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A Report on Antibiotic Susceptibility and Resistance of Pathogens Causing Urinary Tract Infection (UTI) to Human Patients

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Abstract:

The urinary tract infection (UTI) is a widespread bacterial infection known to affect the different parts of urinary tract. The occurrence is common in both sexes of human beings worldwide. Despite the fact, that both the genders are susceptible to infection, women are frequently vulnerable due to anatomy and physiology of urinogenital structures. The infection habitually caused as a consequence of bacterial invasion of the urinary tract including lower and upper parts. It is a recurrent cause of morbidity and mortality, and a major driver of antibiotic resistance to antimicrobial drugs often empirically prescribed. This study revealed urinary tract bacterial contamination, antibiotic susceptibility pattern of the isolates to some commonly used antibiotics and explore the mechanism of multidrug resistant bacteria isolated from urinary tract of infected patients.

Keywords: Urinary tract infection (UTI), Reproductive physiology, Bacterial invasion, Antibiotic resistance.

1. INTRODUCTION

The urinary tract infection (UTI) is an infection from microbes. Most of the UTIs are caused by bacteria, but some due fungi and rarely by viruses' infection (James, 2018). The UTIs are most common infections among human beings. An UTI can happen anywhere in your urinary tract. Our urinary tract is made up of kidneys, ureters, urinary bladder, and urethra. Most UTIs only involve the urethra and bladder, in the lower tract. However, UTIs can involve the ureters and kidneys, in the upper tract also. Although upper tract UTIs are rarer than lower tract UTIs, but usually more severe (Cappuccino and Sherman, 2005). The urinary infections are fairly common, like cystitis. Often there is burning or stinging of the urine and urinary frequency is the most common symptom of UTIs (Ouno et al., 2013). The urine may be quite offensive and sometimes contains blood also. About 30% of women will be troubled by these distressing symptoms at some stage. By contrast, when less common infections like pyelonephritis occur in the upper part of the urinary tract, the person is usually quite sick often with a high fever, back pain and shivers. This type of infection is far more likely to be associated with underlying abnormalities and follow-up investigations are always advised. Urinary tract infections (UTI) are painful and uncomfortable, yet avoidable. Over 50% of women have had at least one UTI and over 20% have had multiple (Fig. 1). The UTIs are responsible for over 8 million doctor's visits per year. The sexual activity is a high risk factor for developing UTI's in women (Gupta and Stamm, 1990; Eckburg et al., 2005).

The UTI's are most typically caused by *Escherichia coli* that have been transferred to urinary tract from the bowel. When *E. coli* enters urinary tract, the bacterium adheres to wall of the urinary mucosa

using a type of fimbrial adhesion called P-fimbriae. These P-fimbriae are used by *E. coli* strands that colonize the urethra to specifically bind to glycoprotein receptors on urothelial cells. These glycoproteins have a mannose residue that is the binding site for the P-fimbriae proteins. The current treatment for an UTI caused by the gram negative *E. coli* is an antibiotic regiment. There are several common antibiotics used to treat UTIs, which are typically diagnosed on symptoms alone. Antibiotic resistance in gram negative bacteria is of increasing concern, particularly for broad spectrum antibiotics, which are used more and more frequently for urinary infections. The recurrent and long term antibiotic use risks increased bacterial resistance (Iqra et al., 2014).

As bacterial populations in the vagina are killed due to antibiotics taken to treat a UTI, vaginal yeast populations have the opportunity to proliferate. This leads to further infection, discomfort, and anti-fungal medication. This is a growing problem for treating UTI's specifically, which can lead to more serious infections. It is extremely important that antibiotics are used sparingly, and that alternative prevention options are made available (Kline and Lewis, 2016). The aim of this study is to explore the identification and evaluation of the prevalence of bacterial contaminants from urinary tract infected patients. Due to emerging incidence of multi-drug resistant organisms this study also aimed at determine the scenario of antibiotic resistance profile and detecting the multi-drug resistant organism.

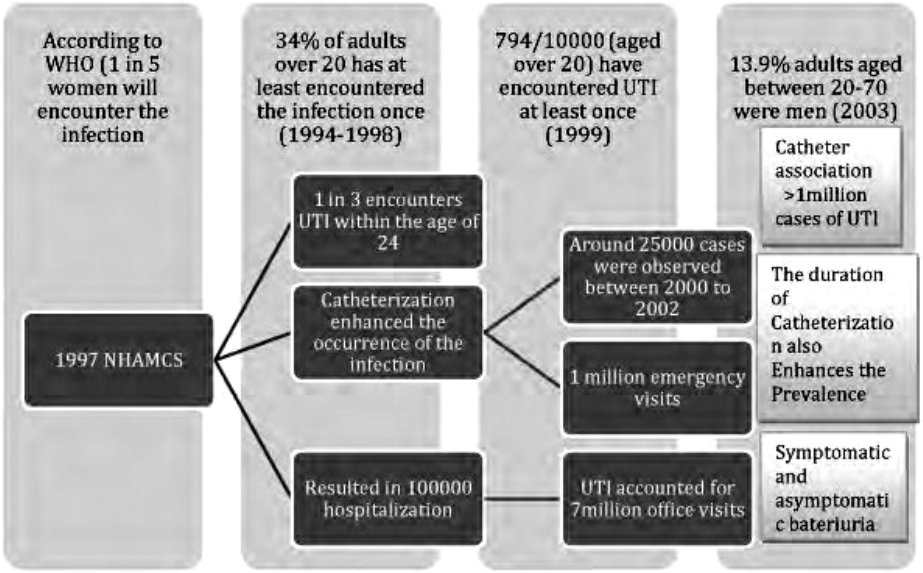

Figure 1: A glimpse of urinary tract infection and symptoms in human population. (*Source WHO).*

2. NORMAL FLORA OF HUMAN BODY

The normal flora refers to the population of microorganisms that reside in the skin and mucus membranes of a healthy normal person without causing any disease (Brooks et al., 2007). They protect us from disease by competing with invaders for space and nutrients, by producing bateriocins which kill harmful bacteria and lowering the pH so that others cannot grow.

Table 1: The normal flora of the different parts of human body

S. No.	Human body	Normal flora
1.	Skin	Staphylococci, Micrococci, Diptheroids
2.	Oral and upper respiratory tract	*Neisseria*, *Bordetella*, *Corynebacterium*, *Streptococcus*
3.	Conjunctiva	*Haemophilus* and *Staphylococcus*
4.	Gastrointestinal tract	Enterococci, non-haemolytic *Streptococcus*, *E. coli*, *Lactobacillus*
5.	Genital tract	*Corynebacterium, Lactobacillus*, non-pathogenic *Neisseria*

3. CAUSES OF UTIs

The urinary tract infections typically occur when bacteria enter the urinary tract through the urethra and begin to multiply in the bladder. Although the urinary system is designed to keep out such microscopic invaders, these defenses sometimes fail. When that happens, bacteria may take hold and grow into a full-blown infection in the urinary tract. The most common UTIs occur mainly in women and affect the bladder and urethra (Cappuccino and Sherman, 2005; Brooks et al., 2007).

4. CLASSIFICATION OF UTI

It is understood that the infection targets the different parts of the urinary tract and as a consequence results in the contagion of the lower and the upper urinary tracts. The infection is named on the basis of site of infection. The infection of urethra and ureter are referred as urethritis and ureteritis respectively whereas cystitis and phylonephritis corresponds to bladder and kidney infections. The cystitis is a common type of infection whereas the infection associated with the renal damage is an issue of serious concern (James, 2018). Therefore the infection of bladder and urethra are referred as the infection of the lower urinary tract whereas the kidney and ureter infection is an indication of upper tract infection. Generally UTIs are classified based on the factors that trigger the infection and the nature of occurrence. Taking these aspects in to consideration, UTIs can be classified as follows: (a) Uncomplicated or complicated (based on the factor that triggers the infection), and (b) Primary or recurrent (depending on the nature of occurrence).

5. UTI SYMPTOMS

Symptoms of a UTI depend on what part of the urinary tract is infected. The lower tract UTIs affect the urethra and bladder with symptoms like burning with urination, increased frequency of urination without passing much urine, increased urgency of urination, bloody urine, cloudy urine, urine that has a strong odor, pelvic pain in women, and rectal pain in men. However, the upper tract UTIs affects the kidneys (Ouno et al., 2013). These can be potentially life threatening if bacteria move from the infected kidney into the blood. This condition, called urosepsis, can cause dangerously low blood pressure, shock, and death ultimately.

6. RISK FACTORS OF UTIs

Urinary tract infections are common in women, and many women experience more than one infection during their lifetimes. Risk factors specific to women for UTIs includes:

a) **Female anatomy:** A woman has a shorter urethra than a man does, which shortens the distance that bacteria must travel to reach the bladder.
b) **Certain types of birth control:** Women who use diaphragms for birth control may be at higher risk, as well as women who use spermicidal agents.
c) **Menopause:** After menopause, a decline in circulating estrogen causes changes in the urinary tract that make you more vulnerable to infection.
d) **Urinary tract abnormalities:** Babies born with urinary tract abnormalities that don't allow urine to leave the body normally or cause urine to back up in the urethra have an increased risk of UTIs.
e) **Blockages in the urinary tract:** Kidney stones or an enlarged prostate can trap urine in the bladder and increase the risk of UTIs.
f) **A suppressed immune system:** Diabetes and other diseases that impair the immune system i.e. the body's defense against germs can increase the risk of UTIs.
g) **Catheter use:** People who can't urinate on their own and use a tube (catheter) to urinate have an increased risk of UTIs. This may include people who are hospitalized, people with neurological problems that make it difficult to control their ability to urinate and people who are paralyzed.
h) **A recent urinary procedure:** Urinary surgery or an exam of your urinary tract that involves medical instruments can both increase your risk of developing a urinary tract infection.

7. CAUSATIVE AGENT

Urine generally considered to be sterile and is believed to be germ free. Any source of possible infection occurs through urethra which initiates the incidence of the infection. The predominant pathogen responsible for UTI is *E. coli* which constitutes up to 80-85% and is followed by *Staphylococcus saprophyticus* which accounts to 5-10% (James, 2018). The occurrence of the infection due to viral or fungal agents is a rare phenomenon. In addition to the above mentioned bacterial species, *Klebsiella*, *Proteus*, *Pseudomonas* and *Enterobacter* are associated with UTI. The bacteria enter the bladder through urethra and the infection can also occur through blood and lymph. The microbial etiology of UTIs is deemed to be well established and frequent (Brooks et al., 2007). Pathogens like *E. coli* and *S. saprophyticus* are associated with population acquired acute uncomplicated infection whereas *Klebsiella*, *Enterococcus*, *Proteus Species*, *Enterobacter, Bacillus, Shigella* are known to confer uncomplicated cystitis and phylonephritis that are sporadic (Ouno et al., 2013).

8. ANTIBIOTIC RESISTANCE

Antibiotics are type of antimicrobial drugs which are used in the treatment and prevention of bacterial infections caused by bacterial pathogens. Antibiotic resistance is one of the biggest threats to global health, food security, and development today. Multidrug resistance refers to antimicrobial resistance shown by the organisms to multiple antimicrobial drugs usually at least two or more than two antibiotics. The WHO list is divided into three categories according to the urgency of need for new antibiotics as critical, high and medium priority (Table 2).

Multiple drug resistance: The high prevalence of multidrug resistant bacteria encoding various multidrug resistance genes has now become a major threat to public health. Without effective antimicrobials, medical procedures such as organ transplantation, cancer chemotherapy, diabetes management and major surgery (for example, caesarean sections or hip replacements) become very high risk. Globally, 480,000 people develop multi-drug resistance each year, and drug resistance is starting to complicate the fight against HIV and malaria, as well (Tanwar et al., 2014). An influential report from the O'Neill Commission predicts that antibiotic resistance will lead to 10 million deaths per year by 2050, surpassing cancer as a source of human mortality.

Mechanisms of multi-drug resistance: Antibiotic resistance genes might be transferred to pathogenic bacteria infecting humans, particularly under the selection pressure of antibiotics as well as *via* the "SOS" response (Ubeda et al., 2005). Besides long term exposure of microorganisms to high concentration of antibiotics also gave rise to the multi-drug resistant organisms (Wagenlehner et al., 2005). Researchers have observed that there has been a sigmoidal rise in resistance over time in the presence of a constant rate of antibiotic consumption and a threshold level of antibiotic usage needed to trigger the emergence of resistance to significant levels.

Table 2: The pathogens categories, sources and particular antibiotics resistance (Source WHO)

Categories	Organisms	Resistant to antibiotics
Critical group	*Enterobacteriaceae*	Carbapenem-resistant, cephalosporin-resistant
	Pseudomonas aeruginosa,	Carbapenem-resistant
	Acinetobacter baumannii	Carbapenem-resistant, ESBL-producing
High group	*Enterococcus faecium*	vancomycin-resistant
	Staphylococcus aureus	Methicillin-resistant, Vancomycin-intermediate and resistant
	Salmonellae sp.	Fluoroquinolone-resistant
	Helicobacter pylori	Clarithromycin-resistant

	Campylobacter sp.	Fluoroquinolone-resistant
	Neisseria gonorrhoeae	Cephalosporin-resistant, Fluoroquinolone-resistant
Medium group	*Streptococcus pneumoniae*	Penicillin-non-susceptible
	Shigella sp.	Fluoroquinolone-resistant
	Haemophilus influenzae	Ampicillin-resistant

Emergence of resistance among UTI pathogens: Among UTI causing pathogens bacterial resistance have been going on for the last three decades and the available data and reports confirm that the increase in resistance to commonly employed antibiotics is a consequence of inappropriate use of the antimicrobial agent. Surfacing of resistance among the pathogens responsible for UTI is an issue of serious concern and requires an immediate attention in order to derive suitable remedy to overcome the problem (Ouno et al., 2013). Bacterial urinary tract infections (UTIs) are frequent infections in the nosocomial setting. Nosocomial UTIs are almost exclusively complicated UTIs, although the complicating factors may be very heterogenous. The bacterial spectrum of nosocomial UTIs is broad and antibiotic resistance is common (Wagenlehner et al., 2005).

9. UTIs SCENARIO: PERSPECTIVE TO HEALTH, ANTIBIOTICS SUSCEPTIBILITY AND RESISTANCE

Ouno et al. (2013) investigated on Isolation, identification and characterization of urinary tract infections bacteria and the effect of different antibiotics of Masinde Muliro University of Science and Technology, Department of Medical Laboratory Science. This study focused on the frequency of uropathogens and their antibiotic susceptibility in different gender in Madurai District. Sum of 30 samples were collected from both male and female of different ages. They viewed the prevalence of both gram positive and gram negative bacteria among them *E. coli* were the predominant isolate along with *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Proteus mirabilis* and *Enterococcus faecalis*. Among the antibiotics tested, chloraphenicol and ciprofloxacin (100%) were found to be effective for empirical treatment of UTI and has covered the majority of urinary pathogens followed by tetracycline, gentamycin and kanamycin (83%), Ampicillin (67%). Streptomycin, Rifampicin and amoxicillin were less effective (50%).

Katarzyna et al. (2001) investigated on antibiotic susceptibility of bacterial strains isolated from urinary tract infections. The aim of this study was to obtain data on susceptibility patterns of pathogens responsible for urinary tract infections (UTIs) in Poland to currently used antimicrobial agents. Sum of 141 pathogens from hospital-acquired infections and 460 pathogens from community-acquired infections was collected. The most prevalent aetiological agent was *E. coli* (73.0%), followed by *Proteus* sp. (8.9%) and other species of *Enterobacteriaceae* (9.6%). Few community infections were caused by Gram-positive bacteria (2.2%). Gram-positive cocci were isolated more frequently from a hospital setting (14.1%) and the most common were *Enterococcus* sp. (8.5%). *Pseudomonas aeruginosa* was found only among hospital isolates and was responsible for 10.7% of infections. *E. coli* isolates from both community and hospital infections were highly susceptible to many antimicrobial agents. Of all *Enterobacteriaceae* tested, 38 strains (6.9%) were capable of producing ESBLs.

Annarita *et al.* (2017) studied on multi-drug-resistant Gram-negative bacteria causing urinary tract infection. Due to the high empiric use of antibiotics for the treatment of UTI, antibacterial resistance of *Enterobacteriaceae*, specifically the main uropathogens *E. coli* and *K. pneumoniae*, has significantly increased worldwide. In this article the worldwide epidemiology of resistant Gram-negative bacteria causing UTIs, with a special focus on extended spectrum beta lactamase (ESBL) positive pathogens, as well as new threats such as multi-drug- resistant (MDR) clones (e.g. *E. coli* 131 (ST131) and *K. pneumonia* ST258), are reviewed. The increased prevalence of MDR *Enterobacteriaceae*, limiting available treatment options for infections caused by these organisms, and the lack of new antibiotics provide good rationale for using older antibiotics, such as fosfomycin, that have been shown to retain some activity against MDR bacteria.

Salih et al. (2016) conducted an investigation on isolation of pathogenic gram-negative bacteria from urinary tract infected patients. This study investigated the susceptibility pattern of different bacteria isolated from urinary tract infection to different antibiotics. Total 83 uropathogen bacteria were isolated from 300 urine samples taken from patients attended to Tikrit Teaching Hospital. Bacteria obtained from urine samples were cultured and tested for antimicrobial susceptibility to 16 kinds of antibiotics. The results showed that the bacterial species of *E. coli, Proteus mirabilis, K. pneumonia, Citrobacter diversus, C. freundii, Enterobacter aerogenes, Yersinia pestis, P. aeruginosa, K. oxytoca* and *Hafnia alvei* were identified in 44 (53%), 18 (21.7%), 4 (4.8%), 4 (4.8%), 3 (3.6%), 3 (3.6%), 3 (3.6%), 2 (2.4%), 1 (1.2%) and 1 (1.2%), respectively, of the isolates. The results of antimicrobial susceptibility test showed that 83 (100%) isolates were resistant to ampicillin, rifampicin and erythromycin. The 75 (90.3%) isolates were resistant to cefotaxime, 67 (80.7%) isolates were resistant to tobramycin. The 66 (79.5%), 65 (78.3%), 56 (67.4%) and 48 (57.8%) isolates showed susceptibility to nalidixic acid, tetracycline, nitrofurantoin, chloramphenicol, respectively. The 45 (54.2%) isolates were resistant to azithromycin, norfloxacin and ciprofloxacin. The meropenem, gentamicin, amikacin, and imipenem showed significant effect on 35 (42.1%), 32(38.5%), 27 (32.5%) and 1 (1.2%) isolates, respectively.

Iqra et al. (2014) investigated on Multi-drug resistant *K. pneumonia* causing urinary tract infections in children. Total 1015 urine samples were collected aseptically from the Children Hospital Lahore, Pakistan. Multi-drug resistant (MDR) *K. pneumonia* has been associated with different types of infections and the most important aspectis the emergence of MDR strains particularly in hospitalized children. Antimicrobial susceptibility was determined using Kirby-Bauer disc diffusion method. Of the 1015 urine specimens, 230 (22.6%) were positive for bacterial growth. Out of these positive cultures predominantly Gram-negative rods (90%) were isolated and major pathogens were *K. pneumonia* (40%) and *E. coli* (33%). Antimicrobial susceptibility pattern of *K. pneumoniae* showed that more than 70% of these pathogens were resistant to cephalosporins, 69% to ciprofloxacin and amoxicillin-clavulanic acid and 63% to norfloxacin and nalidixic acid while most effective drugs were pipracillin-tazobactam and meropenem.

Kline and Lewis (2016) studied on Gram-positive uropathogens, polymicrobial urinary tract infection, and the emerging microbiota of the urinary tract. They found that Gram-positive bacteria are a common cause of urinary tract infection (UTI), particularly among individuals who are elderly, pregnant, or who have other risk factors for UTI. In this case the infection mostly caused by *S. saprophyticus, E. faecalis*, and *Streptococcus agalactiae*. Otherwise under reported Gram-positive pathogens of the urinary tract including *Aerococcus, Corynebacterium, Actinobaculum,* and *Gardnerella*. UTI (>90% as defined by the culture of a uropathogen from urine with >100,000CFU/ml). They collected all the samples from elder patients and all the samples showed CFU more than 10^5/ml. Here the studied showed that Gram-positive bacteria such as *Staphylococcus* and *Streptococcus* shows the higher prevalence in elderly patients.

Raul et al. (2011) investigated on UTI infection of women. In a multivariate analysis it was found that urinary incontinence, a history of UTI before menopause, and non-secretory status were strongly associated with recurrent UTI in young postmenopausal women. Another study described the incidence and risk factors of acute cystitis among non diabetic and diabetic postmenopausal women. The diabetic patients are also at high risk between the ages 40-65 years.

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