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Review on basics of antibiotic resistance in uropathogens and implications for Urinary Tract Infection treatment.

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ABSTRACT:

Antimicrobial resistance and urinary tract infections are still the most common problems causing high social and health costs, especially in developing countries. *Escherichia coli* is the gram- negative bacteria that usually causes this infection. The uncontrolled and widespread use of antibiotics is causing a radical change in the resistance patterns of uropathogens. Antibiotic resistance is increasingly treated in outpatient urinary tract infections. Clinicians must be aware of the specific clinical and epidemiologic risk factors for infections caused by multidrug-resistant (MDR) uropathogens, as treatment options for these pathogens are limited. According to published studies, fosfomycin and nitrofurantoin are effective against most MDR *Escherichia coli* urinary tract infections. Clinical efficacy of trimethoprim-sulfamethoxazole persists despite increasing resistance worldwide. Beta-lactams have the highest resistance and the lowest clinical success rates. Resistance to fluoroquinolones is high among MDR uropathogens and is not recommended for use primarily in the treatment of urinary tract infections. In addition to consideration of local resistance, consideration of the patient's risk factors and principles of pharmacological resistance help guide optimal empiric therapy in outpatient therapy.

Keywords: Uropathogen, antibiotic resistance, urinary tract infections, treatment of UTIs

INTRODUCTION:

Urinary tract infection (UTI) is a common health problem in both community and nosocomial disease, occurring particularly in women. UTIs are infections that happen when bacteria, often from the skin or rectum, enter the urethra, and infect the urinary tract. The infections can affect several parts of the urinary tract, but the most common type is a bladder infection.

Kidney infection (pyelonephritis) is another type of UTI. They're less common, but more serious than bladder infections. As reported by the National Ambulatory Medical Care Survey, UTI alone is responsible for nearly seven million patient visits in outpatient department (OPD) as well as up to one million visits in hospital emergency department, resulting in about 100,000 hospitalizations. UTI infections have a significant medical and economic impact. In non-obstructed, non-pregnant adult women, acute uncomplicated urinary tract infection is thought to be a benign condition with no long-term medical consequences. However, UTI increases the risk of pyelonephritis, premature birth, and fetal death in pregnant women, and is associated with kidney failure and end-stage renal disease in children.
It is usually associated with minimal morbidity except in certain subpopulations. However, there is a significant lack of information about its exact prevalence, factors that increase susceptibility to UTI, and the long-term medical consequences of UTI. The clinical consequences of UTI are significant. There is a high incidence of

symptomatic UTI necessitating antimicrobial therapy, as well as an increasing population of highly susceptible patients who require antimicrobials for UTI and/or other infections, resulting in an increased risk of developing antimicrobial resistance among common uropathogens. As a result, there is a growing need to ensure appropriate therapy with agents that maximize success for both community-acquired and nosocomial UTI while minimizing risk of the development of antimicrobial resistance .

Nearly 50–60% of all women suffer from an episode of UTI at least once in their lifetime. Recurrent UTIs are common in women, occurring in up to 25-50% within a year of the first infection. 3-5% of all women experience a recurrence of the disease for several years.

The recurrence of urinary tract infections is also common if the conditions affecting the development of urinary tract infection are not diagnosed and treated in time. If the predisposing factors which are responsible for the occurrence of UTI are not timely diagnosed and treated, then it is also common for UTI episodes to reoccur.

Untreated UTI can lead to serious complications such as kidney damage, kidney scarring and kidney failure. UTIs are usually caused by bacteria, mostly Gram-negative bacteria such as *Escherichia coli*, *Proteus species*, *Pseudomonas aeruginosa*, *Acinetobacter species*, *Klebsiella species*, *Enterobacter species*, and *Citrobacter species.* Among Gram-positive bacteria, *Staphylococcus saprophyticus*, *Enterococcus species*, and coagulase-negative *Staphylococcus* bacteria are a common, predictable spectrum of UTI-causing bacteria.

Compared to non-pathogenic bacteria, causing urinary tract infections have more aggressive virulence factors that enhance their ability to attach, colonize and invade host cells. These bacteria evade the host's immune system by using certain virulence factors, which can consist of various cellular components such as pili, capsule, lipopolysaccharides, and various other cell surface structures.

Some human anatomical and physiological factors also increase the incidence of UTI, for example, the length of the urethra in women is shorter than in men, which increases the risk of UTI. Similarly, incomplete bladder emptying, especially in the elderly, leads to residual urine accumulation in the bladder and vesicoureteral reflux, which is common in pregnant women, an important factor that can predispose the host to UTIs.

A urinary tract infection is often treated with broad-spectrum antibiotics, and therapy is started empirically without culture or sensitivity. This inappropriate and ill-advised use of antibiotics has led to the global development of antibiotic resistance in bacteria, leading to the emergence of multidrug-resistant bacterial pathogens**.**

Community or healthcare-acquired UTIs are clinically divided into complicated or uncomplicated, and among many other factors, this classification determines what antimicrobial agents can be applied for treatment. Complicated UTIs require prolonged therapy and occur in patients with renal failure, anatomical urinary tract abnormalities such as urinary obstruction and retention or in patients that use medical devices such as a catheter.

Complicated UTIs are also associated with immunosuppression and previous antibiotic exposure. This category of UTIs increases the risk of chronic and recurrent infections. Uncomplicated UTIs are found in patients who have no anatomical urinary tract abnormalities and do not use the urinary tract instrumentation. In uncomplicated UTIs, host immune response may successfully fight infection without antibiotic therapy. The symptomatic UTIs are classified as urosepsis, pyelonephritis (infection of the upper UTI) or cystitis (infection of the lower UTI) The presence of numerous UPEC cells in the urine (≥105 CFU/ml) without the clinical symptoms is called asymptomatic bacteriuria (ABU) and in healthy non-pregnant women is not treated in 20–80% of cases.

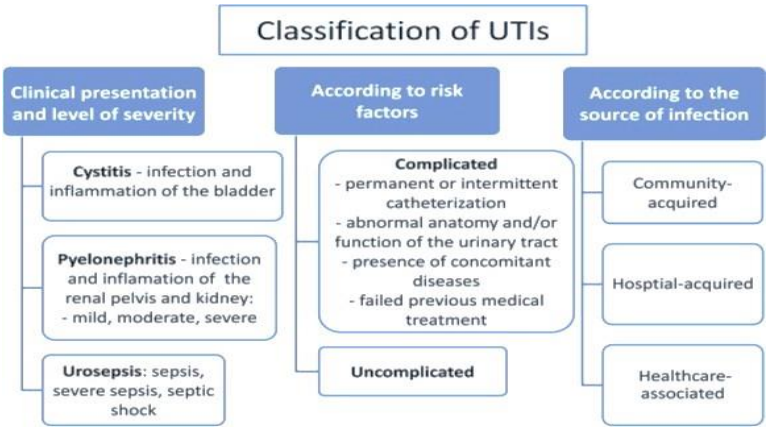


Figure no. 1 Classification of UTIs

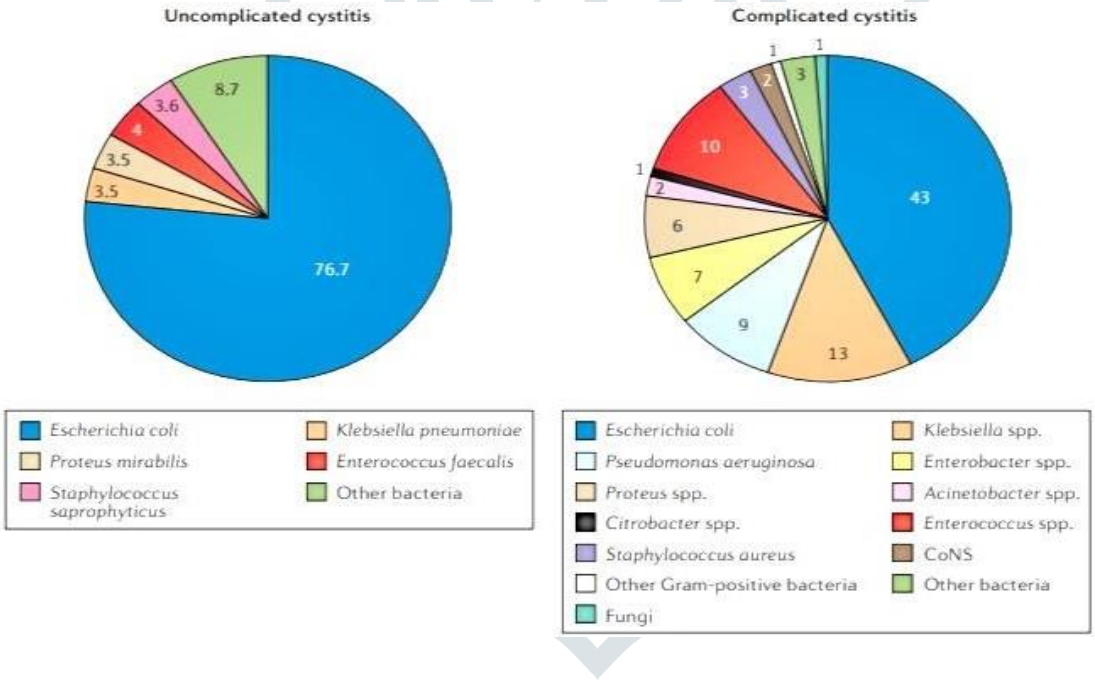
BARBARA KOT "Antibiotic Resistance Among Uropathogenic Escherichia coli", Polish Journal of Microbiology, Vol. 68, No 4, 2019, 403–415.

EPIDEMIOLOGY & ETIOLOGY OF UTIs , UROPATHOPGENS AND THEIR PREVALENCE:

Urinary tract infections (UTIs) are among the most common bacterial infections and are caused by both gram-negative and gram-positive species. Urinary tract infections are classified as simple and complicated and are a major public health problem; this situation is worsened by the proliferation of multidrug-resistant strains. Uropathogens have several virulence factors that are related to the pathophysiology of UTIs. These virulence factors are involved in invasion and colonization and mediate the subversion of host defense mechanisms. Therapies currently in development include vaccines that target bacterial factors important for initial attachment and disease progression (such as adhesins)., toxins, proteases and siderophores) and small molecule inhibitors that block adhesin- receptor interactions. Urinary tract infections (UTIs) are caused by a variety of pathogens, including gram-negative and gram-positive bacteria and fungi. Uncomplicated UTIs usually affect women, children and elderly patients who are otherwise healthy. Complicated urinary tract infections are usually associated with indwelling catheters, urinary tract abnormalities, immunosuppression, or exposure to antibiotics. The most common cause of both uncomplicated and complicated urinary tract infections is uropathogenic *Escherichia coli* (UPEC). These data show that antimicrobial resistance is especially prominent in Gram-negative uropathogens and enterococci. Antimicrobial resistance varies widely by geographical location and clinical conditions. Higher resistance rates are generally associated with specific risk factors, such as age and comorbidity, which need to be taken into account for prognosis and treatment. Such variability makes it impossible to give exact treatment recommendations on a global level; thus, each medical facility needs to run its own resistance surveillance programme to ensure empirical treatment regimens.Irrationale use of antibiotics and increase in numerous multidrug resistance bacterial strains have risen up the cases of antibiotic resistance. *Enterobacteriaceae* family, including *E. coli* and *K. pneumoniae* is the conerened species as they have both acquired plasmids encoding extended-spectrum β-lactamases (ESBLs). In these classifications, patients with uncomplicated UTI have no known risk factors predisposing to UTI, which is common in young healthy women, while patients with cUTI have multiple risk factors. Some risk factors are related to the urinary tract, such as obstruction, urolithiasis, distraction and catheterization, while others are related to kidney disease or non-urogenital conditions, such as diabetes mellitus, malignancy or immunodeficiency. In addition, cUTI, if not treated properly, carries a higher risk of clinical complications than uncomplicated UTIs, such as those of pregnancy and childhood. Risk is sometimes also related to an increased chance of recurrence of the disease.

The classification also takes into account the different bacterial composition of these two disease entities. In uncomplicated UTI, the main pathogen is *E. coli* , while pathogens other than *E. coli* are common in UTI infections, therefore broad-spectrum antimicrobial agents and a longer duration of therapy should be considered. Category for UTI includes both with a wide spectrum of manifestations, the disease is very heterogeneous, which has raised concerns that clinical trial results in patients diagnosed with UTI by one criterion may not apply to patients diagnosed by different criteria. For example, patients with kidney stones have a higher risk of recurrent UTIs than those without stones because of the bacteria inside.

Urinary tract infections are caused by both gram-negative and gram-positive bacteria and certain fungi. The most common cause of both uncomplicated and complicated urinary tract infections is uropathogenic *Escherichia coli* (UPEC). In uncomplicated urinary tract infections, UPEC is followed by *Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis, Group B Streptococcus* (GBS), *Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus, and Candida, P. mirabilis, P. mirabilis. aeruginosa* and GBS9.



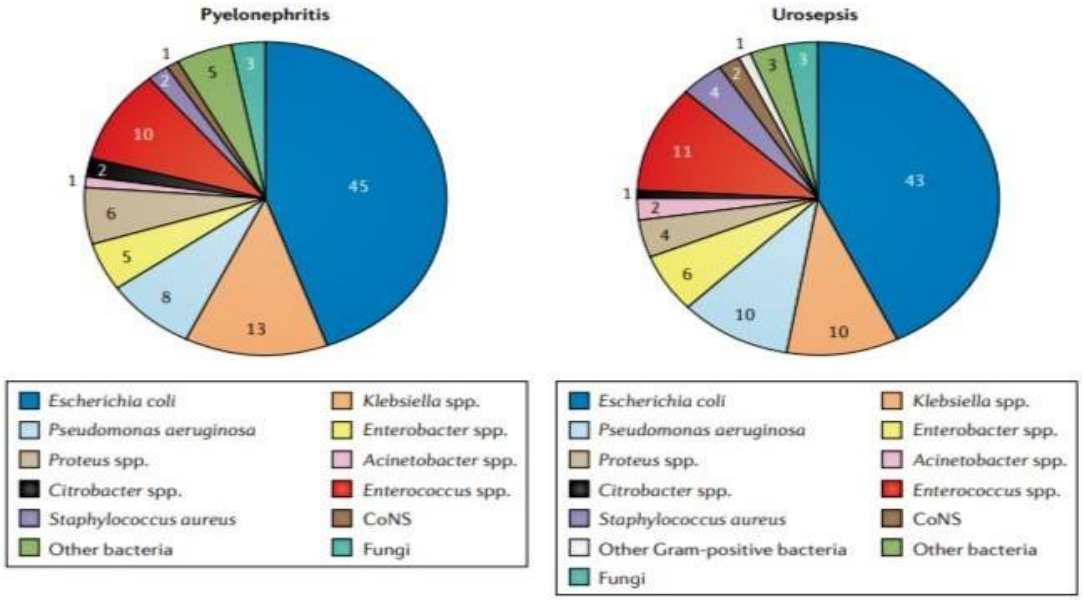


Figure No. 2 Prevalence of uropathogenic bacterial species in various UTI entities. [12]

Wagenlehner FME et al., "Epidemiology, definition and treatment of complicated urinary tract infections. Nat Rev Urol. 2020;17(10):586-600. doi:10.1038/s41585-020-0362

Table 1 | Classical symptoms of different UTI entities [12]

Acronym	Clinical diagnosis	Clinical symptom	Severity grade
CY-1	Cystitis	Dysuria, frequency, urgency, suprapubic pain; sometimes unspecific symptoms	1
PN-2	Mild to moderate pyelonephritis	flank paina , CVA tendernessa ; sometimes unspecific symptoms with or without symptoms of cystitis moderate pyelonephritis	2
PN-3	PN-3 Severe pyelonephritis	AS for PN-2, but, in addition, nausea and vomiting with or without symptoms of cystitis	3
US-4[b]	SIRS	Temperature >38 °C or 90 beats/min, respiratory rate >20 breaths/min or PaCO2 12,000 cells/mm3 or 2 SIRS criteria must be met for US-4 diagnosis)	4
US-5[b]	Severe urosepsis	As for US-4, as well as organ dysfunction, hypoperfusion or hypotension; hypoperfusion and perfusion abnormalities may include but	5

		are not limited to lactic acidosis, oliguria or an acute change in mental status	
US-6[b]	Uroseptic shock	As for US-4 or US-5, as well as hypotension despite adequate fluid resuscitation and the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria or an acute change in mental status; patients who are on inotropic or vasopressor agents may not be hypotensive when perfusion abnormalities are measured	6

CVA, costovertebral angle; SIRS, systemic inflammatory response syndrome; WBCs, white blood cells. a Not seen in transplant patients; instead graft pain may be seen in some cases. b Sepsis definitions have recently been refined and the current definitions will be reconsidered once the new definitions have been validated.

Etiology of Urinary Tract Infection:

The etiology of uncomplicated UTIs has generally remained unchanged over the past 2 decades, although antimicrobial resistance has increased in both community-acquired and hospital-acquired UTIs. The etiology of complicated UTI is more diverse and directly influenced by host characteristics than that of uncomplicated UTI. Most acute uncomplicated community-acquired infections in the United States and abroad are caused by *E.coli* (80%) or *Staphylococcus saprophyticus* (10-15*%). Klebsiella, Enterobacter and Proteus* species and *enterococci* rarely cause uncomplicated cystitis and pyelonephritis. Fungal pathogens, particularly *Candida albicans* or other *Candida species*, account for up to 10% of positive urine cultures in US tertiary care settings, but most are complicated. UTIs. Until recently, the susceptibility of bacteria causing acute uncomplicated UTIs in women was generally predictable, and most are sensitive to trimethoprim- sulfamethoxazole (TMP-SMX). Therefore, the traditional approach to treatment has been empirical short courses with TMP-SMX.2,5. However, the increased antimicrobial resistance of uropathogens that cause acute uncomplicated cystitis has had significant implications for traditional empiric approaches. A recent 5-year study (1992–1996) examined antimicrobial susceptibility patterns in 4,000 isolated women with acute uncomplicated cystitis.6 Despite differences in the distribution of uropathogens over the 5-year period, the prevalence increased significantly *coli* resistance to TMP-SMX (9% to 18%), cephalothin (20% to 28%) and ampicillin (26% to 34%). *E. coli* resistance to nitrofurantoin and ciprofloxacin remained at 1% over the 5 years. A nationwide analysis in 1999 of laboratory-based ambulatory urinary tract infection isolates7 showed that *E coli* resistance to ampicillin is almost 40%. Resistance to fluoroquinolones remained low at about 3 percent.

Table No. 2 Etiology of Uncomplicated Versus Complicated Urinary Tract Infection (UTI)

Uncomplicated UTI Pathogens	Complicated UTI Pathogens
Escherichia coli	*Escherichia coli*
Staphylococcus saprophyticus	*Klebsiella spp.*
Klebsiella spp	*Enterobacter cloacae*
Enterococcus faecalis	*Serratia marcescens*
	Proteus mirabilis
	Pseudomonas aeruginosa
	Enterococcus faecalis
	Group B streptococci

Cases of Urinary tract Implication in Special Population group Pediatrics

Urinary tract infections in children are associated with significantly higher morbidity and longer- term outcomes than in adults, including kidney failure and end-stage renal disease. A urinary tract infection in pre-pubescent girls can eventually lead to possible complications during pregnancy. Recurrent UTI in girls is associated with renal scarring and an associated increased risk of progressive kidney disease in adulthood.80 Children diagnosed with vesicoureteral reflux are at increased risk for UTI-related pyelonephritis. However, circumcision has been shown to be highly protective against UTI in infants. Childhood UTI does not increase the risk of hypertension 20 years later, and unilateral renal scarring after childhood UTI does not affect renal function. However, bilateral scarring is associated with a worse prognosis. Pediatric patients diagnosed with pyelonephritis and a positive dimercaptosuccinic acid (DMSA) scan (renal scintigraphy using DMSA as a tracer) have a 33% risk of renal scarring. Many children with an abnormal DMSA scan have reflux and/or dysuria.

UTI in the Elderly

There are many factors that predispose the elderly to UTIs, including chronic diseases, functional abnormalities, and certain medications. ASB is common in this population but often resolves without treatment and has no long-term consequences. However, symptomatic urinary tract infection in the elderly requires antimicrobial therapy.

UTI During Pregnancy

The consequences of a UTI during pregnancy can be significant, including an increased risk of pyelonephritis, preterm labor, and fetal death. Untreated ASB can cause acute pyelonephritis and anemia in low-birth-weight infants6 and pregnancy-induced hypertension/pre-eclampsia. Therefore, early screening for ASB during pregnancy is highly recommended. In some women, pyelonephritis during pregnancy can present as only lower tract symptoms. More commonly, women present with the traditional symptoms of pyelonephritis, including fever with flank pain, costovertebral angle tenderness (especially on the right side), and possible vomiting and nausea.

Women with pyelonephritis during pregnancy generally should be hospitalized for aggressive hydration and parenteral antibiotic therapy. The majority (86%) of women develop uterine contractions within the first hour of starting antimicrobial therapy, and 50% of women continue to have uterine contractions after 5 hours of therapy. Recent studies show that urinary tract infection during pregnancy can increase the risk of brain damage, paralysis or intellectual disability78 in the offspring. According to a retrospective cohort study, an increased relative risk of mental retardation or developmental delay and fetal death was observed in association with maternal urinary tract infection, especially in the third trimester of pregnancy. Treatment of urinary tract infection in the third trimester did not affect fetal morbidity. The authors recommended early and aggressive screening and treatment for ASB during pregnancy.

Pregnant Patients

Urinary tract infections are the most common bacterial infections in pregnancy, and pyelonephritis is the most common serious bacterial infection complicating pregnancy. About 4–10% of pregnant women develop ASB and 1–4% of pregnant women develop acute cystitis. for the first time during pregnancy. Infant UTI without renal scarring increases the risk of ASB to 27% during pregnancy and 47% with renal scarring. Acute pyelonephritis affects 1-2% of pregnant women, especially in the late second and early third trimesters. Women who have had a history of UTI are at greater risk of developing a UTI during pregnancy. Risk factors for ASB or acute cystitis during pregnancy include lower socioeconomic status, sickle cell trait and anemia, increased parity or age, and lack of medical care during pregnancy. Functional abnormalities of the urinary tract and diabetes can also increase susceptibility to urinary tract infections during pregnancy.

Patients with Multiple Sclerosis

The risk of urinary tract infection and bacteriuria is significantly increased in patients with multiple sclerosis (90% and 74%). UTI often precedes multiple sclerosis relapse, and recurrent UTI is associated with acute exacerbations and neurologic progression.

Persons with HIV/AIDS

The incidence of UTI among both women and men who are seropositive for HIV is greater than among women and men who are HIV seronegative. The incidence of UTI is believed to be even greater among patients with AIDS or who have low CD4 counts ($<0.2 \times 10^9$ /L).11 However, earlier research involving female commercial sex workers in Africa found no significant relation between HIV status, CD4 count, and symptomatic UTI. Nevertheless, research consistently reports that patients with HIV are more likely to have *Enterococcus* species as the predominant uropathogen, in contrast to *E.coli* as the most common uropathogen isolated among seronegative patients.

Patients with Diabetes

Diabetes increases the risk of urinary tract infection and bacteriuria in female patients, but not in male patients. In diabetic patients, the incidence of bacteriuria is usually 2-4 times higher than in non-diabetic patients. The etiology of UTI in diabetic patients includes more unusual uropathogens than in nondiabetic patients. In addition, urinary tract infection caused by diabetes can lead to serious complications such as emphysematous cystitis and emphysematous pyelonephritis.

Patients with Catheters or Spinal Cord Injuries

Catheter-associated urinary tract infection is the most common nosocomial infection, with one million cases occurring each year in US hospitals and nursing homes. Nosocomial infection in newly catheterized patients is

often asymptomatic (90%), and the risk of urinary tract infection increases as catheterization time increases. The overall incidence of bacteriuria is 8% and varies from 3% to 10% per day. Patients with spinal cord injury (SCI) are mostly young men. UTIs are very common in patients with SCI and are always complex in nature. Unlike UTIs in most other subpopulations, UTIs in patients with SCI are associated with significant morbidity and mortality.

ANTIBIOTICS IN THE TREATMENT OF UTIs

The most commonly used antimicrobial agents for the treatment of uncomplicated urinary tract infections are the combination drug trimethoprim and sulfamethoxazole, trimethoprim, β-lactams, fluoroquinolones, nitrofurantoin, and fosfomycin tromethamine. These agents are used primarily because of their tolerability, spectrum of activity against suspected uropathogens, and favorable pharmacokinetic profiles. All antimicrobial concentrations sagents approved for the treatment of UTIs reach an inhibitory concentration in urine that significantly exceeds the serum concentration. Also, agents such as trimethoprim-sulfamethoxazole or fluoroquinolones, which kill aerobic gram- negative flora but have little effect on the anaerobic flora of the vagina and feces, appear to offer the best long-term treatment for uncomplicated UTIs. The purpose of antimicrobial. treatment is to remove the infectious organisms from the urinary tract and relieve symptoms. The table below shows the drugs, their dosages and wholesale prices. Physicians must consider many factors when choosing an antibiotic for UTI, such as the patient's allergy history, cost and tolerability of treatment, prior antibiotic therapy, and most importantly, the prevalence of resistance in the community. In the treatment of UTIs, resolution of bacteriuria correlates with urine antimicrobial concentration rather than serum concentrations.

Single-dose regimens

although single-dose therapy using β-lactams, trimethoprim-sulfamethoxazole, trimethoprim, and fluoroquinolones have shown high cure rates, single-dose therapy is associated with a high rate of recurrence within 6 weeks of initial treatment. Reinfection may be due to the failure of single-dose treatment to eradicate gram-negative pathogens from the perianal area. Aminopenicillins and first- generation cephalosporins have shorter half-lives, which may contribute to their lower efficacy compared with other agents.

Short-course therapy

Treatment with trimethoprim-sulfamethoxazole, trimethoprim, or fluoroquinolones for three days should eradicate uncomplicated cystitis with a rate of over 90% and a low incidence.

Table No. 3 Antimicrobial Therapy for UTIs

Drug	*Dose, mg*	*Frequency*	*Duration, days*	*Cost per complete course, $**
Sulfonamides				
TMP-SMX	160/800†	2×/day	3	6.30-8.80
TMP	100	2×/day	3	0.90-1.40
Fluoroquinolones				
Norfloxacin (Noroxin)‡	400	2×/day	3	22.80
Ciprofloxacin HCl (Cipro)‡	100-250	2×/day	3	17.20-25.00
Levofloxacin (Levaquin)‡	250-500	Daily	3	21.90-25.60
Nitrofurantoin macrocrystals				
(Macrodantin)‡	100	4×/day	7	47.00
(Macrobid)‡	100	2×/day	7	23.00
β-Lactams				
Cefpodoxime (Vantin)‡	100	2×/day	3	18.30
Cefixime (Suprax)‡	400	Daily	3	23.20
Cephalexin	250-500	4×/day	3	6.40-11.50
Amoxicillin	250-500	3×/day	3	2.10-3.50
Miscellaneous				
Fosfomycin tromethamine (Monurol)‡	3,000 (3 g)	Daily	1	30.00

TMP-SMX = trimethoprim-sulfamethoxazole; HCl = hydrochloride.

*Average wholesale price in 2001.

†One double-strength tablet.

‡Proprietary names are given for information only and are not to be construed as endorsement by either the authors or *wjm* editors.

Antimicrobial agents:

Trimethoprim-sulfamethoxazole has long been considered the standard of care for acute and recurrent UTIs because of its activity against most common uropathogens and its low cost and tolerability. The synergistic combination of trimethoprim and sulfamethoxazole acts on two different steps of bacterial folate metabolism, resulting in inhibition of DNA synthesis. Patients with sulfa allergy can receive trimethoprim alone, as studies have shown similar improvement rates to trimethoprim-sulfamethoxazole.

Fluoroquinolones:

Fluoroquinolones are broad-spectrum antibiotics that inhibit topoisomerase II (DNA gyrase) and topoisomerase IV. Although the spectrum of activity of fluoroquinolones varies, they all have good or excellent activity against clinically important gram-negative uropathogens, other *Enterobacteriaceae* and *S saprophyticus*. Ciprofloxacin and levofloxacin are the two most commonly used fluoroquinolones for urinary tract infections and cause minimal side effects such as nausea, diarrhea, dizziness, photosensitivity and headache. Products containing cations such as magnesium, aluminum, calcium, iron, zinc or multivitamins containing minerals can significantly reduce the absorption of fluoroquinolones from the gastrointestinal tract. Patients should be advised to take fluoroquinolones 2 hours before or 4 hours after taking cationic preparations. Ciprofloxacin and levofloxacin may slow the metabolism of caffeine and theophylline. Since the simultaneous use of warfarin and fluoroquinolone can increase the effect of anticoagulants, patients receiving this combination should be monitored. The use of fluoroquinolones is contraindicated for pregnant and lactating women.

β-Lactams*:*

In the past, β-lactam antibiotics such as first-generation cephalosporins (cephalexin) and aminopenicillins (ampicillin, amoxicillin) were routinely used to treat urinary tract infections. Although first-generation cephalosporins and aminopenicillins achieve high concentrations in urine, they are no longer recommended as first-line treatment for UTIs due to resistance and a higher rate of recurrence than other agents. These agents should be used only if urine is produced. the sensitivity of cultural documents. However, third- generation cephalosporins, such as cefixime and cefpodoxime, have a longer half-life, allowing for less frequent dosing. In addition, less resistance to *E coli* has been observed with these agents than with first-generation cephalosporins and aminopenicillins. These agents may be an alternative for patients who cannot tolerate trimethoprim-sulfamethoxazole or have resistant infections.

Nitrofurantoin:

There are two types of nitrofurantoin: macrocrystalline (called macrodantin) and macrocrystalline monohydrate (called macrorobid). In addition to potentially inhibiting the formation of cell walls, nitrofurantoin inhibits a number of enzyme systems involved in bacterial metabolism. Macrobid merely needs to be taken twice a day, whereas macrodanitin must be taken every six hours. The kidneys eliminate 90% of nitrofurantoin through tubular secretion and glomerular filtration. if the estimated clearance of creatinine in the patient is less than 0.83 milliliters per second.

Fosfomycin tromethamine:

A derivative of phosphoric acid, fosfomycin is only used to treat simple urinary tract infections. A single oral dose of three grams is given. The enzyme pyruvyl transferase, which catalyzes the initial stage of bacterial wall production, is inhibited by fosfomycin. The range of bacteria that fosfomycin can kill includes *S saprophyticus* but excludes *Serratia ,E. coli, enterococci,*

Enterobacter, Citrobacter, and Klebsiella species. Fosfomycin comes in powder form, which needs to be combined with three to four ounces of water before being taken orally. It is generally well-tolerated. Diarrhea (9%), nausea, vomiting, and esophageal discomfort are possible side effects. Trimethoprim-sulfamethoxazole or trimethoprim should be used as first-line therapy because of its low cost and efficacy for uncomplicated urinary tract infections in women unless the prevalence of resistance to these agents among uropathogens in the community is greater than 10% to 20%. The fluoroquinolones are more expensive, broader in spectrum, and therefore, should be reserved for communities with rates of resistance to trimethoprim of greater than 10% to 20% or in patients who either cannot tolerate trimethoprim-sulfamethoxazole or have recurrent urinary tract infections. Other options include a 7-day course of nitrofurantoin or a single dose of fosfomycin. The use of first-generation cephalosporins or aminopenicillins is generally not recommended because of high levels of resistance and recurrence. Although resistance to the third- generation cephalosporins is lowe Because of their high rates of resistance and recurrence, first- generation cephalosporins and aminopenicillins are generally not advised. Due to their affordability and effectiveness, third-generation cephalosporins are regarded as third-line treatments even though resistance to them is lower than it was for the first generation.these agents are considered third-line agents because of their cost and efficacy.The optimal characteristics of agents to treat uncomplicated urinary tract infection must include activity against the major pathogens involved in these infections as well as a low potential for development of bacterial resistance. High urinary levels should be present for an adequate period to eliminate the organisms. Side effects should be minimal with minimal effect on the bacterial flora of the community. Treatment programs of single-dose, three days, or five days can be developed depending upon the agent.The patient's clinical course and the minimal inhibitory concentrations of the infecting organism to oxytetracycline correlated well. We draw the conclusion that urine concentrations of antimicrobials, as opposed to serum concentrations, are what determine the effectiveness of antibiotics in treating urinary infections, and

that urine-based antimicrobial sensitivity testing ought to be accessible in clinical settings.

ANTIBIOTIC RESISTANCE AND UTIs IMPLICATION

Both the etiology of UTI-causing bacteria and their susceptibility to antibiotics are changing over time and between different nations. The European Urology Association Guidelines recommend cotrimoxazole as the first-line antibiotic choice for empirical therapy in uncomplicated community-acquired UTIs when the local rates of trimethoprim/sulfamethoxazole resistance in uropathogens are <10–20%. Sensitivity to cotrimoxazole is a crucial feature in this decision- making process. Nonetheless, our investigation showed 58.3% *E. coli*-specific resistance and 49.4% overall trimethoprim/sulfamethoxazole resistance.Similar outcomes were seen in a recent study of this kind carried out in Sultanate Oman by Sharef et al., which showed that this antibiotic was resistant to 47% of the population overall and 50% of *E. coli* specifically. Comparatively speaking, studies carried out in European nations have shown low resistance, ranging from 28% to 30% and in other African nations, resistance is relatively high, ranging from 88.3% to 98.6%.

The Ministry of Health, KSA, recently took steps to restrict the over-the-counter sale of antibiotics without a doctor's prescription; the implementation of this rule will have a significant impact in controlling antibiotic resistance. The high resistance in the trimethoprim/sulfamethoxazole susceptibility pattern may be due to nonjudicious use and over-the-counter selling of this antibiotic. Children's UTIs can be caused by a variety of organisms, and treatment options can be significantly hampered by antibiotic resistance. Regular use of broad-spectrum antibiotics can alter the flora in the gut, which can lead to bacterial resistance. Given that uropathogen prevalence and features can change with time and location, routine surveillance of local uropathogens and their susceptibility to antibiotics is thought to be helpful in directing empirical therapy. The National Guideline Clearinghouse, the American Academy of Pediatrics, and the Royal College of Physicians of London advise empirical and precocious treatment of UTIs based on the susceptibility standard to the antibiotics that are routinely used, with the aim of lowering the risks of pyelonephritic scarring.There aren't many studies that have been done to identify the most recent patterns in the etiological agents that cause UTI in the community and among outpatients. On the other hand, since 1980, there have been documented changes in the causes of UTIs acquired in hospitals. To accurately diagnose and determine the antibiotic susceptibility pattern of the pathogens causing UTI, laboratory tests are essential, particularly urine culture and sensitivity tests.the most common isolated organisms from hospitalized patients in the urology department include *E. coli*, *Klebsiella pneumonia*, *Proteus mirabilis,* and *Pseudomonas aeruginosa*. It is important to note that *E. coli* and *Klebsiella* species together cause around three quarters of all cases of UTIs in our study population. Focusing on the best antibiotics selection which can successfully treat these two organisms can guide empirical treatment whenever needed. In the urology department, the most frequently isolated organisms from hospitalized patients are *Proteus mirabilis, E. Coli, Klebsiella pneumonia*, and *Pseudomonas aeruginosa*. Notably, a combination of *E. coli* and *Klebsiella* species accounts for about 75% of UTI cases in our study population. It can be useful to concentrate on selecting the best antibiotic to treat these two organisms when empirical treatment is necessary. The bulk of *E. Coli* and *Klebsiella* species isolated from hospital- and community-acquired UTIs are amenable to the antibiotics Meropenem, Imipenem, Fosfomycin, Nitrofurantoin, and Colistin, according to our research. Among the best drug choices are Imipenem, Meropenem, Fosfomycin, Nitrofurantoin, and Colistin. The cumulative incidence of antibiotic resistance was higher in UTIs obtained in hospitals than in UTIs obtained in the community. Antibiotic resistance cumulative incidence was greater in hospital-acquired UTIs than in community-acquired UTI. Independent predictors of antimicrobial resistance were a history of previous use of antibiotics within last three months, the occurrence of hospital-acquired UTI, DM, old age patient, and recurrent UTI. This will guide doctors in recognizing patients with a high risk of developing antimicrobial resistance. hospitalized patients with UTIs had significant MDR predictors and a high level of antimicrobial resistance.

Regular evaluation of resistance patterns in our hospitals is essential for maintaining antimicrobial stewardship programs, rational antibiotic use, and better, more effective antibiotic treatment. To guarantee the best possible care, empirical therapy for UTIs should be customized based on the susceptibility of the possible pathogens. Using

antibiotics strategically is crucial to halting future increases in AMR. New biological systems or pharmaceuticals that are specifically designed to counteract UTI pathogen resistance should be the main focus of future research. Further research is necessary for promising new biological compounds against multidrug-resistant organisms that are novel compared to traditional antibiotics, given the concerning issue of antibiotic resistance and the emergence of multidrug- resistant bacterial strains that impede the global control of infectious diseases. To guarantee the best possible care, empirical therapy for UTIs should be customized based on the susceptibility of possible pathogens. Antibiotic use must be reasonable in order to stop the spread of AMR. It is acknowledged that antibiotic resistance poses a significant threat to public health. Antibiotic resistance is perceived as unrelated to prescribing decisions because primary-care clinicians report that they rarely encounter treatment failure due to antibiotic resistance, and members of the public view the risk of antibiotic resistance as something that affects society at large and in the distant future rather than as a risk to their own health. The community's expectations for antibiotics and decisions about their prescription may be impacted by this significant evidence gap. Antibiotic resistance may have significant effects for patients with common infections treated in the community, even though the effects of antibiotic-resistant infections in hospitalized patients are well-known (higher mortality, longer hospital stays, and increased healthcare costs). The most significant risk factor for the spread of antibiotic-resistant bacteria and the emergence of ensuing antibiotic-resistant infections is the use of antibiotics. Less is known about the clinical significance of antibiotic resistance for patients with common community infections. The purpose of this systematic review is to compare the clinical outcomes for patients with respiratory tract, urinary tract, skin, and soft tissue infections in the community between antibiotic-resistant and antibiotic- sensitive infections. To maximize the use of antibiotics when treating UTIs in order to possibly lower the risk of antibiotic resistance. Nowadays, the majority of primary care patients with lower urinary tract infections are treated with antibiotics the same day without having their microbiology examined. Treatment for antibiotics is largely confined to two agents, trimethoprim and nitrofurantoin, in accordance with national guidelines, with little variation. Although the re- prescription of antibiotics is not common, it is on the rise and needs more investigation. The same antibiotic is prescribed to about one in five re-prescribed patients. We advise auditing practices in order to reduce this percentage. Antibiotic resistance to medications used for first and second line therapy may be minimized by taking recent antibiotic use into account when managing UTIs.

Antimicrobial Susceptibility of Bacterial Isolates

Bacterial cultures and ongoing monitoring of uropathogen antibiotic susceptibility are essential in light of the growing trend toward antibiotic resistance. In Uganda, the use of ciprofloxacin and amoxicillin as empirical treatments for UTIs should be stopped. Clinicians may find the study's conclusions helpful as they could enhance empirical treatment. Eleven patients had mixed infections, and the overall prevalence of UTI with bacterial growth was 64.0% (n = 89) (95% CI, 56.1–72.0). Consequently, one hundred microorganisms were isolated. *Escherichia coli* (28%), followed by *Enterococcus spp.* (57%) were the most prevalent uropathogens. The best medication

was nitrofurantoin (81.7% in Gram-positive and 87.3% in Gram-negative bacteria), imipenem (94.2% and 74.5%, respectively), and then imipenem. Amoxicillin and ciprofloxacin showed the highest resistance rates (66.2% and 44.6%, respectively). Bacterial cultures and ongoing monitoring of uropathogen antibiotic susceptibility are essential in light of the growing trend toward antibiotic resistance. In Uganda, the use of

ciprofloxacin and amoxicillin as empirical treatments for UTIs should be stopped. The findings of this study may be useful for clinicians, as they may improve empirical . treatment. The main urinary pathogens' susceptibility patterns have changed significantly in recent years. For example, there has been a gradual rise in infections brought on by *enterobacteria* that produce the enzyme extended-spectrum beta-lactamase (ESBL) or even bacteria that produce carbapenemase. As a result, the empirical treatment for these infections has changed. But in addition to altering empirical treatment, the rise in resistance needs to spur initiatives that promote the prudent use of antibiotics. The dearth of antibiotics and the inability to make a reliable etiological diagnosis—which is frequently made worse by the lack of antimicrobial sensitivity testing—make antimicrobial resistance a major issue in rural hospitals in developing nations. Collectively, these variables result in the overuse and misuse of broad- spectrum antibiotics, which has detrimental effects on these societies' economies and health because of things like extended hospital stays and ineffective treatment.

STRATEGY AND MANAGEMENT OF ANTIBIOTICS RESISTANCE FOR UTIS IMPLICATION

Treatment options for an episode of an uncomplicated UTI include a range of antibiotic strategies and antibiotic-sparing techniques.The EAU Guidelines for antimicrobial therapy in simple urinary tract infections suggest using fosfomycin, trometamol, various nitrofurantoin formulations, and pivmecillinam as first-line treatments. It is important to adhere to the therapy's dosages and duration. Interestingly, the European Commission prohibited the use of fluoroquinolone and quinolone antibiotics in 2019 due to severe, potentially life-long side effects. As a result, they are no longer recommended for the treatment of simple UTIs.There are ways to minimize the risk of antibiotic resistance in UTIs by optimizing the prescription of antibiotics. Without a microbiological investigation, the majority of patients diagnosed with lower urinary tract infections in primary care today receive same-day antibiotic treatment. There is minimal variationin the use of antibiotics, which are typically restricted to two medications, trimethoprim and nitrofurantoin, in accordance with national guidelines. Although the rate of re-prescription of antibiotics is low, it is steadily rising and needs more research. Five out of every ten patients who receive a re-prescription end up receiving the same antibiotic. To reduce this percentage, we advise auditing the practice. In order to minimize the development of antibiotic resistance to medications used for first and second line therapy, management of UTIs may need to take recent antibiotic use into account. Treatment for Lower Urinary Tract Infections Outcomes and Risk Factors for Antibiotic Re-prescription in Primary Care. In most of UTI cases cranberries, probiotics, D- mannose, methenamine hippurate, estrogens, intravesical glycosaminoglycans and immunostimulants. Treatment for antibiotics is largely confined to two agents, trimethoprim and nitrofurantoin, in accordance with national guidelines, with little variation. Although the re- prescription of antibiotics is not common, it is on the rise and needs more investigation. The same antibiotic is prescribed to about one in five re-prescribed patients. Many Clinical Investigators are working on theoretical model of Antibiotic heterogeneity like antibiotic cycling to defeat antibiotic resistane. The concept is under discussion for its practicality. Mar Pujades-Rodriguez et al. recommend auditing practices in their study as a way to lower this proportion. In order to avoid the development of antibiotic resistance to drugs used in first and second line therapy, it may be necessary to consider recent antibiotic use when treating UTIs. The public, patients, healthcare professionals (e.g., primary-care physicians, pharmacists, and medical students), and children (e.g., through schools and day care centers) should all be educated about the distinct characteristics of bacterial infections and antibiotics, the importance of prudent antibiotic prescribing as a positive construct, and personal hygiene (e.g., handwashing). The only way to reduce the issue of antibiotic resistance is for everyone in society to work together to maintain the effectiveness of antibiotics. Better Compliance with hand hygiene recommendation can minimise the hospital acquired infection rates. It's also critical to cut back on the use of antibiotics in agriculture, particularly for food animals. If the introduction of resistance genes into the human microbiome through diet or contact with the environment

is not limited, the issue of antibiotic resistance in human medicine will not be resolved. A number of strategies, such as making the best use of currently available vaccines, enhancing hygiene, employing health-improving enzymes, probiotics, prebiotics, and acids, and substituting antibiotics with bacteriocins, antimicrobial peptides, and bacteriophages, should be carefully considered in order to fortify the immune system and encourage the growth of food animals. Policies to alter the use of antibiotics in agriculture include stricter drug licensing regulations, financial incentives for developing livestock-specific antibiotics, prohibitions or restrictions on the use of medically necessary antibiotics, and sanctions for noncompliance. The final, and most crucial, tactic should be to accelerate the development of antibiotics in order to guarantee the constant supply of new tools to fight infections that are resistant to them. Even though it can seem impossible to find new antibiotic targets, especially when it comes to Gram- negative bacteria, the search for creative solutions and regulations must go on. In summary, concerted efforts of people involved in various fields, including prescribers, farmers, the public, politicians, and researchers, are needed to manage of antibiotic resistance.

Above all things, continuous efforts to educate people about antibiotic resistance are the very important strategy. The multidisciplinary core group, including physicians, pharmacists, microbiologists, epidemiologists and infectious disease specialists, can educate various members of society. In hospitals, prescribers should use antibiotics, based on the recommendation of guidelines and ASPs, and through considering various data such as PK/PD and MIC/MPC of antibiotics, diagnostic testing results, AST results, clinical response, and effects on the microbiota. Thorough hospital disinfection and personal hygiene of healthcare workers, especially hand washing, are also important to prevent hospital-acquired infections. The guideline for the farmers should be quickly made. Farmers should think about using vaccines, bacteriocins, antimicrobial peptides, and bacteriophages as antibiotic alternatives instead of using medically significant antibiotics like carbapenems and vancomycin. It is a good idea to use enzymes, probiotics, prebiotics, and acids to support the immune system in food animals. Enhancing farm hygiene holds significant importance as well. The general public should practice good personal hygiene, which includes washing their hands and taking baths, and use antibiotics responsibly in accordance with doctor's prescriptions. Public service announcements and campaigns can help dispel public misconceptions regarding antibiotics. To encourage the development of novel antibiotics, legislators should create laws pertaining to antibiotic resistance and devise creative policies. Researchers ought to keep an eye on instances of antibiotic resistance in environments, hospitals, and animals. To find new classes of antibiotics, innovative methods for screening-based approaches and rational design are required. Reducing the use of antibiotics can be accomplished through the development of rapid, efficient molecular methods for identifying resistance genes and the search for diagnostic biomarkers, such as procalcitonin, that can be used as a guide when stopping antibiotic treatment. Antibiotic resistance can be successfully minimized if society as a whole assumes responsibility for preserving the efficacy of antibiotics and fulfills its obligations.

DISCUSSION & CONCLUSION :

Globally, UTIs place a significant financial and emotional strain on people as well as health resources. Doctors and specialty nurses, as well as patients and their carers in the community, encounter significant challenges in effectively managing UTIs. Although patients clearly benefit from receiving antibiotics for symptoms suggestive of UTIs and rUTIs, misuse and inappropriate usage have contributed to an international problem of antimicrobial resistance (AMR), which is becoming a greater concern to public health.

System have been developed to optimize clinical outcomes while reducing inappropriate antibiotic use have been developed to provide guidance encouraging prudent and appropriate antibiotic prescribing that minimizes the unintended consequences of antibiotic overuse, including antibiotic-related adverse events and the emergence of resistant bacterial strains .When antibiotic therapy is indicated for treating UTIs or rUTIs, choosing an appropriate antibiotic based on local resistance and susceptibility patterns is essential, guided by evidence-

based clinical guidelines such as those compiled by the EAU, which recommends first-line therapy with fosfomycin trometamol, nitrofurantoin, or pivmecillinam as first-line antimicrobial therapy for uncomplicated UTIs.there are opportunities to optimise antibiotic prescribing for UTIs that could potentially reduce the risk of antibiotic resistance. Most patients currently diagnosed with lower UTI in primary care receive same-day antibiotic treatment, without microbiological investigation. There is little diversity in antibiotic treatment, which is generally limited to two agents, trimethoprim and nitrofurantoin, reflecting national guidelines. The rate of antibiotic re-prescription is low but is gradually increasing and requires further study. Approximately one in five patients with re- prescription receives the same antibiotic again. We recommend that practice is audited to drive down this proportion. Management of UTIs might need to consider recent antibiotic use to minimise development of antibiotic resistance to drugs used for first and second line therapy.