

Urinary Tract Infections & Treatment

Chapter 1

Urinary tract infections & treatment

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Abstract

This chapter focuses on the urinary tract infections (UTI) which is caused due to the invasion of microorganisms into the urinary tract, mostly by bacterial species. It is one of the most commonly occurring disease in human worldwide, next to the common cold and flu and it predominantly affects women as compared to men. In this chapter, we discussed about the UTI pathogenesis, various natural compounds and antibiotics used for treating this infection. UTI starts with the invasion of uropathogens into the urinary tract; followed by the evasion from the immune system, thereby it colonizes and gets multiplied. The bacterial toxins produced by uropathogens mediate the lysis of host epithelial cells and favors the bacteraemia. It can transfer from one individual to other via direct contact. In UTI, the host factors such as menopause, plays a major role where in post-menopausal women, the decolonization of lactobacillus species facilitates the colonization of *E.coli*. The diagnostic method for UTI varies from conventional method to advanced diagnostic tools such as from urine culture (microbiological plate culture) to MRI and Pyelogram. Certain phytochemicals from plants have some bactericidal properties and they are

used for the treatment of UTI. This overview of UTI gives us a better knowledge to focus and therapeutic aspects towards the remedial measures.

Keywords: urinary tract; pathogenesis; uropathogens; phytochemicals

1. Introduction

Urinary tract infections (UTI) predominantly occurs in the urinary tract and it is caused by the microorganisms, most often by the bacterial species. The urinary tract comprises of kidney, ureter, bladder and urethra. Based on their infection site, the urinary tract infections involve cystitis (bladder), pyelonephritis (kidney) and prostatitis (prostate) whereas bacteriuria is one of the symptoms that could be observed in all UTI's. Sometimes, immunosuppressive conditions and microbiota modulation can also facilitate the opportunistic pathogens to cause UTI. These infections are more prevalent among women when compared to men. This infection increases the risk of pyelonephritis, premature delivery and fetal mortality in pregnant women. In the United States, about 1.6 billion dollars has been spent for UTI every year [1]. Next to the common flu and cold, UTI accounts the second common infection that occurs mostly in women. Approximately 20% of women develop one UTI in their lifetime and they also have the chances of recurrent infection [2]. UTI are classified into complicated and uncomplicated UTI. The structural and functional abnormalities such as prostate enlargement, renal calculi, septic shock, epididymitis, seminal vesiculitis and diverticula increases the probability of acquiring the bacteria in the urinary tract and is known to be a complicated infection. Uncomplicated UTIs does not involve any structural and functional abnormalities [3]. The urinary tract infections are more common in under developed countries than in the US [4].

2. Epidemiology

UTI generally occurs in around 1-3% among school girls and the incidence increases in adolescence with sexual activity [5]. The incidence of UTI ranges from 25-30% among adult women (age group between 20-40 years) and 4-43% among older women (above 60 years of age) [6]. In women, the bacterium reaches the bladder easier because of the short urethra and the length is about 1.5 inches and 8 inches in women and men respectively which is considered to be the most common characteristic to increase the chances of acquiring UTI in women. It is reported to be rarely occurring among men but the anatomical and functional abnormality of the urinary tract increases the probability in elderly men. In men, the prevalence of bacteriuria increases as age increases and shows 1 in 4 men over 70 years of age and also higher in elder patients [7].

3. Etiology

UTI is most commonly caused by the microbes, these microbes invades into the urinary tract and thus forms the colonies [8]. Emerging evidences describes that the lower urinary

tract can have the urinary microbiota [9]. Among all other pathogens, the most common microorganism that causes UTI is *Escherichia coli*. The bacterial species that causes UTI includes both gram negative bacteria and as well as gram positive bacteria – *Escherichia coli*, *Proteus mirabilis*, *Klebsiella species*, *Enterobacter species*, *Serratia marseciens*, *Citrobacter species*, *Staphylococcus species*, *Gardnerella vaginalis*, *Pseudomonas aeruginosa*, *Mycoplasma species* and *Urea plasma species* [9,10]. Some of the opportunistic pathogens that are present in the vaginal mucosa such as *Candida* species also cause UTI. During the immunosuppressive conditions or when the normal microbial flora gets modulated, these opportunistic pathogens will invade and cause the infection by inhibiting the growth of normal microbiota in the mucosal membrane. The most commonly known *candida* species is the *Candida albicans* [11].

4. Pathogenesis

The pathogenesis of UTI refers to the interaction and the biological mechanism between the host and microorganism that develops the infection in the urinary tract. Pathogenesis generally proceeds with the mode of pathogen entry, evasion from the immune system, multiplication and invasion to other tissues or organs of the host [13].

4.1 Mode of entry

Microorganisms enter the urinary tract from the external environment and cause the infection [12]. Due to the less distance of the urinary tract, this mode of infection is more common in women. The microorganisms navigate in the circulatory blood stream and it colonizes in the kidney and then causes the infection. From kidney, it spreads to other organs of the urinary tract via urine and leads to more chronic infection.

4.2 Adherence and colony formation

The initial step that takes place during the pathogenesis of UTI is the adherence. The pathogen present in the gut starts to colonize the urethra and moves into the bladder by the action of flagella and pili. In the bladder, epithelium receptors are recognized by the bacterial adhesion proteins and thus it initiates the colonization. The colonized pathogens produce toxins and proteases that lyse the host cell and provide the nutrients to the pathogen for its survival. The pathogen is then resistant towards the host immune system and migrates into the kidney. With the help of adhesion and pili, the bacteria colonizes in kidney and later it over comes the epithelial barrier and spreads into the blood stream, thereby it leads to bacteremia condition [14].

The pathogenic bacteria adhere to the urinary tract, produce colonies and cause UTI against the host defense mechanism - pH, urea concentration, various organic acids, urinary salt content, urinary inhibitors to bacterial adherence e.g. Tamm-Horsfall protein (THP),

bladder mucopolysaccharide, low-molecular-weight oligosaccharides, secretory IgA and also lactoferrin [15-18].

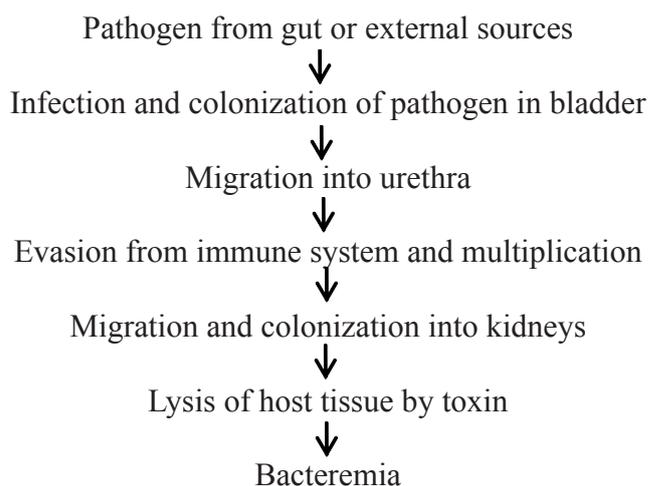


Figure 1: Urinary Tract Infection Pathogenesis

4.3 Host factors for susceptibility of UTI

Menopause and age plays the major role in UTI pathogenesis. Generally, 10-15% of 60 year and above aged women has higher chances or is more susceptible of getting UTI [19]. In woman during premenopausal stage, the formation of lactobacilli colony is due to the increasing level of circulating estrogen in the blood. *Lactobacillus* will produce lactic acid and thereby it maintains the low vaginal pH which inhibits the growth of other pathogens [20]. In post-menopause women, the vaginal pH starts to increase and thus it reduces the lactobacilli colonies. So, in the absence of lactic acid, *Escherichia coli* form the colony and causes UTI [21]. There are other different intrinsic and acquired factors that impact the risk of UTI which includes genetic background of women, exposures to spermicides, antibiotics, etc [22].

5. Clinical syndromes of UTI

Table1: List of uncomplicated and complicated UTI [23]

Uncomplicated UTI	Complicated UTI
Acute cystitis in women	Acute cystitis in men
Acute pyelonephritis in young healthy women	Acute prostatitis
	Chronic prostatitis
	Acute pyelonephritis in men
	UTI along with pregnancy
	UTI along with gross hematuria
	UTI associated with nephrolithiasis
	UTI associated with neurogenic bladder
	UTI in diabetic or immunocompromised patients
	Recurrent Urinary tract infections

5.1 Uncomplicated UTI

Some of the uncomplicated urinary tract infections are described below:

5.1.1 Cystitis

The symptoms of cystitis include dysuria, urinary frequency, nocturia, hesitancy, suprapubic discomfort and gross hematuria. Fever is a more common symptom in case of any invasive infection in the kidney. The C-reactive protein (CRP) level will not increase since it is not a systemic infection.

5.1.2 Pyelonephritis

Pyelonephritis is a disease that is normally associated with the renal parenchyma. In acute pyelonephritis, the CRP level is highly increased. Frequency, urgency, dysuria, fever, chills, back pain, flank pain, vomiting, malaise, nausea, anorexia and abdominal pain are the clinical symptoms of pyelonephritis [24].

5.2 Complicated UTI

5.2.1 Prostatitis

Prostatitis refers to the infection in the prostate gland. It is caused often by the bacterial species. The clinical symptoms of prostatitis include fever, malaise, perineal pain, urgency, frequency and dysuria [25].

5.3 Catheter associated UTI

Among the patients undergoing short term catheterization, 10% of them develop c-UTI. Fever, chills, altered mental state, malaise, acute hematuria, pelvic discomfort, flank pain and costovertebral-angle tenderness is some of the clinical symptoms of c-UTI [26].

5.4 Urosepsis

Urosepsis implicit serious infection of urinary tract and male genital tract with the characteristics stable with systemic inflammatory response syndrome. It is generally linked with hypo-perfusion, hypo-tension and multiorgan dysfunction. Eventhough sepsis is more common in men than the women, but urosepsis seems to be more common in women. Complicated UTI founds to be the commonest precursor of urosepsis [27,28].

6. Diagnosis

UTI diagnosis can be performed on the basis of history and clinical examinations. But more than 60% women who showed symptoms of cystitis did not develop UTI [29].

6.1. Urinalysis

Usually, microscopy is used as a diagnostic tool to detect UTI in patients with UTI symptoms but it has its own set of limitations. So, a dipstick test of leucocyte esterase and nitrite can be used to detect pyuria and bacteriuria (detects nitrite produced by the bacterial metabolism of the urinary tract) [30].

6.2. Urine culture

The standard and conventional diagnosis of UTI is the urine culture and sensitivity assay. This diagnosis method is used to detect the causative agents and also to determine the antimicrobial treatment for UTI. The crystal clear urine sample is collected and cultured to diagnose and also to identify the sensitivity. The midstream urine is generally preferred to prevent approximately 30% of risk of vaginal and skin contamination. The non-invasive techniques like renal ultra sonography and MRI can be used to obtain urinary tract images and thus the UTI can be diagnosed with more consistently. The congenital, structural and urogenital anomalies can be detected using Intravenous Pyelogram (IVP) and a CT scan [31,32].

6.3. Rapid UTI identification by real time PCR

Real Time PCR technique increases the probability to detect DNA in the urine of patients. The usage of microbiological culture method is the well-established one in diagnosing UTI. But the main disadvantage is time consumption of that method. Recently, real time PCR based methods such as SeptiFast was created to augment the culture methods for pathogen identification [33].

7. Treatment

7.1. Oestrogen

The post-menopausal patient lacks the secretion of oestrogen, thus it leads to the elimination of lactobacillus colonies. The proliferation of lactobacillus is stimulated by the oestrogen in the vaginal epithelial layer and it reduces pH. This reduced pH prevents the colonization and multiplication of other pathogens [33,34].

7.2. Cranberry juice/extract

The natural compounds like tannin and proanthocyanidin from cranberry juice or extract reduces the E.coli colonization in vagina. These two compounds normally prevent the adherence of E.coli to the urinary tract epithelial cells [35-37].

7.3. Solidago gigantea (golden rod)

The ethanol extract of *S.gigantia* leaf and flower can be administered as a treatment for UTI patients. It has been reported to minimize the effect of electrolyte excretion in the urine and it also has the anti-inflammatory properties [38].

7.4. Probiotics

Experimental and clinical evidences have suggested that normal indigenous vaginal microbiota plays an important protective role against colonization by pathogenic micro-organisms. The numerically dominant and most prevalent of these are lactobacilli [39], which appear to act by competing for adhesion receptors and nutrients as well as by producing specific antimicrobial substances such as lactic acid, H₂O₂, and bacteriocidins [40].

Probiotics are defined as ‘live micro-organisms, which, when administered in an adequate amount, confer a beneficial effect on the host’ (“Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria,” 2001). Oral supplementation of probiotic may represent an effective option to treat bacterial vaginosis. The close proximity of the vagina and bladder to the rectum may trigger and maintain a microbial colonisation of the region. Administration of such non-harmful microorganisms such as probiotics prevents the UTI. This lactobacillus maintains the pH and avoids the multiplication of uropathogens [41,42].

7.5. *Arcostaphylos uv-ursi*

The leaf of *Arcostaphylos uv-ursi* constitutes the glycoside arbutoside. In the gut, the arbutoside is hydrolyzed into glucose and aglycone hydroquinone. The liver absorbs aglycone hydroquinone and converts it into hydroquinone glucuronide. It gets transported to the kidney and later it is excreted along with the urine. If pH reaches alkaline by invasion of pathogens in the urinary tract, the hydroquinone glucuronide breakdown into hydroquinone and it acts as an antimicrobial agent [43,44].

7.6. Antibiotics

7.6.1. Acute cystitis

Nitrofurantoin, Trimethoprim-sulfamethoxazole, Fosfomycin trometamol, Pivmecillinam are found to be effective and safe drugs against the acute cystitis. Ceftolozane-tazobactam is a cephalosporin combined with β-lactamase inhibitor developed against the antimicrobial resistance in gram-negative pathogens. In certain studies, the treatment with ceftazobactam is more effective than the high dose levofloxacin in patients with complicated lower urinary tract infection [45,46].

7.6.2. Acute pyelonephritis

Oral ciprofloxacin, Ceftriaxone I/V, Oral trimethoprim-sulfamethoxazole, Oral beta-lactam agents, Intravenous Fluoroquinolones, an aminoglycoside, an extended-spectrum cephalosporin or extended-spectrum penicillin or a carbapenem are used for patients diagnosed with the acute pyelonephritis [47].

7.6.3. San Babila clinic female health protocol (ReGenera Res Group-validated)

The current approach for urogenital infections, namely bacterial vaginosis and UTI associated condition includes oral and topical administration of antibiotics and antimycotics. However, although these often prove to be effective, relapses and antibiotic resistances may intervene thus requiring a multimodal approach. To further complicate the matter, it has also to be considered that the reported involuntary leakage of urine, termed as, stress urinary incontinence (SUI), seems to affect up to 50% of women aged between 20 to 80 years. Moreover, even an analysis clustering a younger group (20-49 years) may still suffer of SUI up to 47% [48]. This condition may also trigger further detrimental factors affecting quality of life, low libido included, and yet only about 20% of symptomatic women having vaginal atrophy and UTI seek specialized medical help (Fernand Labrie). At San Babila Clinic (Milano), the clinical hub of ReGenera Research Group for Aging Intervention, it has been devised a multimodal diagnostic and therapeutic protocol which has been proven to yield a statistically significant benefit in UTI in menopause and pre-menopause female population. This protocol implies at first a thorough gynecological clinical assessment together with a Europe-unique gut microbiota gene test and soon, also a vaginal microbiota gene test. At the same time, sublingual (if no contraindication) and topical bio-identical hormones are prescribed (according to hormonal profile), together with oral probiotics (personalized by the gut gene test) and also vaginal probiotics. This is associated to selected phytochemicals, as outlined above in the chapter and, when needed, a short course of antibiotics. A maintenance treatment is then tailored according to each single case. Some cases of SUI may be treated with a further addition of natural compound with adaptogenic properties. Some cases of urinary incontinence still not reaching a full benefit are dealt with by the gynecologist with a number of minimally invasive day-surgery options of long-lasting structural success although all the other integrated interventions aimed to vaginal epithelial tropism and bacterial flora balance have to be maintained.

7.7. Vaccination

The prevention of UTI by vaccination progress towards a less cost and more effective alternative to the antibiotic treatments. There is a successful uropathogenic *Escherichia coli* (UPEC) vaccine development done by identifying the protective antigens that specifically target UPEC. This developed UPEC vaccine found to be effective to prevent human urinary tract infections [49].

7.8. Prophylaxis

Prophylaxis for preventing recurrent urinary tract infections (UTIs) with antibiotics should only be taken into account in some women and long term antibiotics need to be avoided. The intermittent prophylaxis along with antibiotics generally results in less antibiotic exposure than daily usage and may be preferable in women with UTIs who are temporally related to sexual activity [50].

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