bacteria and inhibit cell wall synthesis by blocking the transpeptidation of peptidoglycan. They also activate autolytic enzymes in the cell wall that can produce lesions resulting in bacterial death (Marshall & Blair, 1999).

Resistance to cephalosporins can be attributed to poor permeation of bacteria by the drug, lack of PBP for a specific drug and degradation of drug by β-lactamases. There are certain second and third generation cephalosporins that can induce special β-lactamases in gram-negative bacteria (Sanders & Sanders, 1992). Nevertheless, in general, cephalosporins tend to be resistant to the β-lactamases produced by staphylococci and common gram-negative bacteria that hydrolyze and inactivate many penicillins. Since many cephalosporins are

excreted mainly by the kidneys, renal insufficiency may cause accumulation of the drug and induce toxicity. For ease of reference, cephalosporins have been arranged in to major groups called “generations”. First generation cephalosporins are very active against gram-positive cocci- except enterococci and methicillin resistant staphylococci (MRSA). They are moderately active against gram- negative rod- primarily *E coli*, *Proteus* and *Klebsiella*. None of the drugs from this generation are first choice drugs for any infections (William & Petri, 2006). Second generation cephalosporins are all active against micro-organisms covered by the first generation with extended coverage against gram-negative rods including *Proteus* and *Klebsiella* but not *P aeruginosa* (William & Petri, 2006).

Cefuroxime

This is a second-generation cephalosporin that can be used to treat a number of bacterial infections including pneumonia, meningitis, sepsis, otitis media, Lyme disease as well as urinary tract infections. It can be administered either orally or via intravenous or intramuscular routes. The common side effects are nausea, diarrhea and allergic reactions, however, severe side effects like anaphylaxis, *C. difficile* infection and Steven-Johnson-Syndrome can also occur. It is safe in pregnancy and can be used by mothers during breast feeding. If taken orally, it should be ingested after meals to prevent the adverse side effects of nausea and vomiting. Besides the bioavailability increases from 37% on an empty stomach up till 52% when taken after food. The half-life for elimination is 80 minutes and the drug is eliminated mostly unchanged in urine (Foord, 1976).

Cefuroxime Axetil (CAE)

This is an acetoxyethyl ester prodrug of cefuroxime that is effective when taken orally. It is rapidly hydrolyzed to the active parent compound Cefuroxime which has a broad spectrum of activity against methicillin-sensitive staphylococci and the common respiratory pathogens such as *S.pneumoniae, H. influenzae, M. catarrhalis and group A beta-haemolytic streptococci* (Scott, et al., 2001).

Ceftriaxone

This is a third-generation cephalosporin that are used to treat resistant organisms. It is the choice of treatment for bacterial meningitis caused by *pneumococci*, *meningococci* and *H. influenzae*. It is also used to treat vulnerable enteric gram-negative rods such as *E. coli*. This drug is active against *S. marcescens, Citrobacter spp* and strains of *Haemophilus* and *Neisseria* that produce beta-lactamase. It is given as intramuscular or intravenous routes. The most common adverse effects noted are local reaction at administration site, rashes and diarrhea. It has a half- life of between 5-8 hours and is excreted in the kidneys and in bile (Lamb, et al., 2002).

Cefoperazone/ Sulbactam

This is a combination drug where cefoperazone is a β- lactam antibiotic and sulbactam is a β- lactamase inhibitor that prevents bacteria from breaking down cefoperazone. It is effective in the treatment of UTIs (Jones, et al., 1987).

Cefepime

Cefepime is a fourth- generation cephalosporin that has a broad spectrum of activity against both gram positive and gram- negative bacteria. It has good activity against some important pathogens such as *S. aureus*, *P. aeruginosa* and multi drug resistant *S. pneumoniae.* It also has good activity against *Enterobacteriaceae* and hence is valuable in treating UTIs. Unlike other cephalosporins, cefipime cannot be degraded by chromosome and plasmid mediated β- lactamases (Chapman & Perry, 2003).

2.4.4 Carbapenems

These are β-lactam antibiotics that contain a fused β-lactam ring as well as a five-membered ring system that is different in structure from penicillin due to being unsaturated and containing a carbon atom instead of a sulfur atom. This class of antibiotics has a broader spectrum of activity than most other β-lactam antibiotics (Breilh, et al., 2013).

Imipenem

This drug is derived from a compound produced by *Streptomyces cattleya* and is marketed usually in combination with cilastatin, a drug that prevents the breakdown of imipenem by renal tubular dipeptidase. Like other β-lactam antibiotics, imipenem binds to penicillin-binding proteins, disrupts bacterial cell wall synthesis, and causes death of susceptible micro-organisms. It is very resistant to hydrolysis by most β-lactamases. The activity of imipenem is excellent for a wide variety of aerobic and anaerobic micro-organisms. Streptococci, enterococci (excluding *E. faecum* and non- β-lactamase- producing penicillin- resistant strains), staphylococci and *Listeria* are all susceptible to this drug. Although some strains of methicillin-resistant staphylococci are susceptible, many strains are not. Activity is excellent against the Enterobacteriacea, including organisms that are cephalosporin resistant. Anaerobes including *B. fragilis* are highly susceptible. Most strains of *Pseudomonas* and *Acinetobacter* are inhibited. Imipenem is not absorbed orally and the drug is broken down rapidly by a dipeptidase found in the brush border of the proximal renal tubule. Because of this, the concentrations of the drug were low in urine. To combat this, an inhibitor of the dehydropeptidase has been synthesized and a preparation containing equal amounts of imipenem and cilastatin has been developed (Balfour, et al., 1996). As a result, when the combined drug is used, 70% of imipenem is recovered in urine as the active drug. Normally, after intravenous administration of 500 mg of imipenem, average peak concentration in plasma is about 33μg/ml. Both imipenem and cilastatin have a half-life of about 1 hour. In patients with renal insufficiency, dose modification is necessary. The most common adverse reactions are nausea and vomiting. In about 1.2% of patients, seizures have also been reported, especially on administration of high doses in patients with CNS lesions and in patients with renal insufficiency. Hypersensitivity reactions may occur in patients who are allergic to other β-lactam antibiotics (Hellinger & Brewer, 1991). Imipenem-cilastatin is effective in the treatment of a wide variety of infections including urinary tract infections and lower respiratory infections, intra-abdominal and gynecological infections; and skin soft tissue, bone and joint infections. This drug has been efficiently used in the treatment of cephalosporin-resistant nosocomial bacteria such as *Citrobacter freundii* and *Enterobacter* species. It would be wise to use imipenem for the empirical treatment of serious infections in

hospitalized patients who have recently received other β-lactam antibiotics due to the increased risk of infection with cephalosporin or penicillin resistant bacteria. It should not be used as monotherapy for infections due to *P. aeruginosa* due to the risk of developing resistance to the drug during therapy (Balfour, et al., 1996).

Meropenem

Meropenam is a dimethyl-carbamoyl pyrolidinyl derivative of thienamycin. Since it is not sensitive to renal dipeptidase, it does not require coadministration with Cilastatin. Its toxicity is similar to that of imipenem; however, it is less likely to cause seizures. Also similar to imipenem is its in vitro activity, with additional activity against some imipenem resistant *P.aeruginosa*, with less activity against some gram positive cocci. Therapeutically its clinical activity is equivalent to that of imipenem (Baldwin, et al., 2008).

Ertapenem

Ertapenem is another carbapenem that is different from imipenem and meropenem by having a larger serum half-life that allows a once daily dosing. However, it has inferior activity against *P.aeruginosa* and *Acinetobacter* spp. Owing to its spectrum of activity against gram-positive organisms, Enterobacteriaceae, and anaerobes; it is used in intraabdominal and pelvic infections (Solomkin, et al., 2003).

2.4.5 Aminoglycosides

This is another group of antibiotics used primarily to treat infections caused by aerobic gram-negative bacteria. They are bactericidal inhibitors of protein synthesis. These agents contain amino sugars linked to an aminocyclitol ring by glycosidic bonds. They are polycations and their polarity is largely responsible for their pharmacokinetic properties that is shared by all members of the group. None of the members in this group are absorbed adequately after oral administration, concentrations found in the cerebrospinal fluid are inadequate, and all are excreted relatively rapidly by the normal kidney. Though aminoglycosides are widely used and important agents, serious toxicity such as nephrotoxicity and ototoxicity (involving the auditory and vestibular functions of the eighth cranial nerve) limit their use (Krause, et al., 2016).

Aminoglycosides are natural products or semi-synthetic derivatives of compounds produced by a variety of soil actinomycetes. They are usually not indicated for the treatment of uncomplicated urinary tract infections, although one older study shows that a single dose of intramuscular gentamicin injection (5mg/kg) has effectively cured more than 90% of uncomplicated infections of lower urinary tract (Varese, et al., 1980). However, as strains of *E. coli* have acquired resistance to β-lactams, trimethoprim-sulfamethoxazole, as well as fluroquinolones; use of aminoglycosides may increase. In a seriously ill patient with pyelonephritis, an aminoglycoside alone or in combination with a β-lactam antibiotic offers broad and effective initial coverage. Once the causative microorganism is isolated and its sensitivity to antibiotics is determined, the aminoglycoside should be discontinued if the infecting micro-organism is sensitive to less toxic antibiotics (Krause, et al., 2016).

Gentamicin

These are broad spectrum antibiotics derived from species of the actinomycete *Micromonospora*. It is an important agent for the treatment of many serious gram-negative bacillary infections. Because of its low cost and reliable activity against all except the most resistant gram-negative aerobes, it is the aminoglycoside of first choice. Preparations are available for parenteral, ophthalmic and topical administration. Although many different types of infections can be treated successfully with this drug, due to its toxicity, prolonged use should be restricted to life threatening infections or treatments where a less toxic agent is contraindicated or less effective (Appel & Neu, 1978).

Amikacin

This drug is a semi-synthetic derivative of kanamycin. The spectrum of antimicrobial activity is the broadest in this group. Because of its resistance to many of the aminoglycoside- inactivating enzymes, it has a special role in hospitals where gentamicin- and tobramycin- resistant microorganisms are widespread. The recommended dose of amikacin is 15mg/kg daily as a single dose or as two or three doses divided equally and that must be reduced in patients with renal failure. The drug is absorbed rapidly after intramuscular injection and peak concentrations in the plasma of 20μg/ml after injection of 7.5mg/kg. If the same dose is given as an intravenous infusion for over 30 minutes, the

peak concentration is nearly about 40μg/ml at the end of infusion which falls to 20 μg/ml after 30 more minutes (Ristuccia & Cunha, 1985). Amikacin has become the preferred agent for the initial treatment of serious nosocomial gram-negative bacillary infections in hospitals. It is active against the vast majority of aerobic gram-negative bacilli in the community and the hospital. This includes most strains of *Serratia, Proteus* and *P.aeruginosa*. It is also active against neatly all strains of *Klebsiella, Enterobacter*, and *E. coli* that are resistant to gentamicin and tobramycin. Resistance to amikacin is found among strains of *Acinetobacter, Providencia, Flavobacter,* and strains of *Pseudomonas* other than *P.aeruginosa* which are all unusual pathogens. Amikacin is less active than gentamicin against enterococci. It is not active against the majority of gram-positive anaerobic bacteria. It is active against *M. tuberculosis* including streptomycin-resistant strains and atypical mycobacteria. Hence it has been used in the treatment of disseminated atypical mycobacterial infections in AIDS patients (Chambers, 2006).

2.4.6 Quinolones

Nalidixic acid was the first quinolone isolated as a by-product of the synthesis of chloroquine. It has been available for the treatment of UTI for many years. Introduction of fluroquinolones such as **ciprofloxacin** has been a therapeutic advance since these agents have broad antimicrobial activity and are effective after oral administration for the treatment of a wide variety of infectious diseases (Andriole, 2000). The quinolone antibiotics target bacterial DNA gyrase and topoisomerase IV (Drlica & Zhao, 1997). While most gram-positive bacteria have topoisomerase IV activity that is mainly inhibited by quinolones, many gram-negative bacteria have their DNA gyrases as the primary quinolone target. Fluroquinolones are potent bactericidal agents against *E. coli* and various species of *Salmonella, Shigella, Enterobacter, Campylobacter and Neisseria.* Resistance to quinolones may develop during therapy through mutations in the bacterial chromosomal genes encoding DNA gyrase or topoisomerase IV, or by active transportation of the drug out of the bacteria (Hooper, 2001). These group of drugs are well absorbed after oral administration and are distributed widely in body tissues. Peak serum levels are reached within 1 to 3 hours of an oral administration of 400mg. Food does not impair absorption, but delays the time needed to reach peak levels. Bioavailability is greater than 50% for all

fluroquinolones with some having bioavailability as high as 95%. The concentration of the drug in urine, kidney, lung, prostate tissue, stool bile, macrophage and neutrophils are higher than serum levels. It is lower than serum levels in cerebrospinal fluid, bone and prostatic fluid (Tomé & Filipe, 2011).

2.4.7 Tigecycline

Tigecycline is the only glycylcycline currently in use. Glycylcycline are synthetic analogs of tetracyclines and they share the same binding site on the ribosomes as the tetracyclines. Tigecycline binds more keenly to the ribosome and this stronger binding is likely responsible for the enhanced activity against tetracycline-resistant organisms (Livermore, 2005). The drug is active against a broad spectrum of gram-positive and negative pathogens. Compared to tetracyclines, it is more active against methicillin-resistant *S aureus* and *S epidermidis*, drug susceptible and drug-resistant *S pneumoniae,* and enterococci. In terms of gram- negative aerobes, tigecycline has enhanced activity against several *Enterobacteriaceae,* including *Salmonella* and *Shigella* species and *Acinetobacter* species. It does not have good activity against *P aeruginosa, S maltophilia* or *Burkholderia cepacia.* Tigecycline also has good activity against many anaerobic bacteria including *B fragilis.* Owing to poor bioavailability, the drug is currently available only as a parenteral preparation. It has rapid and widespread distribution in tissues and protein binding ranges from 73% to 79%. The half-life for tigecycline is long, approximately 40 hours with elimination of the drug through biliary duct and into the faeces. Renal clearance is a secondary route of elimination (Pankey, 2005).

2.4.8 Nitrofurantoin

This drug is a synthetic nitrofuran, used to prevent and treat urinary tract infections. For its antimicrobial activity, enzymes that can reduce nitrofurantoin are of utmost important. Bacteria reduce this drug more than human cells and hence this drug is selective for antimicrobial activity. Nitrofurantoin is active against many strains of *E. coli* and enterococci; and susceptible bacteria rarely become resistant during therapy. The drug is, however, resistant to most species of *Proteus* and *pseudomonas*; and many species of *Enterobacter* and *Klebsiella*. At concentrations of 32 μg/ml or less, this drug is

bacteriostatic, and at concentrations of 100 μg/ml or more it is bactericidal. The antibacterial activity is higher in acidic urine (McOsker & Fitzpatrick, 1994). Although nitrofurantoin is absorbed rapidly and completely from the gastrointestinal tract, antimicrobial concentrations are not reached in the plasma since it is also eliminated rapidly. Plasma half-life is between 0.3 to 1 hour and around 40% is excreted unchanged in urine. The average dose yields a concentration of around 200 μg/ml in urine. Alkalinized urine reduces activity of the drug and excretion is linearly dependent on creatinine clearance (Conklin, 1978). Most common adverse effects are nausea, vomiting and diarrhea. Other adverse effects include various hypersensitivity reactions like fever, chills, leukopenia, granulocytopenia, hemolytic anemia, cholestatic jaundice and hepatocellular damage (McOsker & Fitzpatrick, 1994).

2.4.9 Colistin

Colistin is a polymyxin that is produced by *Bacillus colistinus*. It is available as colistin sulfate for oral administration and as colistimethate sodium for parenteral administration that is not recommended. Antimicrobial activity of colistin is restricted to gram- negative bacteria such as *Enterobacter, E. coli, Klebsiella, Salmonella, Pasteurella, Bordetella and Shigella* which usually are sensitive to concentrations of 0.05 to 2 μg/ml. Colistin interacts strongly with bacterial phospholipids and disrupt the structure of cell membrane (Biswas, et al., 2012).

2.4.10 Trimethroprim-Sulfamethoxazole (TMP-SMX)

The antimicrobial activity of the combination of trimethoprim and sulfamethoxazole results from its action on two steps of the enzymatic pathway for the synthesis of tetrahydro folic acid. Sulfonamide inhibits the incorporation of *para*-amino benzoic acid (PABA) in to folic acid, and trimethoprim prevents the reduction of dihydrofolate to tetrahydrofolate. Bacterial resistance to Trimethoprim-Sulfamethoxazole is a rapidly increasing problem although resistance to the combination is lower that to either of the drugs alone. Resistance often is due to achievement of a plasmid that codes for an altered dihydrofolate reductase. Treatment of uncomplicated lower UTI with cotrimoxazole is often highly effective for sensitive bacteria. In the family of Enterobacterecea, the combination drug shows a better

therapeutic effect than either of the drugs used alone. This combination has special efficacy in treating chronic and recurrent infections of the urinary tract (Smilack, 1999).

2.5 Prevention and control

Practicing good personal hygiene is one of the easiest ways to prevent or reduce the risk of developing UTI. Always wiping from front to back after a bowel movement is essential to prevent colonization of intestinal bacteria in to the vagina as well as the urethra. Women should also use good hygiene practices during their menstrual cycle in order to avoid infections. Changing pads and tampons frequently can help achieve this. Drinking plenty of water is another step in the prevention of UTI. It is recommended to drink around six to eight glasses of water per day as this removes extra bacteria from the urinary tract. Likewise, urination habits need to be changed as frequent urination decreases the risk of UTI, especially if there is history of recurrent UTI. This habit can be encouraged by drinking plenty of water. Additionally, drinking cranberry juice has shown a reduction in incidences of UTI (Beerepoot, et al., 2013). Moreover, it is sensible to urinate before and after copulation to flush out any bacteria's that could have been introduced during sexual intercourse. Washing genitals using warm water after sex is a safe practice. Birth control methods such as use of diaphragm, spermicide-treated condoms, etc., can all contribute to bacterial growth hence causing UTI. Thus, birth control methods need to be changed. Additionally, tight fitting and synthetic undergarments should be avoided and regular change of undergarments should be practiced. In case of catheterized patients, the catheter must be inserted for a short duration and proper care should be taken to prevent catheter-associated urinary tract infections. These should be inserted using sterile technique in hospital settings and kept sealed (Lam, et al., 2014). Lately, vaccination strategies have been employed in the prevention of UTIs. OM89 (Uro-Vaxom) is one such vaccine that is registered in Germany and Switzerland to prevent recurrent UTIs. This vaccine contains lyophilized bacterial lysates that were derived from 18 strains of *E. coli* that are usually implicated as causing UTI. Another vaccine Urovac consists of 10 heat- killed species of uropathogenic bacteria, six of which are different serotypes of *E. coli*. Recently ExPEC4V was developed that contains four biconjugates and have the O-antigens of *E. coli* serotypes O1A, O2, O6A, and O25B (Aziminia, et al., 2019).

2.6 Antimicrobial resistance

This is an emerging global concern that threatens public health sectors throughout the world. Antimicrobial resistance occurs when bacteria, that were previously sensitive to certain antibiotics, now become unresponsive on use of these medicines. Bacteria that become antibiotic resistant may infect humans and animals with the resulting infection being much harder to treat than non-resistant bacteria. As a result, prolonged hospital stays, higher medical costs and increased mortality rates pursue. Apart from development of new antibiotics, changes in behavior are also necessary to limit the spread of resistant bacteria (WHO, 2020).

Incidence of antimicrobial resistance is specifically higher in developing countries where antibiotics are not properly prescribed, or are misused. Due to lack of adequate monitoring of products, poor quality of drugs is produced and dispensed over the counter without any required prescription. National poverty (leading to malnutrition, poor healthcare standards, chronic and repeated infections, unaffordability of more effective and costly drugs) is another factor associated with growing antibiotic resistance (Ayukekbong, et al., 2017; Sosa, et al., 2010). Nevertheless, antibiotic resistance in the developed world is also common. However, the causes due to which resistance grows are different. Poor regulations of antibiotic use in hospitals and over use of antibiotics in food producing animals play a major role in developing resistant strains here (Chokshi, et al., 2019).

2.6.1 Resistance pattern in humans

Among human beings, the resistance for antibiotics vary across the globe. In Europe, the incidences of antibiotic resistance for UTI causing pathogens are higher in the southern countries as compared to the north (Kandil, et al., 2016). This could be related to the fact that the top four antibiotic consumer countries (Italy. France, Greece, Cyprus) are located in the south (Adriaenssens, et al., 2011). In these countries, *E. coli* was the most frequent bacteria isolated followed by *Enterococcus spp.*, *Klebsiella spp.*, *P. aeruginosa* and *Proteus spp.* The prevalence of resistant bacteria somewhat changed with time and prevalence seemed to increase for resistant *E. coli* and *Proteus spp* (Hrbacek, et al., 2020). Resistance for ampicillin is over 50% while that for amoxicillin/clavulanic acid is 10%. In case of cephalosporins, cefotaxime and ceftazidime are preferred over cefuroxime since

the latter has over 10% incidences of antibiotic resistance. Ciprofloxacin resistance was found to be over 40% in cases of gram-negative organisms. In case of aminoglycosides, amikacin was preferred since strains resistant to gentamycin were found.

The burden of antibiotic resistance is much higher in Asia with particular antibiotic resistant bacteria being more prevalent in specific locations that are now spreading worldwide. One such example is the New-Delhi metallo-β- lactamase (NDM) producing Enterobacteriaceae that was initially identified in India and is now present in many other nations. (Lai, et al., 2014). For *S.aureus*, Methicillin-resistant strains (MRSA) accounted for 25.5% of community acquired infections and 67.4% of nosocomial infections (Lai, et al., 2014). Additionally, reduced susceptibility to vancomycin was also reported and led to development of Vancomycin-intermediate *S.aureus* (VISA) and heterogenous vancomycin-intermediate *S.aureus* (hVISA). For enterococci, Vancomycin Resistant Enterococci (VRE) have become a threat especially in hospital related infections across Asia (Song, et al., 2009). *S. pneumoniae* has shown resistance to penicillin and ceftriaxone in selected Asian countries. In case of Enterobacteriaceae, multi drug resistance has been observed for E. coli, and K. pneumoniae. Extended spectrum β-lactamase producing Enterobacteriaceae are also a common finding in many countries in Asia with the highest rates found in South Asian countries like India, Sri Lanka, etc. Carbapenam Resistant Enterobacteriaceae (CRE) has recently emerged and has made clinical conditions of the patients quite complicated due to limited treatment choices. Other multi drug resistant bacteria that are quite prevalent in Asia are *P. aeruginosa, Acinetobacter spp*. etc. In Indonesia, *E. coli* and *K. pneumoniae* have a prevalence of more than 50% (Ginting, et al., 2019). A meta-analysis on the prevalence of antibiotic resistance among the Asian countries identified several medications that the micro-organisms developed resistance against. From population-based surveys, prevalence of resistance to Nitrofurantoin ranged between 7.7% and 31.4%. However, in Sri Lanka a higher prevalence of 54.1% was observed (Sugianli, et al., 2021). The prevalence for fosfomycin resistance was reported in Hong Kong and Indonesia alone, and were 1.8% and 1.63% respectively. High prevalence for cotrimoxazole resistance were observed in studies from Bhutan (52.9%) and India (64.2%-73.9%). Similarly, high prevalence for ciprofloxacin, ceftriaxone and cefotaxime

were also reported in studies from India and Indonesia. In Sri Lanka, there is an increasing resistance of uropathogens to carbapenems (25%).

When it comes to resistance of antibiotics to uropathogens, Bangladesh isn't far behind. The country poses a high number of antibiotic resistances leading to global threat. Majority of UTIs are caused by bacteria, with the most common causative organisms being the host's endogenous microbial flora, as well as gram negative rods. Hence, antibiotics play a major role in UTI treatment. Physicians usually prescribe susceptible antibiotics for a week or two to completely ensure the infection has been cured. In certain cases where the infection has spread to the kidney or different parts of the urinary tract patient require several weeks of antibiotic treatment. However, in recent years according to WHO, UTI treatment has become very complicated because there has been a surge in antibiotic resistance and a decline in rate of new antibiotic development (Chokshi, et al., 2019). Within Asia, Bangladesh has one of the highest prevalence of uropathogens that are resistant to commonly used antibiotics such as cotrimoxazole, ciprofloxacin and ceftriaxone. Additionally, resistance to carbapenem drugs is developing steadily with over 50% of uropathogens already resistant to meropenem (Sugianli, et al., 2021). In a study performed in Comilla Medical College Hospital, Bangladesh in July 2015-June 2016, it was seen that meropenem, imipenem, amikacin, tazobactam, gentamycin, nitrofurantoin, and mecillinam were found to be resistant against 0% to 12% of the urological pathogens. Around 60% to 86% bacteria produced high degree of resistance against commonly used antibiotics - amoxycillin, amoxiclav, cephradine and cefixime. The antibiotic resistance pattern of uropathogenic bacteria is increasing gradually. Between 2011 and 2016, a significant increase in resistance to antibiotics like ceftriaxone, and amoxiclav were detected. Some of the major reasons for such antibiotic resistance are due to irrational prescribing of antibiotics by physicians, unnecessary or inappropriate use of antibiotics, self-medication among patients, and situations are further worsened by indiscriminate use of antibiotics in agriculture and farming (Biswas, et al., 2014; Sutradhar, et al., 2014). On the other hand, due to causes unknown, decrease in resistance to nalidixic acid, mecillinam, cefixime and cefuroxime were also noted. Antibiotics like imipenem, amikacin, tazobactam, gentamycin, and mecillinam, were found to be the most effective antibiotics against the urological pathogens (Majumder, et al., 2019).

2.6.2 Resistant pathogen in wildlife

Wild life also contributed generously to the antibiotic resistance dilemma with high percentages of resistant organisms reported prevalent among wild animals. Cephalosporin resistance is as high as 51% in wild birds and chloramphenicol resistant organisms were found only in insects such as houseflies. Also found were high percentages of organisms that were resistant to macrolids both in wild life and in insects (Ramey & Ahlstrom, 2020).

2.6.3 Resistant pathogen in environment

Antibacterial resistant pathogens within the environment usually come from animals or humans. Contamination of the environment with residual antibiotics and resistant organisms or genes can be made by humans through waste disposal of pharmaceutical plants, untreated waste waters and hospital wastes. This increases the risk of antibacterial resistance in countries with low resource settings (Davies & Davies, 2010). One study found the highest prevalence of *E. coli* in food sources, followed by insects, wildlife, the environment and then domestic animals (Khan, et al., 2020). The food chain is the major source of transmission of these pathogens in to human beings. Among all the antibiotics that were found resistant, tetracycline resistance against *E. coli* ranged from 34% to 70.4%, while aminopenicillin resistance was between 47 - 200% among samples from wildlife, food sources, domestic animals and insects. About 28% of the environmental samples consisted of resistant strains of *E. coli*. In case of *Salmonella Spp.* tetracycline resistance varied from 94.3 to 173.5% and aminopenicillin resistance ranged from 82.4% to 200%. Most of the resistant *Salmonella* species have spread to various countries through food (Ellerbroek, et al., 2010).

2.6.4 Resistant pathogen in food producing animals

In domestic animals, antibiotic resistance pattern against gram negative organisms is quite alarming since options to treat such infections are limited to a few antibiotics. Infections due to bacteria such as *P. aeruginosa*, *Acinetobacter* and Enterobacteriaceae are becoming resistant to nearly all available antibiotics including carbapenems (Alonso, et al., 2017). The universal use of antibiotics for animal health and production purposes surpasses the use in humans, and most of the drugs designed solely for veterinary use are closely related

or belong to the same antimicrobial classes as those indicated for humans (Cantas, et al., 2013; Aarestrup, et al., 2008).

Antibiotics are used in food producing animals not only to avoid infections but also to promote growth when given at low subtherapeutic levels. Although use of antibiotics to promote growth has been banned in Europe in 2006, this action has not been implemented elsewhere and hence antibiotics are used even today in many countries of the world. In Africa, tetracyclines and β- lactams(penicillin) Sulphonamides and Macrolids (Tylosin) are commonly used to enhance growth followed by fluroquinolones. The highest rate of antibiotic usage is suspected to be in chickens since the highest amount of resistance strains have been isolated from them. The highest rates of resistance among animals have been found for tetracyclines, trimethoprim/sulfamethoxazole and ampicillin. Some studies have reported high prevalence of resistance of quinolones in cattle. One study attempted to identify the Plasmid-Mediated Quinolone Resistant (PMQR) genes in poultry and pigs (Ogbolu, et al., 2011). Four different gene variants located on five different plasmid types suggested that Food Producing Animals (FPA) could act as PMQR determinants. Furthermore, the *qnrS*1 gene that codes for low quinolone resistance was also found in commensal *E. coli* isolates from poultry. All the strains in this study also carried the bla_{TEM}-*1* gene for β-lactamase and one strain was positive for *CTX-M-15* (Fortini, et al., 2011). Another study identified the emergence of plasmid mediated colistin resistant gene *mrc-1* among chicken in three different countries. Isolated from chicken imported from France showed the presence of both bla_{TEM}-*1* and *mrc-1* colocalized on the same plasmid. These plasmids were also isolated from calves in France (Haenni, et al., 2016) and food samples in Portugal (Tse & Yuen, 2016). Polymixin is considered a last resort antibiotic in humans, yet it has been used extensively in animals resulting in the potential development of resistant strains (Rhouma, et al., 2016).

Regarding surveillance on Shiga-toxin producing *E. coli* O157, high prevalence of MDR resistant isolates were reported. Elevated rates of resistance for tetracycline and sulphamethoxazole was found, but more alarming was the detection of genes for third generation cephalosporin resistance. Healthy domestic animals, particularly cattle and sheep are natural reservoirs for this. In case of ESBL producing *E. coli* CTX-M-15 is the

predominant enzyme that was detected among livestock in Africa. Carbapenamase resistant genes were found among different dairy cattle farms from Egypt where four *E. coli* strains having bla_{OXA-48} and one having $bla_{OXA-181}$ carbapenemase genes, all of them phenotypically resistant to meropenem and imipenem were detected. Also, necessary to mention is the ertapenam resistant strain of *E. coli* among chicken in Nigeria. In South East Asia, integrated farming is common where organic wastes from livestock as well as poultry are used to feed fish farms. Thus, the antimicrobial residue within poultry and livestock wastes provides sufficient selection pressure for antimicrobial resistance genes thus increasing resistance between livestock and aquatic environment. In Bangladesh, commercial poultry production is rapidly increasing and this is considered as a high risk for emergence of resistance against antibiotics. This is because of the excessive use of probiotics and unregulated and unnecessary use of antibiotics without any prescriptions in the domestic animals through their food and water supply. The antibiotic resistance bacteria and the antibiotic resistant genes then spread to the surrounding environment through urine and feces of these domestic animals (Bengtsson-Palme & Larsson, 2015). In a report published on 'antimicrobial sensitivity tests', on broiler and layer farms in 2005, it has been observed that a high prevalence of drug resistant micro-organisms is harbored by these animals.

2.7 Antimicrobial resistance against *Escherichia coli*

One of the major causes of UTI is *E. coli* and high resistance to 3rd generation cephalosporins has been reported for *E. coli*. This means that the treatment of severe infections must rely on carbapenems, the last option to treat severe community and hospital acquired infections. These antibacterials are comparatively more expensive and are not highly available in constrained settings. Additionally, carbapenamase producing bacteria have also emerged and this is creating a major problem. *E. coli* has been reported to be highly resistant to fluroquinolones which has cause a major limitation in orally treating UTI. Because of an increase in antibiotic resistance, patients develop severe infections by the resistant strains, ultimately increasing the risk of a fatal outcome and also consuming more healthcare resources (WHO, 2014).

2.8 Prevention and control of antimicrobial resistant strains

In order to prevent and control the development of antibiotic resistant strains of uropathogens, three important steps should be considered. Firstly, physicians need to improve their method of prescribing antibiotics. Even today, antibiotics are prescribed in generous amounts in both inpatient and outpatient setting despite lack of evidence that it is necessary. At times, the choice of antibiotics the dosage or the duration of treatment with this are inappropriate (CDC,2011; Shapiro, et al., 2014). Furthermore, there are wide variations in prescription rates of antibiotics across different countries or even different regions or states of the same country that cannot be explained by a variation in patient population or rates of bacterial diseases (Hicks, et al., 2013). This is true not only in cases of UTI but also other infections such as respiratory tract infections (Hersh, et al., 2013), gastrointestinal tract infections, and many more. Since antibiotic use is the principal driver of antibacterial resistance, limiting its use to only when it is necessary can help prevent further emergence of resistant strains. Thus, surveillance and exploration of physicians prescribing behavior with development of evidence based on empirical therapy for treating UTI is highly recommended. Constant monitoring of culture sensitivity patterns of specific organisms in different healthcare center must be carried on regular basis. At the same time, community awareness program should be undertaken for adherence to treatment protocol considering bacterial resistance. Secondly, resistant strains should be stopped from spreading everywhere by preventing infections altogether. This can be achieved with the help of immunization and rigorous infection control such as hand washing. Patient counselling by the doctor on how to avoid spreading or becoming infected with resistant pathogens within the community is necessary. Finally, reporting resistant cases to public health authorities is necessary. Notification of high priority antibiotic resistant infections at a national level could further enhance data collection and hence show a better scenario of the prevalence of resistance strains within our country. Furthermore, gathering analyzing and distributing information on the prevalence of resistant micro-organisms that can help in both clinical and public health strategies and decision making. An important hint on identifying resistant strains is the cause of unexpected treatment failure. Patients that return with persistent infection or recurrence in infection shortly after treatment need to be retested by culture and antimicrobial susceptibility testing. In case of any treatment failure

or positive culture test after receiving empirical treatment, the local health authorities should be notified. Afterall, public health surveillance depends on doctors and laboratories (WHO, 2019).

The nightmare situation of a pan-resistant bacterial distribution is a frightening yet real possibility. Already there are cases of untreatable infections occurring; and preventing and controlling resistance strains requires a multisectoral approach in the society (Cantas et al.,2016). However, the physician's role in this effort is exceptionally very important. As the threat becomes more urgent, it is the leadership of the medical community that is most critical to ensure a successful response.

CHAPTER 3- MATERIALS AND METHODS

3.1 Description of the study area

The district of Chattogram is an administrative region of the Chattogram Division that is located in southeastern Bangladesh. Being a large port city and is considered as the commercial capital of Bangladesh. The geographical diversity of Chattogram is very different from other districts in the country owing to its mountains, valleys, seas and forests. The district is bounded in the north by Feni district as well as the Indian state of Tripura, in the south by Cox's Bazar district, on the east by Bandarban, Rangamati and Khagrachhari districts; and on the west by Noakhali district and the Bay of Bengal.

Figure 3.1: Map of Chattogram

Apart from the archipelago, Sandwip island is also a part of Chattogram. The entire district has an area of 5,263 km^2 with a population of 6,913,375 (Portal, 2021). The Chattogram metropolitan area currently has a population of about 5 million (World Population Review, 2021). It is placed between the Chittagong Hill Tracts and the Bay of Bengal, lying at the banks of the Kornophuli River. A high degree of religious and ethnic diversity exists within Chattogram despite having an overwhelming Bengali Muslim majority. Minorities include Bengalis of other faiths such as Hindus, Christians and Buddhists. Others minorities like the Chakmas, the Marmas and the Bohmong usually reside within the hill tracts of Chattogram. The district has a tropical monsoon climate with temperatures between 21°C to 30°C. It is also known for its rich biodiversity with hills and jungles laden with flowing river streams and elephant reserves. Economically, Chattogram contributes to a substantial share of Bangladesh's national GDP making up about 12% of the nation's GDP (The Chittagong chamber of commerece and industry, 2021). About 75% of the country's total export and 80% of total import occurs through the city of Chattogram.

Epic Healthcare Ltd is a diagnostic center well known for its advanced testing facilities and reliability in test results. It is located opposite to Chittagong Medical College Hospital, where many cases from around the city are referred. Consequently, for proper evaluation of the samples, many cases are referred to this diagnostic center.

3.2 Study Design

The study was a cross-sectional study that was conducted in the city of Chattogram using secondary data collected from the above-mentioned laboratory. Only urine culture and sensitivity reports obtained from this diagnostic center was included in our study.

3.3 Study period

Data was collected for this study over a period of two years from January 2019 to end of December 2020.

3.4 Sample size calculation

Sample size was determined according to (Thrusfield & Brown, 2017), using the estimated prevalence of 50%. The following formula was used.

$$n = \frac{(1.96)^2 \text{Pexp}\ (1-\text{Pexp})}{d^2}$$

where:

n = required sample size;

P_{exp} = expected prevalence;

d = desired absolute precision.

Since the expected prevalence of 50% is to be estimated with a desired absolute precision of ± 5 (i.e., the limits of the associated 95% interval are 25% and 35%), then:

P_{exp} =0.50,

d =0.05

Substituting these values in the formula:

$$n = \frac{(1.96)^2 \text{x}\ 0.5\ (1-0.5)}{(0.05)^2} = 384$$

To avoid bias and other unwanted errors, 400 samples were taken for this study.

3.5 Collection of data

As many as 400 culture and sensitivity reports that came back positive for *E. coli* were consecutively collected after obtaining permission from appropriate laboratory authorities. Data such as age and gender were collected by the laboratory personnel from the patient when they came to submit their urine sample for culture and sensitivity. To protect patient privacy, only gender, age and date of sample collection along with case registration number were provided along with the culture-sensitivity test reports.

3.6 Laboratory procedures

3.6.1 Sample collection

Patients were given a wide mouthed, leak proof, sterile and lidded container that was labelled with their name, registration number, date of birth and date. They were then advised to collect midstream urine. Once the sample was collected, it was immediately refrigerated and then delivered to the laboratory.

3.6.2 Isolation and identification of *E. coli* and susceptibility testing

About 0.01ml of well mixed urine sample was first inoculated in MacConkey's agar and incubated for 24 hours at 37°C. A colony count of minimum 10^5 CFU/ml for a single sample was taken as positive culture. All isolates were initially screened by their colony morphology, production of pigments and Gram staining techniques. Further isolation was made by other relevant tests. An isolate that was indole and methyl-red positive, citrate negative and urea negative; produced gas and acid; and was motile was considered to be *E. coli.* The pure isolated colony were then separated from the blood agar or SDA plate and then inoculated once again in a Vitek ID tube.

Vitek ID tube inoculation and antimicrobial sensitivity testing

At least 3 mL of sterile saline was aseptically transferred into a clear polystyrene 12×75 mm test tube. Using sterile cotton swabs, a homogenous organism suspension was prepared by transferring several isolated colonies from the plates to the saline tube. The suspension was then adjusted to the McFarland standard required by the ID reagent using a calibrated V2C DensiCHEK Plus Meter. In case of gram-negative micro-organisms, the required inoculum concentration should be between 0.5 to 0.63 McF ranges. The prepared suspensions were then placed in the cassette and the vitek compact system was used to read the samples. The results get saved on to the computerized Vitek software and the results can be printed out.

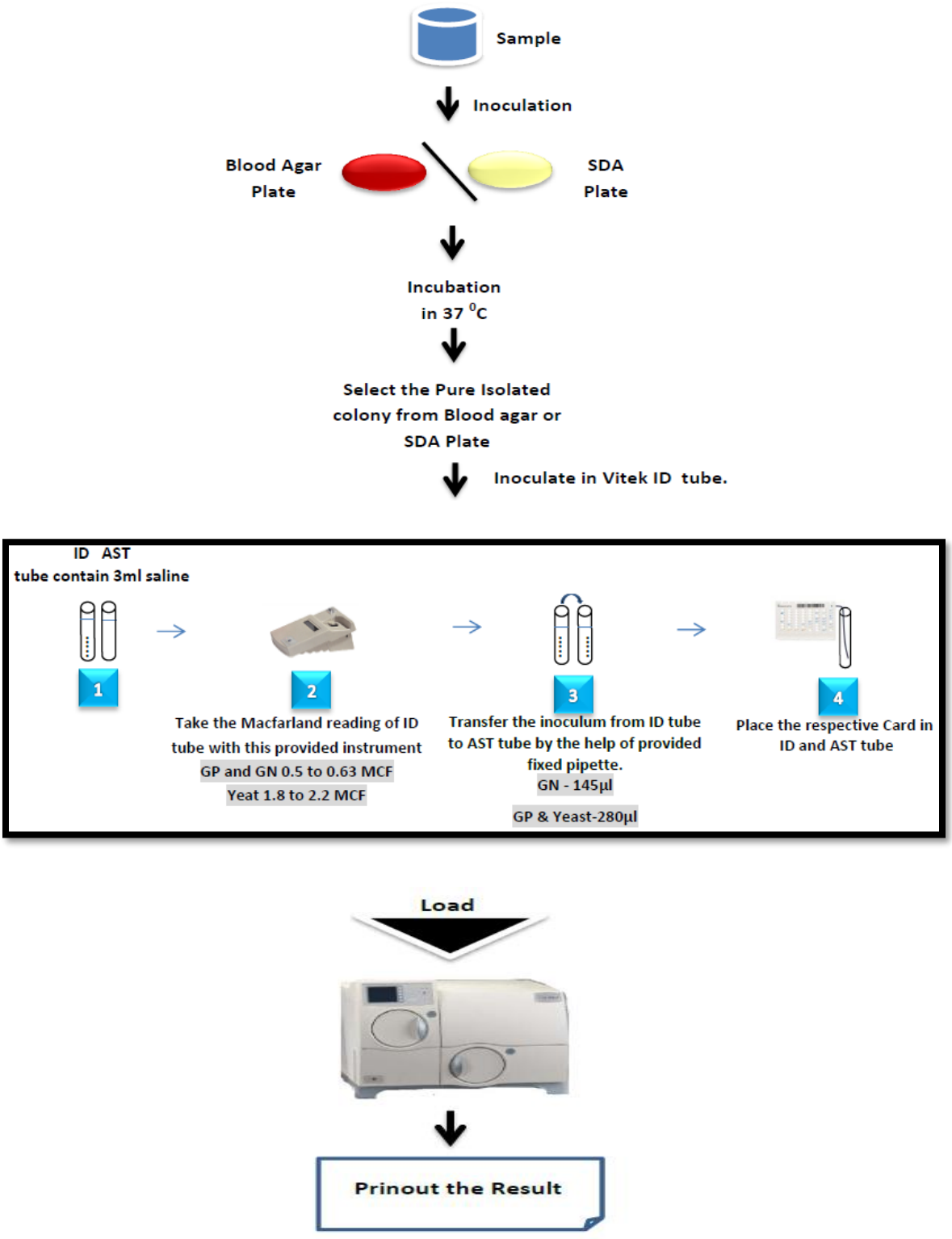

Figure 3.2: Sample processing

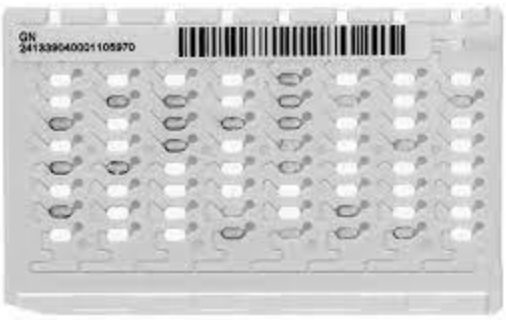

Figure 3.3: Vitek 2 GN cassette

3.7 Data analysis

Data that was electronically collected from the data warehouse within the laboratory were compiled on to a Microsoft excel spreadsheet. The data was then analyzed using STATA/IC 1 (StataCorp 4905, Lakeway Drive, College Station, Texas 77845, USA).

3.7.1 Descriptive analysis

Prevalence of antibiotic sensitivity patterns were calculated by dividing number of sensitive strains by the total number of culture positive samples expressing the result as a percentage. Prevalence of antibiotic resistance patterns were also done in a similar way. Stacked bar graphs were used to present these. The frequency of samples against the number of drugs they are resistant to, were presented in a table and also expressed as a percentage to the total.

3.7.2 Risk factor analysis

A univariable analysis were conducted against the dependent variable for age and gender of the study subjects. Chi square test was done to identify significant risk factors for the sensitivity and resistant patterns of the antibiotics. A p- value of <0.05 was considered as statistically significant. Univariate analysis was also conducted against multi-drug combinations and the results were presented in a table with frequency at 95% confidence intervals (CI).

CHAPTER 4- RESULTS

4.1 Antimicrobial resistance based on gender

To find out the variations about antimicrobial resistance between men and women, a univariate analysis was conducted for all twenty-two antibiotics using chi-square test. A p-value < 0.05 was considered as significant.

Table 4.1. Univariate association between antimicrobials and gender:

Antimicrobials	Gender	Resistant n (%)	Sensitive n (%)	P value
Ampicillin	Female	248 (97.64)	6 (2.36)	0.573
	Male	131 (98.50)	2 (1.5)	
Amoxicillin	Female	148 (58.27)	106 (41.73)	0.080
	Male	89 (67.42)	43 (32.58)	
Piperacillin	Female	85 (32.95)	173 (67.05)	0.360
	Male	50 (37.59)	83 (62.41)	
Cefuroxime	Female	245 (96.08)	10 (3.92)	0.367
	Male	133 (97.79)	3 (2.21)	
Ceftriaxone	Female	246 (94.62	14 (5.38)	0.895
	Male	131 (94.93)	7 (5.07)	
Cefixime	Female	1 (50)	1 (50)	0.709
	Male	2 (66.67)	1 (33.33)	
Cefoperazone	Female	75 (29.64)	178 70.36	0.053
	Male	52 (39.39)	80 (60.6)	
Cefepime	Female	169 (66.02)	87 (33.98)	0.061
	Male	103 (75.18)	34 (24.82)	
Ceftazidime	Female	2 (66.67)	1 (33.33)	0.248
	Male	0	1 (100)	
Ertapenem	Female	34 (13.65)	215 (86.35)	0.137
	Male	25 (19.53)	103 (80.47)	
Imipenem	Female	33 (12.64)	228 (87.36)	***0.040***
	Male	28 (20.44)	109 (79.56)	
Meropenem	Female	34 (13.39)	220 (86.61)	***0.028***
	Male	29 (22.14)	102 (77.86)	
Amikacin	Female	25 (9.54)	237 (90.46)	***0.014***
	Male	25 (18.12)	113 (81.88)	

Gentamicin	Female	52 (19.92)	209 (80.08)	***0.028***
	Male	41 (29.71)	97 (70.29)	
NalidixicAcid	Female	238 (92.97)	18 (7.03)	0.498
	Male	122 (91.04)	12 (8.96)	
Ciprofloxacin	Female	206 (78.63)	56 (21.37)	0.441
	Male	113 (81.88)	25 (18.12)	
Levofloxacin	Female	2 (28.57)	5 (71.43)	0.429
	Male	3 (50.00)	3 (50.00)	
Tigecycline	Female	4 (1.54)	255 (98.46)	0.961
	Male	2 (1.48)	133 (98.52)	
Nitrofurantoin	Female	50 (19.23)	210 (80.77)	***0.014***
	Male	41 (30.15)	95 (69.85)	
Colistin	Female	1 (0.39)	255 (99.61)	0.637
	Male	1 (0.75)	132 (99.25)	
Trimethoprim	Female	138 (53.70)	119 (46.30)	0.147
	Male	84 (61.31)	53 (38.69)	
Azithromycin	Female	5 (71.43)	2 (28.57)	0.612
	Male	5 (83.33)	1 (16.67)	

The table above shows the differences in sensitivity patterns against different antibiotics among male and female population in this study. We did not find any significant difference between male and female subjects regarding the antibiotic resistant pattern for most of the drugs. However, there were a few antibiotics that were more resistant in male study subjects as compared to the females. These are imipenem, meropenem, amikacin, gentamicin and nitrofurantoin.

4.2 Univariate analysis of antimicrobial resistance against age group

The study population was divided in to four different age groups; below 20 years, 21-40, 41-60 and more than 60 years. A chi-squared test was used to compare between the ages for each of the twenty-two antibiotics.

Table 4.2. Univariate association between antimicrobials and Age categories:

Antimicrobials	Age	Resistant n (%)	Sensitive n (%)	P value
Ampicillin	≤ 20	77 (98.72)	1 (1.28)	0.622
	21-40	73 (96.05)	3 (3.95)	
	41-60	130 (98.48)	2 (1.52)	
	≥ 60	99 (98.02)	2 (1.98)	
Amoxicillin	≤ 20	53 (67.95)	25 (32.1)	0.531
	21-40	44 (57.14)	33 (42.86)	
	41-60	78 59.54)	53 (40.46)	
	≥ 60	62 (62)	38 (38)	
Piperacillin	≤ 20	33 (42.31)	45(57.69)	0.116
	21-40	26 (32.91)	53 (67.09)	
	41-60	36 (27.48)	95 (72.52)	
	≥ 60	40 (38.83)	63 (61.17)	
Cefuroxime	≤ 20	76 (97.44)	2 (2.56)	0.783
	21-40	73 (94.81)	4 (5.19)	
	41-60	129 (96.99)	4 (3.01)	
	≥ 60	100 (97.09)	3 (2.91)	
Ceftriaxone	≤ 20	76 (97.44)	2 (2.56)	0.138
	21-40	73 (92.41)	6 (7.59)	
	41-60	130 (97.01)	4 (2.99)	
	≥ 60	98 (91.59)	9 (8.41)	
Cefixime	21-40	1 (100)	0	0.659
	41-60	1 (50)	1 (50)	
	≥ 60	1 (50)	1 (50)	
Cefoperazone	≤ 20	28 (35.90)	50 (64.10)	0.234
	21-40	25 (32.89)	51 (67.11)	
	41-60	35 (26.72)	96 (73.28)	
	≥ 60	39 (39)	61 (61)	

Cefepime	≤ 20	59 (75.64)	19 (24.36)	0.074
	21-40	50 (63.29)	29 (36.71)	
	41-60	99 (74.44)	34 (25.36)	
	≥ 60	64 (62.14)	39 (37.86)	
Ceftazidime	21-40	2 (100)	0	***0.046***
	21-40	0	0	
	41-60	0	0	
	≥ 60	0	2 (100)	
Ertapenem	≤ 20	10 (13.16)	66 (86.84)	0.077
	21-40	12 (16.22)	62 (83.78)	
	41-60	14 (10.94)	114 (89.06)	
	≥ 60	23 (23.23)	76 (76.77)	
Imipenem	≤ 20	10 (12.82)	68 (87.18)	0.184
	21-40	14 (17.50)	66 (82.50)	
	41-60	15 (11.19)	119 (88.81)	
	≥ 60	22 (20.75)	84 (79.25)	
Meropenem	≤ 20	11 (14.10)	67 (85.90)	0.109
	21-40	14 (18.42)	62 (81.58)	
	41-60	15 (11.45)	116 (88.55)	
	≥ 60	23 (23)	77 (77)	
Amikacin	≤ 20	10 (12.82)	68 (87.18)	0.221
	21-40	14 (17.50)	66 (82.50)	
	41-60	11 (8.15)	124 (91.85)	
	≥ 60	15 (14.02)	92 (85.98)	
Gentamicin	≤ 20	20 (25.64)	58 (74.36)	0.582
	21-40	18 (22.50)	62 (77.5)	
	41-60	35 (25.93)	100 (74.07)	
	≥ 60	20 (18.87)	86 (81.13)	

NalidixicAcid	≤ 20	75 (96.15)	3 (3.85)	0.408
	21-40	69 (89.61)	8 (10.39)	
	41-60	120 (90.91)	12 (9.09)	
	≥ 60	96 (93.20)	7 (6.80)	
Ciprofloxacin	≤ 20	65 (83.33)	13 (16.67)	0.101
	21-40	59 (73.75)	21 (26.25)	
	41-60	104 (77.04)	31 (22.96)	
	≥ 60	91 (85.05)	16 (14.95)	
levofloxacin	21-40	2 (50)	2 (50)	0.850
	41-60	1 (33.33)	2 (66.67)	
	≥ 60	2 (33.33)	4 (66.67)	
Tigecycline	≤ 20	3 (3.85)	75 (96.15)	0.108
	21-40	0	79 (100)	
	41-60	3 (2.24)	131 (97.76)	
	≥ 60	0	103 (100)	
Nitrofurantoin	≤ 20	14 (17.95)	64 (82.05)	0.083
	21-40	12 (15.19)	67 (84.81)	
	41-60	34 (25.56)	99 (74.44)	
	≥ 60	31 (29.25)	75 (70.75)	
Colistin	≤ 20	0	78 (100)	0.568
	21-40	1 (1.30)	76 (98.70)	
	41-60	1 (0.76)	130 (99.24)	
	≥ 60	0	103 (100)	
Trimethoprim	≤ 20	44 (57.14)	33 (42.86)	0.458
	21-40	45 (57.69)	33 (42.31)	
	41-60	80 (60.15)	53 (39.85)	
	≥ 60	53 (50)	53 (50)	
Azithromycin	21-40	3 (100)	0	0.532
	41-60	3 (75)	1 (25)	
	≥ 60	4 (66.67)	2 (33.33)	

On comparing antibiotic sensitivity pattern to age of study subjects, no significant difference was observed for sensitivity patterns between age groups among any of the antibiotics except ceftazidime. Although ceftazidime shows a p-value of 0.046, the number of cases were very low with only two cases that showed resistance in the 21-40 years old age group.

4.3 Prevalence of antimicrobial resistance among the study population

To acknowledge the antimicrobial resistance patterns and the prevalence of resistance against different antibiotics, bar graphs depicting antibiotic sensitivity and resistance were erected.

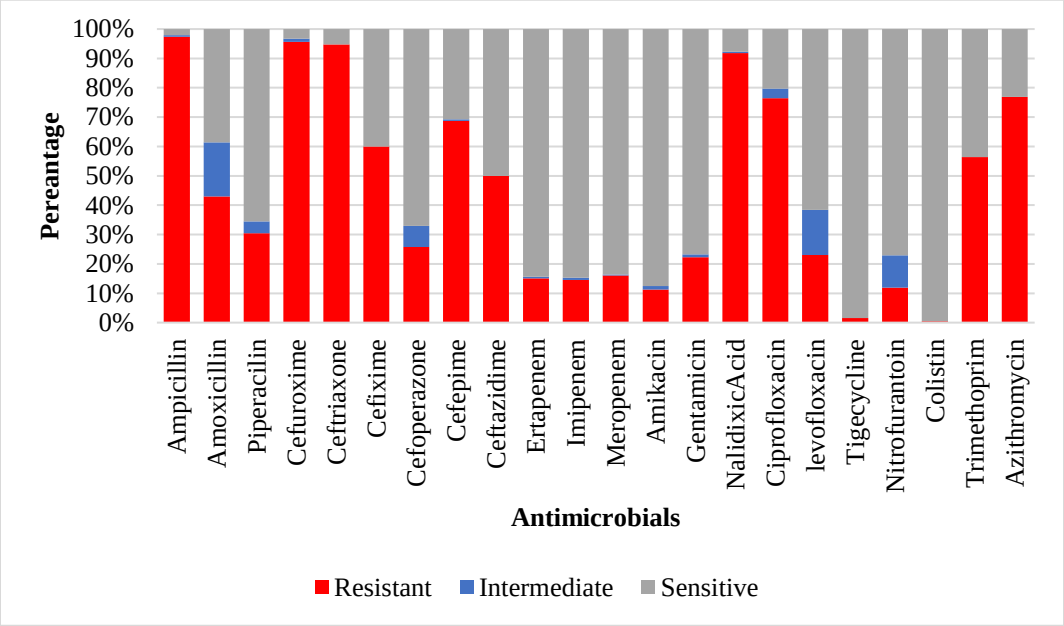

Figure 4.1: 100% Stacked bar graph of antimicrobial resistance pattern

The figure above demonstrates the level of resistance among the different antibiotics that are commonly used to treat UTI. In this study we found the uropathogenic bacteria to be highly susceptible to colistin (99.49%) and tigecycline (98.48%). This was followed by amikacin (87.5%), imipenem (84.67%), ertapenem (84.35%), meropenem (83.64%), nitrofurantoin (77.02%), gentamycin (76.69%), cefoperazone (67.01%), piperacillin (65.47%), levofloxacin (61.54%), ceftazidime (50%), trimethoprim (43.65%), cefixime (40%), amoxicillin (38.6%), cefipime (30.79%), azithromycin (23.08%) and ciprofloxacin

(20.25%). Only a few samples were susceptible to nalidixic acid (7.69%), ceftriaxone (5.28%), cefuroxime (3.32%) and ampicillin (2.07%). A number of cases also were interpreted as intermediate for some antibiotics. The antibiotic that was required in maximum recommended doses to inhibit bacterial growth in descending order of frequency were amoxicillin (18.39%), levofloxacin (15.38%), nitrofurantoin (11.11%), cefoperazone (7.27%), piperacillin (4.09%), ciprofloxacin (3.25%), amikacin (1.25%), cefuroxime (1.02%), gentamycin (1%), imipenem (0.75%), ertapenem (0.53%), ampicillin (0.52%), nalidixic acid (0.51%), cefipime (0.51%) and meropenem (0.26%).

On observing the resistance patterns the antibiotics that most bacteria were resistant to were ampicillin (97.42%), the cephalosporin (cefuroxime (95.65%) and ceftriaxone (94.72%)) nalidixic acid (91.79%), azithromycin (76.92%), ciprofloxacin (76.5%), cefepime (68.7%), cefixime (60%), trimethoprim (56.35%), ceftazidime (50%), amoxicillin (43.01%), piperacillin (30.43%), cefoperazone (25.71%), levofloxacin (23.08%), gentamycin (22.31%), meropenem (16.1%), ertapenem (15.12%), imipenem (14.57%), nitrofurantoin (11.87%) and amikacin (11.25%). Very few samples were resistant to tigecycline (1.52%) and colistin (0.51%).

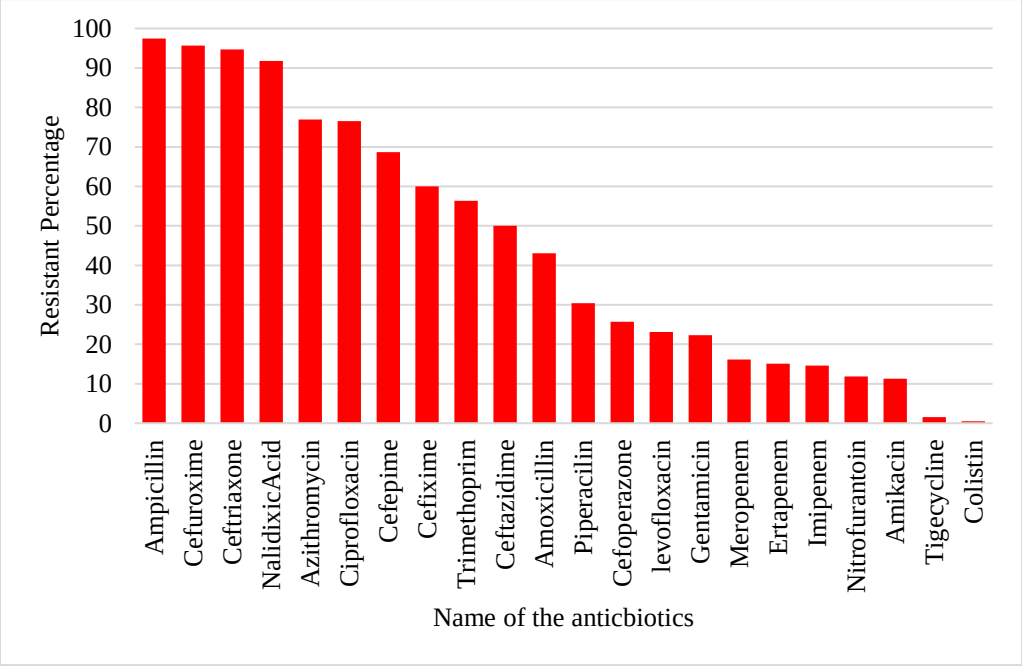

Figure 4.2: Pattern of resistant antimicrobials

From the figure above, it is evident that ampicillin, nalidixic acid, azithromycin, ciprofloxacin, trimethoprim, and almost all cephalosporin (except cefoperazone) are resistant in at least 50% of the cases. About 20% of the cases were also resistant to the carbapenems (meropenem, imipenem and ertapenem), nitrofurantoin, amikacin and tigecycline. Colistin was the only medication to which no *E. coli* isolated from the samples were resistant.

4.4 Multi drug resistant strains of *E. coli* in the study population

Initially, the *E, coli* isolated from four hundred different samples were tested against a panel of twenty-two antibiotics. Then the samples were categorized based on the number of drugs they were resistant to. Figure 9 below displays the combinations of multiple drugs and the number of study subjects resistant to these strains. Around one fourth of our study population had grown resistant to at least six different combinations of antibiotics. The prevalence of resistance was observed to be around 19% for ten or even more varieties of multiple antibiotics in different patterns. Only a few numbers of study population (6%) showed resistance to three or below number of antibiotics combination.

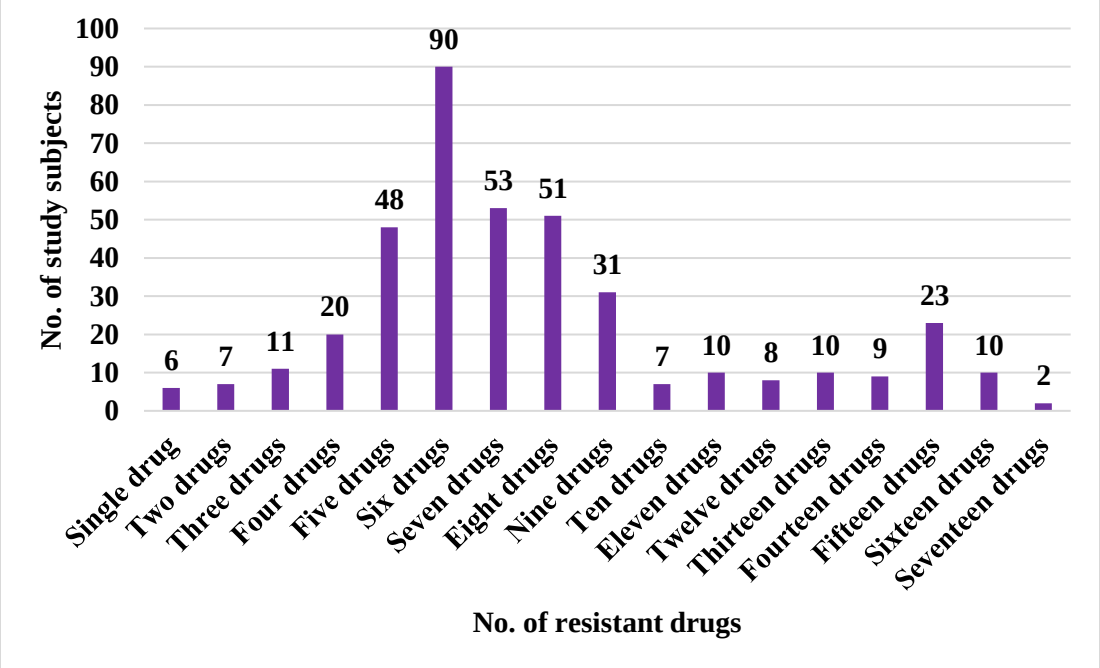

Figure 4.3: Frequency of multidrug resistance among different antibiotics

In order to further analyze the drug combinations that E. coli is resistant to, frequency of sample isolates that are resistant to multiple combinations of drugs is shown in the following table.

Table 4.3: Pattern of multidrug resistance combinations

No. of drugs	combination	Frequency (%; 95%CI)
5 drugs (N=48)	Ampicillin-Amoxicillin-Cefuroxime-Nalidixic Acid-Ciprofloxacin	1 (2.08; 0.05-11.07)
	Ampicillin-Cefuroxime-Ceftriaxone-Cefepime-Ciprofloxacin	1 (2.08; 0.05-11.07)
	Ampicillin-Cefuroxime-Ceftriaxone-Nalidixic Acid-Ciprofloxacin	20 (41.67; 27.61-56.79)
	Ampicillin-Cefuroxime-Ceftriaxone-Cefepime-Nalidixic Acid	13 (27.08; 15.28-41.85)
	Ampicillin-Cefuroxime-Ceftriaxone-Cefepime-Trimethoprim	2 (4.17; 0.51-14.25)
	Ampicillin-Amoxicillin-Cefuroxime-Ceftriaxone-Cefepime	3 (6.25; 1.31-17.20)
	Ampicillin-Cefuroxime-Ceftriaxone-Nalidixic Acid-Trimethoprim	6 (12.5; 4.73-25.25)
	Ampicillin-Cefuroxime-Ceftriaxone-Gentamicin-Nalidixic Acid	1 (2.08; 0.05-11.07)
	Ampicillin-Amoxicillin-Piperacilin-Cefuroxime-Ceftriaxone	1 (2.08; 0.05-11.07)
6 drugs (N=90)	Ampicillin-Cefuroxime-Ceftriaxone- Cefepime- Nalidixic Acid- Ciprofloxacin	35 (38.89; 28.79-49.74)
	Ampicillin-Cefuroxime-Ceftriaxone- Cefepime- Nalidixic Acid- Trimethoprim	13 (14.44; 7.92-23.43)
	Ampicillin-Cefuroxime-Ceftriaxone- Nalidixic Acid-Ciprofloxacin- Trimethoprim	28 (31.11; 21.77-41.74)
	Ampicillin-Cefuroxime-Ceftriaxone-Cefoperazone-Cefepime- Nalidixic Acid	1 (1.11; 0.03-6.04)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Nalidixic Acid- Trimethoprim	1 (1.11; 0.03-6.04)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Cefepime- Trimethoprim	2 (2.22; 0.27-7.80)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Nalidixic Acid- Ciprofloxacin	2 (2.22; 0.27-7.80)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Cefepime- Nalidixic Acid	2 (2.22; 0.27-7.80)

	Ampicillin-Cefuroxime-Ceftriaxone- Gentamicin-Nalidixic Acid- Ciprofloxacin	1 (1.11; 0.03-6.04)
	Ampicillin-Cefuroxime-Ceftriaxone- Cefoperazone-Nalidixic Acid- Nalidixic Acid-	1 (1.11; 0.03-6.04)
	Ampicillin-Cefuroxime-Ceftriaxone- Cefoperazone-Nalidixic Acid- Ciprofloxacin	1 (1.11; 0.03-6.04)
	Cefuroxime- Gentamicin-Nalidixic Acid- Ciprofloxacin-Trimethoprim-Azithromycin	1 (1.11; 0.03-6.04)
	Cefuroxime-Ceftriaxone-Cefixime- Ciprofloxacin-Trimethoprim-Azithromycin	1 (1.11; 0.03-6.04)
	Ampicillin-Amoxicillin- Piperacilin-Cefuroxime-Ceftriaxone- Cefepime	1 (1.11; 0.03-6.04)
7drugs (N=53)	Ampicillin-Amoxicillin- Piperacilin-Cefuroxime-Ceftriaxone- Nalidixic Acid- Ciprofloxacin	3 (5.66; 1.18-15.66)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Cefoperazone- Cefepime- Nalidixic Acid	2 (3.77; 0.46-12.98)
	Ampicillin- Cefuroxime-Ceftriaxone- Cefepime- Nalidixic Acid- Ciprofloxacin- Trimethoprim	30 (56.60; 42.28-70.16)
	Ampicillin- Cefuroxime-Ceftriaxone- Cefoperazone-Cefepime- Nalidixic Acid- Ciprofloxacin	1 (1.89; 0.48-10.07)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Cefepime- Nalidixic Acid- Ciprofloxacin	2 (3.77; 0.46-12.98)
	Ampicillin- Cefuroxime-Ceftriaxone- Gentamicin-Nalidixic Acid- Ciprofloxacin- Trimethoprim	2 (3.77; 0.46-12.98)
	Ampicillin-Amoxicillin- Piperacilin-Cefuroxime-Ceftriaxone- Nalidixic Acid- Trimethoprim	1 (1.89; 0.48-10.07)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Nalidixic Acid- Ciprofloxacin-Nitrofurantoin	3 (5.66; 1.18-15.66)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Nalidixic Acid- Ciprofloxacin- Trimethoprim	3 (5.66; 1.18-15.66)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Gentamicin- Ciprofloxacin- Trimethoprim	1 (1.89; 0.48-10.07)
	Ampicillin- Cefuroxime-Ceftriaxone- Cefepime- Nalidixic Acid- Nitrofurantoin- Trimethoprim	2 (3.77; 0.46-12.98)
	Ampicillin- Cefuroxime-Ceftriaxone- Cefepime-Gentamicin- Nalidixic Acid- Ciprofloxacin	2 (3.77; 0.46-12.98)
	Ampicillin- Cefuroxime-Ceftriaxone- Cefepime- Nalidixic Acid- Ciprofloxacin- Nitrofurantoin	1 (1.89; 0.48-10.07)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Cefepime- Gentamicin- Nalidixic Acid- Trimethoprim	1 (1.96; 0.04-10.45)

8 drugs (N=51)	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Cefepime- Nalidixic Acid- Ciprofloxacin- Trimethoprim	5 (9.80; 3.26-21.41)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Cefepime- Nalidixic Acid- Ciprofloxacin- Nitrofurantoin	2 (3.92; 0.48-13.46)
	Ampicillin-Amoxicillin- Piperacilin- Cefuroxime-Ceftriaxone- Cefepime- Nalidixic Acid- Ciprofloxacin	7 (13.73; 5.70-26.25)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Cefepime- Nalidixic Acid- Ciprofloxacin-Colistin	1 (1.96; 0.04-10.45)
	Ampicillin- Cefuroxime-Ceftriaxone- Cefepime-Gentamicin- Nalidixic Acid- Ciprofloxacin- Trimethoprim	11 (21.57; 12.90-35.32)
	Ampicillin- Cefuroxime-Ceftriaxone- Cefepime- Nalidixic Acid- Ciprofloxacin- Nitrofurantoin- Trimethoprim	6 (11.76; 4.44-23.87)
	Ampicillin-Amoxicillin- Piperacilin- Cefuroxime-Ceftriaxone- Cefoperazone- Nalidixic Acid- Ciprofloxacin	3 (5.88; 1.23-16.24)
	Ampicillin-Amoxicillin- Piperacilin- Gentamicin- Nalidixic Acid- Ciprofloxacin- Nitrofurantoin- Trimethoprim	2 (3.92; 0.48-13.46)
	Ampicillin-Amoxicillin- Piperacilin- Cefoperazone-Cefepime- Nalidixic Acid- Ciprofloxacin- Trimethoprim	3 (5.88; 1.23-16.24)
	Ampicillin-Amoxicillin- Piperacilin- Cefepime-Gentamicin- Nalidixic Acid- Ciprofloxacin- Nitrofurantoin	2 (3.92; 0.48-13.46)
	Ampicillin-Amoxicillin- Piperacilin- Cefuroxime-Ceftriaxone- Nalidixic Acid- Ciprofloxacin- Trimethoprim	2 (3.92; 0.48-13.46)
	Ampicillin-Amoxicillin- Piperacilin- Cefuroxime-Ceftriaxone- Cefoperazone- Cefepime- Nalidixic Acid	2 (3.92; 0.48-13.46)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Gentamicin- Nalidixic Acid- Nitrofurantoin- Trimethoprim	1 (1.96; 0.04-10.45)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Cefepime- Gentamicin- Nalidixic Acid- Ciprofloxacin	1 (1.96; 0.04-10.45)
	Ampicillin-Amoxicillin- Cefuroxime-Ceftriaxone-Gentamicin- Nalidixic Acid- Ciprofloxacin- Trimethoprim	2 (3.92; 0.48-13.46)

A total of 48 sample isolates showed resistance to nine different antibiotic combinations, each consisting of five drugs. The highest frequency was observed in the panel containing the antibiotics ampicillin-cefuroxime-ceftriaxone-nalidixic acid-ciprofloxacin. In this panel of antibiotics, ampicillin was the ubiquitous one. Ninety sample isolates showed resistance to 14 different combinations made up of six drugs. The combination of drugs that had the highest number of resistance strains was ampicillin-cefuroxime-ceftriaxone-

cefepime- nalidixic acid- ciprofloxacin. In all the combinations, cefuroxime was the abundant one.

Similarly, about 53 *E. coli* sample isolates were resistant to seven drugs with thirteen antibiotic combinations. The most common combination panel was ampicillin-cefuroxime-ceftriaxone- cefepime- nalidixic acid- ciprofloxacin- trimethoprim with thirty isolates resistant to this combination. Around 12.75% of the *E. coli* samples isolated were resistant to eight drugs in sixteen different combination panels. The panel that majority of bacteria were resistant to is ampicillin- cefuroxime-ceftriaxone- cefepime- gentamicin-nalidixic acid- ciprofloxacin- trimethoprim, and 11 sample isolates were resistant to this panel.

CHAPTER 5- DISCUSSION

The present study describes the antimicrobial resistance in uropathogenic *E. coli* among the residents of Chattogram. It was observed that almost 25% of UTI patients showed resistance to at least six different drug combinations. Only a mere 6% of the population showed resistance to three drugs or less. Among the different drug combinations that patients were commonly resistant to, highest number of resistance strains was observed for ampicillin-cefuroxime-ceftriaxone- cefepime- nalidixic acid- ciprofloxacin. For seven drug combinations, ampicillin- cefuroxime-ceftriaxone- cefepime- nalidixic acid- ciprofloxacin- trimethoprim combination had the highest frequency of resistance. In a study on antimicrobial resistance in asymptomatic children in Peru, around 89% of the patient samples collected were resistant to four drugs or more. As a matter of fact, 26% of the total patient samples were resistant to more than six antibiotics (Bartoloni, et al., 2006). The pattern that included ampicillin, tetracycline, and trimethoprim-sulfamethoxazole (22%) was the most prevalent, followed by that consisting of ampicillin, trimethoprim-sulfamethoxazole, tetracycline and chloramphenicol (15%), as well as that including ampicillin and trimethoprim-sulfamethoxazole alone (10%).

Quite a few studies have been conducted in Asia on antimicrobial resistance in urinary tract infections. Since *Escherichia coli* is one of the most common pathogens responsible for UTI, studies on resistance patterns of this organism have been reported lately. Emergence of resistant strains such as extended-spectrum beta-lactamases (ESBL) resistant *E coli* is currently a major issue in many south Asian countries including India, Nepal and Sri Lanka. Multiple studies have also been conducted in Bangladesh regarding resistant strains of *E. coli* causing UTI (Ara, et al., 2021; Ahsan, et al., 2020; Rahman, et al., 2004). The resistance patterns for each study varied based on the geographic location and year of study. Still, a lot of similarities were found with our study. The spread of antimicrobial resistance (AMR) within *Escherichia coli* pathogen is a complex process that is associated with many mobile genetic elements such as plasmids, transposons, and integrons. In a recent meta-analysis, (Bezabih, et al., 2021) the cumulative global pooled prevalence of ESBL producing *E. coli* that is carried in the human intestines of the community was 16.5% (95% CI 14.3%–18.7%; $P < 0.001$). An upward trend in prevalence was observed where it

increased from 2.6% in 2003–05 to 21.1% from 2015–18. Overall, the highest carriage rate (27%) was observed in South-East Asia while the lowest (6%) was observed in Europe. The emergence of resistant strains such as extended-spectrum β-lactamase (ESBL)-producing bacteria, particularly *E. coli* and *Klebsiella pneumoniae*, has now become a critical concern for the development of antibiotics. It should not be surprising to find such strains in Bangladesh since a significant prevalence of these strains exist in Southeast Asia. The highest incidences of such cases were found in India, followed by Hongkong and then Singapore (Mowla, et al., 2011).

Antibiotic resistance is rising to dangerously high levels with new resistance mechanisms spreading globally and threatening the ability to treat common infections. Where antibiotics can be obtained for man or animals without a prescription, the emergence and spread of resistance is made worse. Similarly, countries that lack standard treatment guidelines, over prescription of antibiotics by health workers and veterinarians and over-used by the public is common (Ayukekbong, et al., 2017). When infections can no longer be treated by first-line antibiotics, more expensive medicines need to be used. In addition, prolonged illness and treatment duration, often while admitted in hospitals, increases health care costs as well as the economic burden on families and societies. Although in well-funded healthcare systems, finding access to second and third-line treatment regimens are usually not an issue, mortality rates among patients with resistant bacterial infections are significantly higher besides the costs of treatment (Llor & Bjerrum, 2014). The disparity in the AMR problems of individual countries is linked to vast differences in how frequently and severely they use antimicrobial drugs. Global consumption of antibiotics in humans rose by almost 40% between 2000 and 2010. However, this figure does not show the patterns of declining usage in some countries and that of rapid growth in others. The BRIC (Brazil, Russia, India and China) countries plus South Africa accounted for three quarters of this growth, while annual per-person consumption of antibiotics varied by more than a factor of 10 across all middle- and high-income countries (Van Boeckel, et al., 2014).

In order to reduce or delay the development of resistant strains, we need to first decrease the spread of resistance genes from environmental bacteria into human pathogens. Additionally, we need to decrease the spread of resistant bacteria to both humans and

animals through food, wastes and water; and minimize the levels of antibiotics as well as antibiotic-resistant bacteria introduced into the environment (Mølbak, 2004). Improved management of waste containing antibiotic residue or resistant micro-organisms is necessary. In case of humans, use antibiotics only when prescribed by a certified health professional. Prevent infections by maintaining proper food hygiene and cleanliness. At government level, a national action plan is necessary to tackle the problem of antibiotic resistance. Improved surveillance of antibiotic-resistant infections and implementing strong laws to prevent and control infections can be initiated to regulate and encourage the proper use of quality medicines. Further investments in research for the development of new antibiotics or other tools can be promoted by the health sector. At the agricultural level, antibiotics should be given to animals only under veterinary supervision. Avoid using antibiotics for growth promotion or disease prevention. Instead vaccinate animals from time- to time to limit the need for antibiotics. Encourage and apply good practices at all stages of production and processing of foods from animal as well as plant sources. With the help of improved hygiene and animal welfare, improve the biosecurity on farms and prevent frequent infections.

AMR is a problem that affects the world globally and has a real implication for human health (Jee, et al., 2018). In developing countries like Bangladesh, the growing threat of AMR is high owing to a large population density, inadequate sanitation and excessive use of antimicrobials in clinical, animal and agricultural sectors (Ayukekbong, et al., 2017). As a result, treatment of UTI with multidrug resistant (MDR) pathogens are more difficult leading to increased morbidity and mortality from complications. Since most UTIs are treated based on clinical diagnosis, proper antimicrobial treatment is needed to improve outcome. The prescribed antimicrobial agents should be determined based on the most likely pathogens and their expected resistance pattern in a specific geographic area. Additionally, regular monitoring should be done for the causative agents of UTI and their resistance patterns.

CHAPTER 6- CONCLUSION

A high prevalence of resistance to common antibiotics such as Ampicillin, 2nd and 3rd generation cephalosporins and Nalidixic acid was observed in this study. Moreover, *E. coli* susceptibility against antibiotics like colistin, tigecycline, amikacin, and the carbapenems has been observed in this study. The frequency of male patients whose E. *coli* isolates were resistant to antibiotics like imipenem, meropenem, amikacin, gentamycin and nitrofurantoin was significantly higher than that of female patients. An overwhelming 93% of *E. coli* samples were resistance to more than three drugs with about 20% of the samples being resistant to at least ten different antibiotics. Among the multi- drug combinations, prevalence of resistance to 6 different drug combinations were the highest. *E. coli* isolated from a total of 90 patients displayed this pattern. Among the various antibiotic groupings, resistance to a combination of ampicillin-cefuroxime-ceftriaxone- cefepime- nalidixic acid- ciprofloxacin was the most frequently observed with a total of 35 samples exhibiting this. In the light of this study, the high antimicrobial resistance among *E. coli* affecting the adult population of Chattogram needs to be addressed and seriously reviewed. It is noteworthy that almost all isolates were found to have increased resistance to routinely used antibiotics. Hence a strict antibiotic prescription policy needs to be stressed upon in order to prevent a future threat of limited antimicrobial options for infections with notoriously resistant strains.

CHAPTER 7 - LIMITATIONS

Since this study was conducted based on laboratory results, most of the limitations found were characteristic of any laboratory-based study. The data collected for this study was from one specific laboratory in Chattogram. Thus, it could not accurately represent the perspective of the entire city as regional variations in antimicrobial resistance patterns do exist. Furthermore, since this study was a cross-sectional one, it was not possible to identify the source of infection. From the previous studies, it was evident that the hospital- acquired infections frequently deliver resistant gene flow more than the infections acquired in the community. However, in this study such a comparison could not be made as no data was available on patient's hospital admission status. Owing to this lack of information, it is difficult to say if the high prevalence of antibiotic resistance patterns observed in this study were actually representative of the community at larger scale. Generally, physicians prefer to empirically treat cases of UTI until complications occur, following which they give advice for culture and sensitivity testing. Since such data were not included in laboratory-based studies, the urine cultures obtained were more likely to be collected from complicated episodes of UTI. This in turn could have further skewed the susceptibility results towards patterns with multiple drug resistance.

CHAPTER 8- RECOMMENDATIONS

Conducting a study involving a larger sample from different laboratories across the city of Chattogram is recommended so that a more accurate representation of AMR resistance patterns in UTI cases can be made. Further studies comparing the pattern of antibiotic resistant *E. coli* found in UTI with that obtained from food samples, environmental sources and domestic as well as wildlife within the same area are suggested. As found in different literatures, resistance of *E. coli* to antibiotics is thought to be developing through different sources of the One Health component via the food chain. Hence, finding an association between the two could help better understand the mode of transmission to humans. Continued surveillance and monitoring of AMR issues in hospital acquired infections and community infections are of paramount importance. One study by Flanagan et al (2007) recommended the use of four different approaches to limit development of infections with AMR strains. First of all, effective antimicrobial prescription practices should be implemented. This means guidelines for prescribing important antibiotics should be followed properly. Best practices in both choice of antibiotic and duration of use need to be adhered to when prescribing empirical antimicrobial therapy. Secondly, there should be adequate information as well as resources available for controlling AMR at hospital settings. For this, hospitals need to provide feedback on the impact of antibiotic resistance (length of stay, costs, etc) among their patients. Any significant changes in antimicrobial resistance should be promptly reported. Appropriate resources to prevent and control antimicrobial resistance should be available in hospitals. Thirdly, there should be organizational support for infection control practices. In other words, it should be made sure that the recommended guidelines are well practiced at all hospital settings. Nurse managers, chiefs of services and top-level hospital administrators should all reinforce and support infection control policies. And finally, isolation of patients infected with AMR strains should be ensured. This includes rapid detection of patients infected by resistant strains, rapid notification and isolation of such patients. With these few steps, prevalence of AMR infections can be reduced to a great extent.

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