Urinary Tract Infection Causing Microbes and their Resistance with Antibiotics

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Abstract

Urinary tract infection (UTI) represents one of the most common diseases occurring from neonate to the geriatric age groups encounters in medical practices. UTIs are among the most common bacterial infections in humans, both in community and hospital settings and have been reported in all age groups in both sexes, women are more likely than men to get UTI because of their urinary tracts design, nearly half of the all women have a UTI at some point in their lives. Most of the UTI are caused by gram negative bacteria like *E. coli*, *Proteus mirabilis*, *Proteus vulgaris*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Acinetobacter*, *Serratia* and *Morganellamarganii*. UTI are also caused by gram positive bacteria like *Enterococcus*, *Staphylococcus* especially coagulase negative *Staphylococci* and *Streptococcus agalacticae*. Antibiotics are the main treatment for all UTIs. A variety of antibiotics are available, and choices depend on many factors including whether the infection is complicated or uncomplicated or primary or recurrent. In the present time multiple drug resistance in microbial pathogens become a serious health problem to humankind worldwide. It is aroused due to indiscriminate and repetitive use of antimicrobial drugs. Antibiotic resistance occurs when bacteria change in some way that reduces or eliminates the effectiveness of drugs, chemicals or other agents designed to cure or prevent infection. The bacteria survive and cause more harm. A number of multiple drug resistant strains and appearance of the strains with reduced susceptibility to antibiotics are continuously increasing. The past record of rapid, widespread emergence of resistance of newly introduced antimicrobial agents indicates that even new families of antimicrobial agents will have a short life expectancy.

Key words: Antibiotics, Antimicrobial agents, Gram positive bacteria, Gram negative bacteria, Multidrug resistance, UTI.

Paper cited: Sharma, S., Singh, Y., Jayanand; Singh, N.P., Saxena, R.S. and Prakash, D.A. (2017). Urinary Tract Infection Causing Microbes and their Resistance with Antibiotics. *South Asian Journal of Food Technology and Environment*, 3(1): 418-431.

Introduction

Urinary tract infection (UTI) represent one of the most common diseases occurring from neonate to the geriatric age groups encounters in medical practices (Raju and Tiwari, 2004). UTIs are among the most common bacterial infections in human population, both in community as well as in hospital settings and have been reported in

almost all age groups in both genders (Hooton *et al.*, 1995). Urinary tract infection is associated with the entry of bacteria in the urinary tract. women are generally more likely to get infected than men due to their urinary tracts design, due to larger urethra in men, it is more difficult for bacteria to get in the urinary tract. Nearly half of the all women have a UTI at some point in their lives (Marild and Jodal, 1998; Craig, 2001; Foxman 2003). UTI are classified as

uncomplicated or complicated. Uncomplicated UTIs occur in sexually active healthy female patient with structurally and functionally normal urinary tracts. Complicated UTIs are associated with the complications of urinary tract that prolong the need for the treatment or increase the chances for the therapeutic failure. These conditions include any kind of abnormalities in the urinary tract that hinder urine flow, the impedance could be caused by the existence of a foreign body (e.g., indwelling catheter, stone) or infection with multidrug resistant pathogens. UTIs in male patients are generally considered as complicated. Despite involvement of upper urinary tract pyelonephritis can be considered as uncomplicated when it occurs in a healthy patient (Stamm and Norrby, 2001). The term 'cystitis' (bladder infection) has been used to describe the syndrome showing dysuria, frequency and occasionally suprapubic pain. Acute pyelonephritis describes the clinical syndrome characterised by flank pain and fever, often associated with dysuria, urgency and frequency (Mandell *et al.*, 2005).

About 150 million people developed a urinary tract infection every year (Flores-Mireles *et al.*, 2015). It is more common in women than men. In women, it is the most common form of bacterial infection. A study conducted by the National Center for Health Statistics revealed that most frequently treated infections in American emergency rooms showed that only pneumonia is treated more than UTI (Pitts *et al.*, 2008). According to a recent study UTI account for as many as 8.1 million visits to health care providers every year (American Urological Association Foundation, 2012). Another study estimated that by 2050, the number of women who have surgery to treat urinary infection will increase by almost 50%, to more than 300,000 women (Wu *et al.*, 2011).

The spectrum of urinary conditions which ranges from asymptomatic bacteriuria, to

symptomatic UTI, to sepsis is ultimately associated with UTI requiring hospitalization (Nicolle, 2002). Asymptomatic bacteriuria in women can be defined as presence of at least 10⁵ CFU/mL of the same uropathogen in 2 consecutive clean catch midstream urine samples which are obtained from the patients without any symptoms or signs attributable to urinary infection. Asymptomatic bacteriuria is simply a colonization state of uropathogen and that not requires treatment (Monane *et al.*, 1995; Kaye *et al.*, 1989; Nicolle, 2009). For establishing a diagnosis of symptomatic UTI, it requires a patient to show symptoms and signs of a UTI and laboratory tests must confirm the diagnosis (for bacteriuria $\geq 10^5$ CFU/mL and for pyuria ≥ 10 white blood cells/ high-powered field). Uncomplicated symptomatic Urinary tract infection is present when there is a symptomatic bladder infection evidenced by fever, deteriorated urinary urgency or frequency, dysuria, suprapubic pain, costovertebral angle pain or tenderness with no recognized cause, and laboratory tests revealing UTI. The symptom of fever is usually not diagnosed during symptomatic UTI (localized to the bladder). Complicated UTI is defined as having a symptomatic UTI in the individual caused by a functional or structural abnormality; having had urinary instrumentation; systemic diseases such as renal insufficiency, diabetes, or immunodeficiency; or having undergone organ transplantation etc. (Mathews and Lancaster, 2011; Epp *et al.*, 2010; Nicolle *et al.*, 2005; Mazzulli, 2012).

Causal organisms

Most of the UTI are caused by gram negative bacteria like *E.coli*, *Proteus mirabilis*, *Proteus vulgaris*, *Klebsiella* spp., *Pseudomonas aeruginosa*, *Acinetobacter*, *Serratia* and *Morganella morganii*. UTI are also caused by gram positive bacteria like *Enterococcus*, *Staphylococcus* especially coagulase negative

Staphylococci and *Streptococcus agalacticae* (Tangho and Mcaninch, 2004). About 80% of the uncomplicated cystitis and pyelonephritis are due to *E. coli* only, whereas *Proteus mirabilis* and *Klebsiella pneumoniae* infection accounts 10% and 6% respectively. Many research studies revealed that *E. coli* is the dominant uropathogen (30%) isolated in acute community acquired uncomplicated infections, followed by *Staphylococcus saprophyticus* (10-15%). The pathogens which are traditionally associated with UTI are actually changing many of their features, particularly because of antimicrobial resistance. The etiology of UTI is also affected by the underlying factors that complicate UTI, factors like age, diabetes, spinal cord injury, or catheterization. Consequently, complicated UTI has a more diverse etiology compare to that of uncomplicated UTI and organisms that rarely cause disease in healthy patients can cause significant disease in host having anatomic, metabolic, or immunologic underlying disease. Etiologic pathogens related with UTI among patients having diabetes diagnosed with the species of *Klebsiella*, Group B *Streptococci* and *Enterococcus* spp. as well as *E. coli*, the patients having spinal cord injuries commonly have *E. coli* infections. Other common uropathogens include *Pseudomonas* and *Proteus mirabilis* (Ronald, 2003).

Remedial measures

Antimicrobial therapy: Antimicrobial therapy is the major treatment for UTIs, with the supreme objective being the extermination of bacterial growth in the urinary tract by an effective, safe and cost-effective antimicrobial agent (Hooton and Stamm, 1991).

Oestrogen: Oestrogen use to triggers the growth of *Lactobacillus* in the vaginal epithelium, reduces pH and avoids vaginal colonization by uropathogens. After menopause, oestrogen levels and the number of *Lactobacilli* drop; this

plays a crucial role in the development of bacteriuria, and makes post-menopausal women highly susceptible to UTIs. Use of vaginal oestrogen use reduces RUTIs by 36–75% and has minimum systemic absorption (Perrotta *et al.*, 2008; Brown *et al.*, 2001).

Cranberry juice and tablets: The use of Cranberry juice and tablets have been shown to reduce RUTIs as they contain a compound known as tannin, or proanthocyanidin, which reduces *E. coli* vaginal colonization (Schmidt and Sobata, 1988; Zafriri *et al.*, 1989). Although earlier, smaller studies have shown that consuming cranberry juice or tablets can prevent RUTIs, an updated Cochrane review showed that evidence for its benefit in any longer for UTI prevention is small therefore, cranberry juice cannot be recommended any longer for UTI prevention (Epp *et al.*, 2010).

Antiseptics: Methenaminehippurate is a unique salt used for prophylaxis and treatment of RUTIs. Methenamine is broken down to ammonia and formaldehyde when in acidic urine, which act as a bactericide to some strains of bacteria (Mayrer and Andriole, 1982).

Antimicrobial resistance: Antimicrobial resistance (AMR) is the ability of microorganism that causes disease to withstand attack by antimicrobial medicines. Resistance is a property of the microbe, not a person or other organism infected by a microbe. Microorganisms coexist with other living organisms and exhibit the greatest genetic and metabolic activity. Microbes have evolved a number of mechanisms which help them to survive the pressure exerted by the competitive environmental challenges. Antimicrobial agents are the drugs that act by eliminating the pathogen. Development of antibiotics for medicinal use has been successful in targeting key components of general areas of microbial

metabolism like: synthesis of cell wall, protein synthesis, synthesis of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA) and intermediary metabolism. The successful use of antibiotics to inhibit and eliminate the infectious organisms has been facing challenges and difficulties because pathogens are developing diverse forms of resistance to the drugs and as the use of antibiotics increases, so do the degree and complicity of the resistance.

Mechanism of acquisition of resistance to antimicrobial agents: Pathogens are known of its versatility for drugs; nevertheless, they have a limited number of mechanisms of acquired antimicrobial resistance (Jacoby and Archer, 1991). The principal genetic mechanisms which lead to antimicrobial resistance are genetic mutation (single point mutations or major deletions or rearrangements), expression of a latent resistance gene and acquiring genes or DNA segments with resistance determinants. Some of the genes are inherited, some emerge by random mutations in microbial DNA and some are imported from other resistant organisms by reproduction. These genetic changes responsible for modification in binding proteins (a), ribosomes (b) alter membrane structure (c) or inactivating enzymes. After a pathogen attains resistance genes to protect itself from various antimicrobial agents, pathogens use several biochemical resistance mechanisms (Giedraitiene *et al.*, 2011).

Drug resistance by target site modification: An interaction between an antibiotic agent and a target molecule is very specific so even slight changes in a target molecule can affect antibiotic binding to a target (Giedraitiene *et al.*, 2011). Antimicrobial agents act at targets that are present in microbial cells but differ sufficiently to mammalian cells to allow for selective inhibition of the bacterial counter parts. Because of the essential cellular functions of the target sites, organisms cannot avoid antimicrobial action by dispensing with them entirely.

However, microbes have been gaining some mutational changes in the target that reduce susceptibility to inhibition whilst retaining their cellular function (Lambert, 2005).

Interference with DNA synthesis: The mechanism of resistance is a modification of mainly two enzymes i.e DNA gyrase (Kim *et al.*, 2002) and topoisomerase IV. Mutations in these genes are followed by replication failure, which leads to reducing drug affinity (Giedraitiene *et al.*, 2011).

Ribosome protection: The mode of action of certain antibiotics is to block protein synthesis in bacteria by binding to target subunit (Vannuffel and Cocito, 1996). Resistance to these drugs is referred to as MLS (B) type resistance and occurs in a wide range of Gram-positive and Gram-negative bacteria (Weisblum, 1995).

Reduced membrane permeability: The outer membrane in gram-negative organisms contains an inner layer that has phospholipids and an outer layer that has the lipid A. Such composition reduces drug uptake to a cell. Drug molecules can be transferred to a cell by the following mechanisms: (i) diffusion through porins, (ii) diffusion through the bilayer, and (iii) by self-promoted uptake. The resistance is acquired to all antimicrobial classes by *P. aeruginosa* is mainly due to low outer membrane permeability (Lambert, 2002).

Active drug efflux: Active drug efflux from the cell is one of the common pathways of antimicrobials resistance in bacteria, the resistance is developed when the rate of drug efflux across the membrane exceeds that of drug influx, and bacterial genomes encode for many membrane-bound multidrug efflux systems. These efflux systems are usually under the control of an intricate regulatory network, which, in the presence of drug and other stress molecules, increases the overall efflux system activity and decreases influx capacity (Misra *et al.*, 2015).

Potential Strategies for Resistance

Probiotics: Probiotics are favorable microorganisms that could protect against urinary infections. The strains of *Lactobacilli* are one of the best-known probiotics and are found in fermented milk products, mainly curd and yogurt (Reid and Bruce, 2006).

Bacteriophages therapy: This therapy mainly involves the application of bacteriophages that on encountering with specific pathogen can infect and kill the pathogen. Bacteriophages specifically dock on bacteria(host species), introduce their DNA, multiply by using host cell machinery and subsequently lyse the bacteria with the release of virion progeny that can re-initiate the cycle. In this way, bacteriophages are unique among antibacterial agents in their ability to increase their counts in the presence of specific bacterial targets (Brock Biology of Microorganisms).

Natural products: Plant produce a vast variety of chemical compounds which are used either directly as precursors or as steer compounds in the pharmaceutical industry and it is expected that plant extracts showing target sites other than those used by antimicrobial agents will be active against drug resistant microbial pathogens (Shokeen *et al.*, 2009).

Acknowledgement

I express my heartfully thanks to my family and friends for their constant support and encouragement.

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Received	: March, 2017
Revised	: May, 2017
Published	: June, 2017