



Urinary Tract Infections: Review

Ananya Dhiman, Saloni Gupta, Smriti Khare, Amit Gupta¹ Dr. Ved Prakash Dubey²

Department of Life Sciences (Microbiology and Biotechnology), Graphic Era Deemed to be University, Dehradun

Associate Professor, Electronics and Communication Engineering, Graphic Era Hill University, Dehradun

*Corresponding author

Dr. Amit Gupta Associate Professor Department of Life Sciences Email address-

dr.amitgupta.bt@geu.ac.in

ABSTRACT

Urinary Tract Infections (UTIs) are one of the usual and conventional diseases originated all around the world. It can be said as one of the challenging topics in Medical Microbiological Laboratories. It has fewer reports of men in comparison to the females who are young, sexually active, pregnant or aged. It occurs in women of all age groups. The symptoms can also be seen in children. It affects the urinary system causing the kidney to be damaged in case of Complicated UTIs. Among all the uropathogens, Escherichia coli is one of the major causes of UTIs estimating 80- 85% of the total population. This review article hereby discusses about UTIs, their diagnosis, pathogenesis, and treatment by mainly natural products.

Keywords: UTIs; microbiology; symptoms; diagnosis; pathogenesis.

INTRODUCTION

UTIs are one of the most familiar and recurrent infections in the community generated by uropathogens [1]. It affects approximately 150 million people annually [2]. The United States alone had official look up for UTI manifestations including 0.9% of all wandering visits and 2-3 million emergency departments come to stay in the year 2007. They cause infections to both genders, but mainly affect females due to their structured reproductive system [3]. UTIs are a noteworthy and consequential cause of diseases in infant boys, aged men and females of all ages [4]. The factor that furthermore affects the increase in infections may be family history, one's history of UTI, age or sexual activities [1].

UTIs can be caused in any part of the urinary system which comprises of kidneys, bladder, ureter and urethra [3, 4]. The UTIs can be divided into cystitis caused in the lower urinary tract which is acute in nature and pyelonephritis in the lower urinary tract [5]. UTIs are also dividing into Uncomplicated UTIs and Complicated UTIs. Uncomplicated UTIs are common in young,

sexually active and in non-pregnant women, elderly people and children by mostly Gram-negative bacteria and less Gram-positive bacteria like *Staphylococcus saprophyticus*, *Enterococcus faecalis*, *Streptococcus agalactiae*. On other hand, complicated UTIs, it is caused due to susceptible functional risk making them very complex to treat [6]. As mentioned above, they can be caused by Gram-positive, Gram-negative bacteria, fungi or viruses [7]. The uropathogenic bacterium *Escherichia coli* cause approximately 80% of UTIs.

SIGN AND SYMPTOMS

Lower UTIs gives symptoms like pain during urination, sudden emergencies, and an increase in urine frequency. These are the most common symptoms. These indicators may differ from lenient to extreme. Moreover, nausea, vomiting, or pus in the urine shows high risk of having UTIs [3-7]. In children, just around 90% of UTIs are provoked by *E. coli*, still there are no symptoms revealed during infancy. The symptoms are later observed as nausea, vomiting, pubic bone pain, cloudy urine, urgency and increased frequency in the urination [8].

PATHOGENESIS

Urethra is the part of the urinary system from where the Urinary Tract Infection causes bacteria enter to reach the bladder. They infect the urethral area first. Other parts like blood or lymph may also be included. Females are at great risk due to their anatomy as the transmission of bacteria occurs from the bowel. The bacteria especially *E. coli* attach to the wall of the bladder and start resisting the immune response. Some resist the immune system through host cell entry or they change their morphology. The bacteria make host cell damage by producing some toxins. This resists the neutrophils and it helps them in multiplying. This results in bacterial invasion in the kidneys resulting in kidney colonization. This damages the host tissues [1, 3].

DIAGNOSIS AND URINALYSIS

A diagnosis is based on urine samples containing bacteria. The performing of urinalysis is based on the age groups. Most important methods or techniques for urine collection i.e.

A) Urinalysis for identification and recognition of UTI [9-12]

Collection of urine samples- In general, urine samples were collected using the clean-catch midstream approach, which is reliable and gives accurate results for routine testing. In addition, suprapubic aspiration along with the straight catheter technique is also used and applied for eliminating the contamination to some extent but this technique is not performed on a routine basis.

Sample processing- After sample collection then we proceed to sample (urine) processing which is mainly influenced based on collection method, handling, and timing. Varieties of urine sample containers were available and it totally depends on the laboratory. As per the guidelines of NCCLS (National Committee for Clinical Laboratory Standards), recommended testing or processing these urine samples to keep away from false-positive outcomes. Otherwise, a diversification of preservatives (especially tartaric/boric acid) is available which may be able to keep the urine at room temperature (24 to 72 h).

Urine microscopy- For analyzing the bacterial content in urine samples using the gram staining method and observed under the microscope. Firstly, centrifuging the urine samples and collecting the pellet (present in a minor concentration) and spread on a slide (microscopic one) and stained using gram staining method. This test is not suitable for those patients where bacterial content is $> 10^5$ CFU/ml and is also unsuitable for UTIs.

Urine nitrite test- The conducive factor for UTIs is Enterobacteriaceae and produce nitrite. In this test, first urine sample was collected in the morning; maximum time (4 h) is indispensable for the bacteria to bring out an appreciable amount of nitrite. Regrettably, other bacteria i.e. Staphylococcus saprophyticus cannot fabricate nitrite, for this test.

Pyuria (pus in urine) - In this test, we estimate the number of pus cells in the urine and should be estimated by various techniques. One of the most reliable and accurate method i.e. microscopy for analyzing the urinary leukocyte excretion rate in urine samples. In addition, other methods i.e. leukocyte esterase tests were applied for detection of pyuria but showed many disadvantages because of the presence of eosinophil in urine.

Urine culture- This is one of the gold standard method for analyzing and diagnosing UTIs. In this test, culture media (blood agar and MacConkey's agar) is used for analyzing the bacterial (aerobic and facultative Gram-negative) content.

B) Urinalysis for identification and recognition of other infectious diseases [13-15]

With the advancement in the medical science field, urine makes use for measuring and diagnosing even a substantial quantity of infectious agents.

Dengue virus- mosquito-borne disease and is detected in urine specimen for the early detection which may be confirmed through RT-PCR and ELISA. In addition, ELISA technique also applied for detecting virus in blood specimen.

Zika virus- mosquito-borne pathogen and is generally detected in serum sample using technique like ELISA and PCR. In some of the studies, virus also detected in mother urine samples are detected through RT-PCR and considered them as one of the most valuable diagnostic tool.

Sexually transmitted disease- Urine specimen is of valuable significance especially for diagnosing sexually transmitted diseases. In addition, Urinalysis may also helpful in determination of Mycoplasma genitalium, Chlamydia, Neisseria gonorrhoeae, Trichomonas vaginalis, and urethritis.

Parasite detection in urine samples- Urine microscopy along with sediment test analysis may helpful for analyzing and identification of urinary parasites (e.g. Schistosoma urinary egg detection).

NEW TECHNOLOGIES AND URINALYSIS

Many novel diagnostic tools and technologies are routinely used and applied in the market sector, and some of them are approved for clinical use. Some of the technologies [16, 17] are applied for urinalysis-

Flow cytometry- One of the most dependable and error-free methods for the bacterial count in urine samples for diagnosis of UTIs. With the improved counting precision over visual counting practices, some highly precise positive outcomes can be procured by this method. Observation and identification of bacteriuria can be attained with clinical standards.

Test strip technology- Major advancement in technology (i.e. test strip) has been made but highly sensitive test strips are being established and provide quantitative results for UTIs. This technology showed favorable and encouraging results in antibiotic susceptibility tests and is also helpful for the diagnosis of diabetes in urine samples.

Automated microscopy- Analysis of urine samples through microscopy is considered one of the reliable methods for UTIs. In contrast, microscopy (manual) is a time-consuming process and takes a lot of time for urine sample analysis. In contrast, digital microscopy requires less time for processing these samples compared to manual microscopy. Recently, automated machines are now accessible in the market with non-identical categories of technologies e.g. laminar flow, digital imaging technology etc.

MALDI-TOF (Matrix-assisted laser desorption ionization–time-of-flight mass spectrometry), proteomics approach and system is entangled for screening, recognition, and segregation of microorganism once from a culture integrated with Gram stain has specified new regulation, saved a substantial amount of time for diagnosing UTI.

Urinalysis and smartphones- Smartphone technologies played a significant and valuable tool in the medical field. This technology is very fast and gets the results within short notice. Several studies were conducted explored the possibilities for diagnosing diseases e.g. Zika, chikungunya, dengue etc.

PREVENTION

The prevention measures of such infections include proper fluid intake and personal hygiene. Some researches show that antibiotics can treat UTIs but it has some risks that may cause recurrent UTIs. The studies describe that there are few non-antibiotic products prevents as well as treat **UTIs [18, 19]**. First is Cranberry Juice which inhibits bacterial entry into epithelial cells. The second is Probiotics that may change the vaginal microbiota and prevent antimicrobial resistance. They can be taken as oral or as intravaginal probiotics. Another one is d-Mannose which is a monosaccharide that is taken and excreted making a resistance for bacteria entering the epithelium cells. Estrogens on the other side stimulate the Lactobacilli, neutralize vaginal pH and increase antimicrobial activity. Vitamins including Vitamin C and D can be counted as the supplements to be given to the Urinary Tract Infected patient. They work by either urine acidification or by the bacteriostatic effect.

In literature, medicinal plant-derived products have medicinal value and also showed therapeutic potential against dreadful pathogens. These plant-derived products are rich in bioactive compounds (primary or secondary metabolites) which may ultimately form the development of new plant-derived molecules. These molecules are screened for various immunobiological activities and analyzed their structure using HPLC, NMR and so on. In this study, we collect the literature and identified the plant which is beneficial for UTI infections. In general, antibiotics were used and applied for UTIs but due to enormous usage showed some imbalance in the gut microbial community which is directly associated with the disease. In contrast, some uropathogens are reported in the bladder during the stressed conditions and showed some structural changes invade uroepithelial cells, and form biofilms to persist and cause recurrent infections. Thus, we need some alternative methods for the treatment of UTIs. Various efforts were taken to reduce the UTI rate using medicinal plants [20-22] as shown in Table 1.

Table 1. Medicinal plants effective against UTIs

S.No	Scientific name	Ayurvedic name	Acts against which bacteria	Improvement area of urinary system
1.	Ocimum sanctum	Tulsi	Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Enterococcus faecalis	Kidneys and bladder
2.	Azadirachta indica	Neem		
3.	Tribulus terrestris	Gokshura		
4.	Punica granatum	Dadima		
5.	Terminalia chebula	Haritaki		
6.	Cinnamomum cassia	Dalchini		
7.	Salvia officinalis	Common sage		
8.	Nelumbo Nucifera	Kamal	Escherichia coli, Enterococcus faecalis	Kidneys
9.	Allium sativum	Lahasun	Escherichia coli, Klebsiella pneumoniae	Kidneys and bladder
10.	Curcuma longa	Turmeric (Haldi)	Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa	

So, further studies are still in progress and understand the mechanism of phytochemicals against different uropathogens. However, scientific validation was required with preclinical and clinical trial reports, which may help us in preventing these UTIs.

CONCLUSION

The UTIs affects the urinary system and is common in women of all ages more than men. UTIs has become the major challenges in the whole world. The antimicrobial drugs today are beneficial for the pregnant women as well as for children. The natural products like cranberry,

ascorbic acid, probiotics are also useful for women and children. The researches going on gives a hopeful discussion on future aspects about the reduction in number of cases of UTIs as well as effective medicines and more natural products without any side effects or increase in the risk of reoccurring of the UTIs. For this, we need to study thoroughly about the challenges and strengths to overcome them in the upcoming time.

REFERENCES

- 1) Head KA. Natural approaches to prevention and treatment of infections of the lower urinary tract. *Altern Med Rev* 2008; 13(3):227–244.
- 2) Cove-Smith A, Almond MK. Management of urinary tract infections in the elderly. *Trends in Urology Gynaecol Sex Health* 2007; 12:31–34.
- 3) Sahib AS, Mohammed IH, Hamdan SJ. Use of aqueous extract of corn silk in the treatment of urinary tract infection. *J Intercult Ethnopharmacol* 2012; 1(2):93–96.
- 4) Pattanayak S, Das DC, Sinha NK, Parida S. Use of medicinal plants for the treatment of urinary tract infections: a study from Paschim Medinipur district, West Bengal, India. *Int J Pharm Bio Sci* 2017; 8(3):250–259.
- 5) Sowmiya S, Soundarapandian P, Rajan S. Bioactive studies of *Mangifera indica* against bacteria isolated from urine samples. *Curr Res J Biol Sci* 2009; 1(3):139–143.
- 6) Dotis J, Stabouli S, Pavlaki A, Papachristou F, Printza N. Cranberry standardized capsules may prevent recurrences of urinary tract infections in children. *Clin Pediatr* 2018; 1:1007.
- 7) Kostakioti M, Hadjifrangiskou M, Hultgren SJ. Bacterial biofilms: development, dispersal, and therapeutic strategies in the dawn of the postantibiotic era. *Cold Spring Harb Perspect Med* 2013; 3: a010306.
- 8) Kosikowska P, Berlicki L. Urease inhibitors as potential drugs for gastric and urinary tract infections: a patent review. *Expert Opin Ther Pat* 2011; 21:945–957.
- 9) Asadi Karam MR, Oloomi M, Mahdavi M, Habibi M, Bouzari S. Vaccination with recombinant FimH fused with flagellin enhances cellular and humoral immunity against urinary tract infection in mice. *Vaccine* 2013; 31:1210–1216.
- 10) Liu YH, Ho CY, Huang CC, Tsai CC. Inhibitory effect of lactic acid bacteria on uropathogenic *Escherichia coli*-induced urinary tract infections. *J Prob Health* 2016;4(2):144–150.
- 11) Schindler G, Patzak U, Brinkhaus B, von Niecieck A, Wittig J, Krahmer N, Glockl I, Veit M. Urinary excretion and metabolism of arbutin after oral administration of *Arctostaphylos uvae ursi* extract as film-coated tablets and aqueous solution in healthy humans. *J Clin Pharmacol* 2002; 42(8):920–927.
- 12) Simerville JA, Maxted WC, Pahira JJ. Urinalysis: a comprehensive review. *Am Fam Physician* 2005; 71: 1153-1162.
- 13) Stone ND, Ashraf MS, Calder J, et al. Surveillance definitions of infections in long-term care facilities: revisiting the McGeer criteria. *Infect Control Hosp Epidemiol* 2012; 33: 965-977.
- 14) Schnarr J, Smaill F. Asymptomatic bacteriuria and symptomatic urinary tract infections in pregnancy. *Eur J Clin Invest* 2008; 38 (suppl 2):50-57.

- 15) Levison ME, Kaye D. Treatment of complicated urinary tract infections with an emphasis on drug-resistant gram-negative uropathogens. *Curr Infect Dis Rep* 2013; 15:109-115.
- 16) Gordon LB, Waxman MJ, Ragsdale L, Mermel LA. Overtreatment of presumed urinary tract infection in older women presenting to the emergency department. *J Am Geriatr Soc.* 2013; 61:788-792.
- 17) Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis.* 2005; 40:643-654.
- 18) Juthani-Mehta M. Asymptomatic bacteriuria and urinary tract infection in older adults. *Clin Geriatr Med* 2007; 23:585-594.
- 19) Wolf JS Jr, Bennett CJ, Dmochowski RR, et al. Best practice policy statement on urologic surgery antimicrobial prophylaxis. *J Urol.* 2008; 179:1379-1390.
- 20) Aquil F, Khan MS, Owais M, Amad I. Effect of certain bioactive plant extracts on clinical isolates of β -lactamase producing methicillin resistant *Staphylococcus aureus*. *J Basic Microbiol.* 2005; 45:106-14.
- 21) Holetz F, Pessini G, Sanches N, Cortez D, Nakamura C, Filho D. Screening of some plants used in the Brazilian folk medicine for the treatment of infectious diseases. *Mem Inst Oswaldo Cruz, Rio de Janeiro* 2002; 97:1027-31.
- 22) Bonjar GHS, Nik AK, Heydari MR, Ghasemzadeh MH, Farrokhi PR, Moein MR, et al. Anti-Pseudomonas and Anti-Bacilli activity of some medicinal plants of Iran. *DARU* 2003; 11:157-63.