Symptoms, risk factors, diagnosis and treatment of urinary tract infections

Rajanbir Kaur, Rajinder Kaur

Department of Botanical and Environmental Sciences, Guru Nanak Dev University, Amritsar, Punjab, India

Correspondence to
Dr Rajinder Kaur, Botanical and Environmental Sciences, Guru Nanak Dev University, Amritsar, India;
rajinder.botenv@gndu.ac.in

Received 23 September 2020
Revised 1 November 2020
Accepted 9 November 2020
Published Online First 24 November 2020

To cite: Kaur R, Kaur R. *Postgrad Med J* 2021;**97**:803–812.

ABSTRACT

Urinary tract infection (UTI) is a common microbial infection found in all ages and sexes which involves inflammation of the urinary tract. These infections can range from simple bladder inflammation, that is, cystitis, to severe cases of uroseptic shock. UTI ranks as the number 1 infection that leads to a prescription of antibiotics after a doctor's visit. These infections are sometimes distressing and even life threatening, and both males (12%) and females (40%) have at least one symptomatic UTI throughout their lives. Diagnostic failures in case of bacterial infections are the main contributing factor in improper use of antibiotics, delay in treatment and low survival rate in septic conditions. So, early diagnosis and appropriate therapy with antibiotics are the most significant requirements for preventing complicated UTI conditions such as urosepsis. This review article summarises the symptoms of the UTIs and the associated risk factors to it. The various conventional and recent diagnostic methods were also discussed in this review, along with treatment therapies with or without antibiotics.

INTRODUCTION: URINARY TRACT INFECTIONS (UTIS)

Infections of the urinary tract are severe public health problems worldwide. The most common reasons of infections are either functional or anatomical abnormalities. These infections are common in all individuals, be it male, female, children or the elderly. This happens because the urethra not only serves as a passage for the outlet of urine but also serves as an entrance for the bacteria into the urinary tract.

The bacteria usually live around the opening of the urinary tract and develop colonies in both men and women. Generally, they get washed out during urination. Infections happen when these colonies are not washed away during urination and reach the bladder before urination. UTIs occur more in women than in men, and about 81% of all UTIs are reported in women.[1] The probability of bacteria reaching the bladder before getting removed by urination are greater in women as the space between the opening of the urethra and the bladder is shorter. The chances of development of bacterial colonies are greater in women because of the presence of vaginal cavity and the close proximity of the rectum to the urethral opening. Another significant fact about these bacterial colonies is that even if they reach the urinary bladder where they get a chance to multiply, the symptoms of UTIs are seldom visible.[2]

UTIs are often classified into lower or upper and complicated and uncomplicated UTIs, depending on the area of infection and the condition of the host's body. Upper UTIs affect the kidneys and the ureters like in case of pyelonephritis, while lower UTIs affect the urethra and the bladder. Further, uncomplicated UTIs are the infections of the urinary tract with no abnormalities, that is, functional or anatomical. Complicated UTIs, on the other hand, are all cases other than uncomplicated UTIs.[3]

SYMPTOMS OF UTIS

Lower UTIs are usually marked by pain during urination with or without frequency, pain in the suprapubic region or visible haematuria. Upper UTIs are generally manifested by fever (>100°F), flank pain, chills, vomiting, costovertebral-angle tenderness, nausea, with or without symptoms of cystitis.[3] Fever is uncommon in lower UTIs and is generally associated with complicated forms of UTIs.[1]

It is significant to note that these symptoms do not confirm that the person is suffering from UTIs. There is only a 50–50 chance that a person showing these symptoms is suffering from UTIs in a primary care setting. This possibility increases to 84%–92% if patients are having a history of a recurring UTI. Further, elderly women suffering from UTIs seldom show the aforementioned symptoms. It is possible that the only symptom they show is urinary incontinence. In women who have already hit their menopause, urine loss increases significantly due to low oestrogen levels in a 3 day period post UTI.[1] The common signs and symptoms of UTI include fever, itching, burning sensation, blister formation in the genital area, suprapubic pain and pyuria. The symptomatic infection shows inflammation and white blood cell (WBC) count of >8 cells/mL in the urine. The urine may be hazy in appearance and the condition is called pyuria or leucocyturia. The terms used to describe conditions in UTIs are discussed in table 1.

SYMPTOMATIC/ASYMPTOMATIC UTIS

Symptomatic and asymptomatic UTIs are caused by growth and proliferation of microbes in the urinary tract. The micro-organisms involved in UTIs may cause symptoms (symptomatic) or may grow without showing any symptoms (asymptomatic).

Symptoms of UTIs include frequent and strong urge to urinate, burning sensation while passing urine, pain in the lower abdomen even when one passes little urine, blood while passing urine and more smell than typical smell of urine. A study

Table 1 Common symptom in UTIs

Symptoms in UTI	Meaning
Urgency	An unstoppable urge to urinate due to sudden involuntary contraction of the bladder muscles
Frequency	Urinating too often and at frequent intervals
Bacteriuria	Presence of bacteria in urine is called bacteriuria, while presence of $>10^5$ bacterial colonies/mL of urine is termed as significant bacteriuria
Pyuria	Presence of pus cells (WBCs) in the urine
Dysuria	Feeling of pain, discomfort or burning sensation while urinating
Nocturia	Frequently waking up at night to urinate because of UTI or bladder infection
Urinary incontinence	Loss of control of the bladder from a slight loss of urine following coughing, sneezing or laughing

UTI, urinary tract infection; WBC, white blood cell.

conducted on both symptomatic and asymptomatic UTIs has suggested that symptomatic UTIs are more frequent than asymptomatic.[4]

Asymptomatic bacteriuria (ABU) is defined as the asymptomatic carriage of $>10^5$ bacteria/mL in urine, with or without pyuria, in two consecutive cultures. Patients with ABU strain may carry bacteria for months or even year or more without showing any symptom. Studies also indicated that ABU is shown to protect the host against symptomatic UTIs.[5]

RISK FACTORS OF UTIS IN WOMEN

Anatomically, men are more resistant to UTIs. The pathogens that are responsible for the infection can effectively use the shorter urethra in women as a bridge between the urinary opening and the bladder. On the contrary, the longer urethra in men facilitates washing out of these pathogens through urine before they reach the bladder. The inevitable colonisation of periurethral mucosa with bacterial species from the bowel flora also facilitates the infection.[6] There is no direct link between recurrent UTIs and frequency of urination, douching, patterns of wiping, delayed voiding habits or use of tight undergarments. However, incontinence, cystocele or postvoidal residual urine is associated with recurrent UTIs.[7]

However, it is not only the physical factors that make females more vulnerable for UTIs than males. There are several other risk factors that contribute to recurring UTIs in women. These are behavioural factors, susceptibility factors, genetic factors, age-specific factors, pregnancy-related factors and urinary catheterisation.

Behavioural factors

In an already anatomically vulnerable female body, microbes capitalise on behavioural factors.[6] Behavioural factors are the strongest risk factors contributing to recurring UTIs in women. The frequency of sexual intercourse is one such behaviour that drives the recurrence of UTIs in young women.[7] Several studies have proven the fact that there exists a relationship between sexual intercourse and recurring UTIs. First infections in young women are found to be at the time of first sexual activity. There is a proportionate relationship between numbers of times in the last 7 days a woman had intercourse to the relative risk index of getting UTIs. The risk of getting UTIs was greater after 2 days of sexual intercourse when compared with days when there is no intercourse involved. Postintercourse behaviours like use of contraceptive measures like spermicides also play a significant role in UTIs. Using spermicides alone or using them with a combination of other contraceptives like a male condom or a diaphragm also enhances the risks of getting UTIs. Vaginal flora is altered by certain spermicides, especially those containing nonoxonol-9.[7 8] This phenomenon facilitates colonisation by periurethral pathogens. Antimicrobial consumption is also linked to increased risks of getting UTIs.

It is interesting to note that Kodner and Gupton published a study in which they mentioned that there is no benefit of changing hygiene behaviours like front to back wiping, postcoital voiding, increase in fluid intakes, proper sanitary napkin use or menstrual hygiene.[7] However, Vyas *et al* in a study published that there is a significant relation between infections of the urinary tract and perineal hygiene. The study mentioned that incorrect techniques of perineal washing, material of the underwear, menstrual hygiene and the use of improper tampons increase the risks of getting UTIs.[9]

Genetic factors

Genetic effect on the tendency to get UTIs is a well-supported fact. Several studies have verified genetic link to infections of the urinary tract. Women who suffer from recurrent UTIs have often history of UTIs in their family. It is observed that women with recurrent UTIs show enhanced *Escherichia coli* binding receptivity. This includes not only urethral and vaginal mucosa but also buccal mucosa, which may be due to genetic differences in mucosal properties rather than differences in local environment.[10] Non-secretor and recessive phenotypes are associated with enhancement in density of uroepithelial receptors available to bind with bacterial adhesions.[6]

In a study on community-dwelling women, a history of UTI in female relatives was strongly and consistently linked with the recurrence of UTI and pyelonephritis. The risk of infection increased with stronger family history indices indicating a genetic factor responsible for increased susceptibility to these infections.[11] In another study, it was found that 6 (HSPA1B, CXCR1 and 2, TLR2, TLR4 and TGF-β1) out of 14 genes investigated in humans can be associated with susceptibility to recurrent UTIs.[12]

Age-specific factors

The most significant age-specific risk factor for UTIs in women is oestrogen. *Lactobacillus* proliferation and acidic vaginal pH act as the strongest host defences against colonisation of pathogens. However, at the time of menopause, oestrogen levels decrease, which facilitates conversion of vaginal flora from *Lactobacillus* to *E. coli* or other members of Enterobacteriaceae, which in turn increases the chances of getting infections. This fact is supported by a study which found that treatment with intravaginal estriol helps in restoration of lactobacilli colonisation. Out of a significant sample of women, 61% experienced restoration of lactobacilli colonisation on treatment with intravaginal estriol compared with no change in the group treated with placebo. However, this change was significant in case of intravaginal oestrogen replacement only as compared with oral replacement therapy.[6]

Another independent study conducted on premenstrual and postmenstrual women found that clinical presentation in postmenstrual women was more severe than in premenstrual women. Also, most of the symptoms in premenstrual women were local, while in postmenstrual women, the symptoms are storage related and generally unspecified. It is also possible that due to decreased lubrication in the vaginal region, there is increased risk of local trauma during sexual intercourse and, in turn, an increased risk of UTIs.[13]

Pregnancy-related factors

Pregnancy is an independent risk factor for infections of the urinary tract. It is interesting to note that the chances of occurrence of ABU are similar in both pregnant and non-pregnant women of childbearing age, but it is the psychological changes induced by pregnancy that enhance the risks of upper UTIs.[6] The maternal Group B *Streptococcus* bacteriuria in pregnant women is an indication for genital tract colonisation. It poses significant risk for UTIs. It is also suggested that risk factors for these infections during pregnancy are older age, lower socioeconomic status of the woman, anatomical abnormalities of the urinary tract, diabetes and sickle cell diseases.[14]

In case of untreated bacteriuria, 25%–40% of pregnant women suffer from pyelonephritis. ABU is observed to be the most common problem that pregnant women face; if not treated in early stage, infected women may develop pyelonephritis. Pyelonephritis is considered to be one of the vital causes of neonatal deaths worldwide. UTIs are common in women during pregnancy and out of those, the primary concern is of asymptomatic UTI. This is the most common infection that requires medical intervention during pregnancy period. Globally 2%–10% of asymptomatic UTIs are reported among pregnant women.[15] There is significant morbidity linked to upper UTIs in pregnancy, and it includes low birth weights, prematurity, caesarean delivery and pre-eclampsia.[6]

Urinary catheterisation

Clean intermittent catherterisation (CIC) and indwelling urinary catheters are categorised with high rates of bacteriuria. It is observed that incidence of bacteriuria, with respect to indwelling catheters, is 3%–6% per day and 1%–3% per catheterisation with CIC.[6] Nicolle's study stated that urinary catheters are the most common indwelling devices, with 23.6% of the patients reported in the USA in 143 hospitals and 17.5% of the patients in Europe in 66 hospitals.[16]

Hospitals now have become common place for acquiring UTIs, with 1%–10% estimated prevalence, representing 30%–40% of nosocomial infections. Presence of urinary catheters is the most prevailing risk factor for the development of nosocomial UTIs, especially when long-term intensive care is provided.[17 18] It is observed that UTIs are the most common morbidity factors in case of surgery for stress urinary incontinence or pelvic organ prolapse. In an analysis conducted in patients undergoing such surgery, it is observed that the risk of UTI was significantly increased by previous history of multiple UTIs, increased distance between the urethra and the anus, and prolonged duration of catheterisation.[19]

BACTERIA INVOLVED IN UTIS

Bacterial ascent from vaginal mucosa or bowel is the reason for most of the upper and lower UTIs in women. Gram-negative bacteria and resident facultative anaerobes are most common pathogens from bowel and vaginal flora. In nearly 85% of UTIs, *E. coli* is the causative pathogen; in 10% of cases, *Staphylococcus saphrophyticus* is the causative pathogen; and rest of the causative minority comprises Enterobacteriaceae species, *Proteus* and *Klebsiella*.[6]

In community-acquired UTIs, *E. coli* is the most frequent uropathogen involved due to the fact of belonging to the normal flora of human intestine that enables it to colonise the urinary tract easily. Few studies on community cases showed that uropathogens involved in most of the cases are *E. coli* (46.4%–74.2%) followed by *Klebsiella* spp (6.0%–13.45%), *Enterococcus* spp (5.3%–9.54%) and *Proteus* spp (4.7%–11.9%). UTIs are generally uncomplicated and bacteria prefer the bladder for colonisation, but there are chances that *E. coli* may ascend to kidneys and cause severe infection. The bacterium *Pseudomonas aeruginosa* is one of the emerging pathogens that can cause UTI in the community and is reported to be associated with10%–15% of the cases.[20] *S. saphrophyticus* is reported to be the most common cause of UTI, among Gram-positive bacteria. *Klebsiella* spp is the third most common cause of UTIs.[21]

The study conducted by Mirsoleymani *et al* suggested that *E. coli* remains the predominant cause of UTIs in both sexes. Its frequency is more in females as compared with males. On the other hand, UTIs due to *Klebsiella* spp is more predominant in males as compared with females. The UTIs due to the bacterium *P. aeruginosa* is reported to be higher in males.[22]

UTIs are categorised under hospital-acquired and community-acquired infections. Numerous surveys have suggested that it can happen at any stage of life and affects both men and women. *E. coli* is the most common cause of UTIs, but some bacteria like *S. saphrophyticus* also account for 5%–15% of UTIs in younger females, while bacteria like *Klebsiella* spp, *Proteus* spp and enterococci are considered to be more frequent cause in older females.[4] Uropathogenic *E. coli* can cause both asymptomatic and symptomatic UTIs. In a study to identify the *E. coli* strains involved in symptomatic and asymptomatic UTIs, it was found that ST95 strains were more significantly associated with symptomatic UTIs (27%) as compared with strains causing ABU (8%) and catheter-associated ABU (10%).[23]

Many researchers reported *E. coli* as the main cause of UTI, although there is some evidence that the incidence of UTIs caused by *E. coli* is declining. In a report by Bronsema *et al* from 1980 to 1991, the incidence of UTIs caused by *E. coli*, *Pseudomonas* sp and *Proteus* sp decreased, whereas the frequency of UTIs caused by yeasts, group B Streptococci and *Klebsiella pneumoniae* increased.[24] Weber *et al* also observed different changes in the causal micro-organisms of UTI, with a decrease in the prevalence of UTI caused by *Enterobacter* species but an increase in the frequency of UTIs caused by *Acinetobacter* sp and *P. aeruginosa*.[25]

DIAGNOSTIC METHODS

In global health issues, uropathogen detection is considered to be the most concerning and of major interest worldwide. Major efforts are being taken for rapid detection, monitoring and quantification of uropathogens. When left undetected in early stages, UTIs can cause serious health implications. UTIs are detected by analysis of bacteria culture in the urine of the patient. Positive sign of symptomatic UTI is generally defined when bacteria count is $>10^5$ cfu/mL in free collection of urine.

There are many techniques used to detect UTIs, such as phenotypical biochemistry or culture identification strategy, which is considered to be slow due to time taken by bacteria to grow (figure 1). Another technique is PCR or immunoassay technique, which is rapid, but former has the limitation of background contamination by exogenous sources of DNA, and the latter one require sensitivity, antigen amounts and time for seroconversion (figure 1). A gold standard technique is quantitative urine culture, but it gives results in approximately 24 hours, and antibiotic susceptibility testing requires another 24 hours. As a result, broad spectrum antibiotics are often prescribed in this case. Surface-enhanced Raman spectroscopy, a rapid diagnostic method based on spectra of bacterial strains grown in urine sample, is the latest technique which is being used to detect UTI.[26]

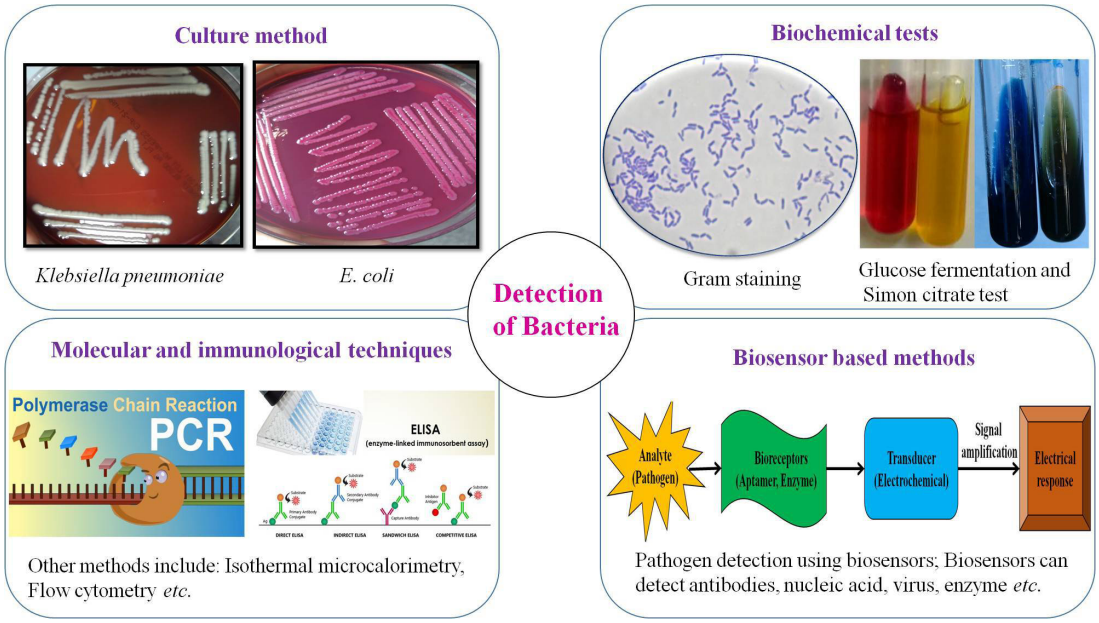

Figure 1 Different methods for the detection of bacteria in the samples.

Conventional methods

These are the techniques which are in use for several years and include culturing and non-culturing methods, ELISA, isothermal microcalorimetry and PCR.

Non-culture method

Urine dipstick method is the most frequently used method for the diagnosis of UTI. In this method, multistix is used, which may be able to detect nitrite, a metabolic product of particular pathogens of the urinary tract, leucocyte esterase, protein and blood (as a sign of inflammation). If nitrite or leucocyte esterase is detected in the sample, it increases the possibility of having a UTI. However, dipstick method for blood and protein has poor sensitivity and specificity in the detection of UTI and may be misleading.[27]

Bacterial growth by Gram staining of uncentrifuged urine specimens is detected microscopically in this method. Gram staining method provides rapid information about bacterial growth and nature. Its drawback is that bacterial growth of $<10^5$ cfu/mL in urine sample cannot be detected through this method.[28]

Culture method

It is one of the oldest methods used for detection of micro-organisms. In this separate culture media and supplement is required for each kind of micro-organism. Routine urine cultures are performed by plating using calibrated loops for the semiquantitative method. This method provides information regarding the number of colony-forming units per millilitre as well as the isolated colonies for identification and antibiotic susceptibility testing. MacConkey agar and blood agar are generally used as culture media.[28]

PCR

It is a molecular method developed to detect bacteriuria from urine, blood and other clinical samples. In this technique, amplification of DNA is done using universal primers or selective primers. n the study by van Der Zee *et al* they developed and evaluated two semiquantitative real-time PCRs for the detection of uropathogens. In this they select single gene targets for bacterial quantification and identification in urine samples using both PCRs.[29] In a recent study, Wojno *et al* reported the use of multiplex PCR for the detection of bacterial UTIs in symptomatic patients. They further revealed that multiplex PCR is a better technique as compared with conventional urine culture method.[30]

Isothermal microcalorimetry

This technique is based on the principle that heat produced during growth of micro-organisms corresponds to their replication rate and metabolism. Heat produced is thus recorded in isothermal microcalorimetry, and graphs are plotted to detect the growing micro-organisms. In a study, Braissant *et al* used isothermal microcalorimetry for the rapid antimicrobial susceptibility testing in case of UTIs and found that it can provide an antibiogram within 7 hours with high sensitivity (95%) and specificity (91%).[31]

ELISA

To detect uropathogens and their growth pattern, ELISA technique is used. It is one of the best techniques to determine the components of bacteria present in clinical samples. All microbial species possess unique antigens, and such type of antigens can be used as specific molecules of detection by ELISA. The variations in ELISA can detect either antigen or antibody, different strains of microbes and also can characterise the epitope distribution on the microbial surface. In a study, Shih *et al* developed a simple and cost-effective paper-based ELISA to detect UTI or ABU caused by *E. coli* in 5 hours.[32]

Biosensor-based detection methods

Conventional methods used to detect components of bacteria in sample are time-consuming and require trained staff to perform the detection tests. Biosensor-based methods are developed to detect micro-organism growth in accurate and lesser duration. Some of the methods based on molecular approach are as follows.

Magnetoelastic sensors

To overcome the limitations of using electrochemical aptamers, researchers developed aptasensors that use magnetic beads to detect the targets. These magnetoelastic sensors have been used to measure different chemical–biological agents (such as glucose, ricin, avidin and endotoxin B), detection of *E. coli* 0157:H7 and measurement of bacterial growth and susceptibility.[28 33] In a study, Lin *et al*[34] reported the use of a wireless magnetoelastic-sensing device for detecting the *E. coli* O157:H7 using chitosan-modified magnetic Fe_3O_4 nanoparticles as signal-amplifying markers. Wikle *et al*'s[35] study demonstrated the role of magnetoelastic biosentinel for the detection of pathogenic bacteria. The biosentinels imitate the role of naturally occurring biological defensive agents (such as WBCs), thus finding and capturing the pathogenic bacteria.[35]

Microcantilever array biosensors

A microcantilever is a device employed for sensing physical, chemical or biological reactions by detecting any changes in the bending or vibrational resonance frequency of a cantilever on molecular adsorption. These sensors have many advantages, such as low cost, high sensitivity, simple procedure, little amount of analyte required and quick response. They are widely used in the field of medicine for the screening of pathogens, diseases and any point mutations.[36] In a study, Nieradka *et al*[37] demonstrated the preparation and use of a microcantilever array for the detection of endotoxins produced by Gram-negative bacteria. In a recent study, Zheng *et al*[38] reported the detection of food-borne bacteria, including *Salmonella*, *E. coli* O157:H7, *Staphylococcus aureus*, *Shigella* and *Listeria monocytogenes* using a gold nanoparticle amplified microcantilever array biosensor. It rapidly and accurately detects low concentrations of pathogenic bacteria present in food, environment and clinical samples.[38]

Electrochemical endotoxin sensors

Limulus amebocyte lysate assay is commonly used to detect the endotoxin that includes turbidimetric, gel clot and chromogenic techniques. In this assay, haemolymph coagulation of the horseshoe crab (*Limulus polyphemus*) was observed. However, this method has some limitations, such as intervention by the sample colour, inherent turbidity, low sensitivity and peptidoglycan, and β-glucan (microbial products) also reacts positively in this assay.[39 40] Yeo *et al*[41] invented an advanced electrochemical endotoxin sensor in which they used a recombinant human toll-like receptor 4 (rhTLR4) and myeloid differentiation-2 (MD-2) complex. The complex of rhTLR4/MD-2 binds specifically to endotoxin, which was immobilised on gold electrodes. The electrochemical signals produced from interactions between the endotoxin and the rhTLR4/MD-2 complex were identified by cyclic voltammetry and differential pulse voltammetry.[41] In a similar study, She *et al*[42] investigated the efficacy of toll-like receptor 5 (TLR5), which selectively binds to flagellins of Gram-negative and Gram-positive bacteria. They revealed that TLR5 biosensors possess the broad-spectrum detection ability to detect the flagellated bacterial pathogens.[42]

Dual signal amplification by enzyme-based target recycling

It is an ultrasensitive electrochemical technique to detect the specific sequence of the target DNA of uropathogens. The sensing programme is based on a dual signal amplification process, which links the signal amplification by the target DNA recycling through catalytic enzyme reaction with the sensitivity improvement by the quantum dot layer-by-layer assembled labels. By combining these two effective signal amplification techniques, the target DNA sequences as low as femtomolar (5 fM) can be detected.[43] In a similar study, Zhou and Li investigated the dual-amplification approach for highly sensitive fluorescence detection of DNA. This strategy involves dual amplification by exonuclease III-mediated target recycling combined with liposome-assisted amplification.[44] Similarly, Zhang *et al* investigated the practicability of AuNP-H1 probes and the dual signal amplification strategy by a fluorescence assay of target DNA in human serum and found that this strategy has good detection limit as low as 47.68 fM.[45]

Aptamer-based biosensors

The synthetic single-stranded oligonucleotides which binds to the target molecules (peptides, proteins, viruses, pathogens and even entire cells) with high affinity are called aptamers. They are easily synthesised, modified and screened through systematic evolution of ligands by exponential enrichment (SELEX) technique. Because of their high affinity, stability and specificity, they have been used in the detection of bacterial pathogens, especially *E. coli*. In a study, Savory *et al*[46] revealed the use of DNA aptamers for the rapid detection of uropathogenic *E. coli*. In this approach, they demonstrate the use of quantitative PCR controlled Cell-SELEX process for identification and selection of DNA aptamers. They also revealed that an aptamer (EcA5-27), selected through this process, displays the ability to differentiate between different *E. coli* strains.[46] Kaur *et al*[47] reported an innovative fabrication method of functionalised three-dimensional bridged rebar graphene over a newly devised nanostructured aptasensor for the detection of pathogenic *E. coli* O78:K80:H11 strain. In a similar study, Hao *et al*[48] proposed an aptasensor based on highly intensified electrochemiluminescence of luminol/AgBr/3D nitrogen doped graphene hydrogel and the aptamer having high selectivity. This new aptamer-based biosensor gives a good performance with a very low detection limit of 0.17 cfu/mL for *E. coli* cells.[48]

TREATMENT OF UTIS

Antibiotics used to treat UTIs and their mode of action

Amoxicillin has been traditionally a first-line antibiotic for UTIs, but with the increased rate of *E. coli* resistance, it has become a less acceptable choice, and studies have found another antibiotic with higher cure rates, that is, trimethoprim/sulfamethoxazole. Other commonly used antibiotics to treat bacterial UTIs include amoxicillin/clavulanate, cefixime, cefprozil, levofloxacin, nitrofurantoin, fosfomycin and nalidixic acid. Introduction of antibiotics has decreased the morbidity and mortality rate due to bacterial infections. But in recent years, we have witnessed an increase in resistance to antibiotics among these uropathogens. For making effective antibiotics, there is a need to understand the mechanism of mode of action of antibiotics (table 2). There are five main mechanisms on which antimicrobial drugs works[49] These are

1. Inhibition of bacterial cell wall synthesis.
2. Inhibition of bacterial nucleic acid synthesis.
3. Inhibition of bacterial protein synthesis.
4. Inhibition of metabolic processes.
5. Inhibition of membrane function.

Non-antibiotic treatments

Treating UTIs with antibiotics is an effective method, but often, in case of minor uncomplicated infections, the body recovers on its own. In such mild cases, people can try some other methods

Table 2 Mode of action of antibiotics

Mode of action of antibiotics	Mechanism	Antibiotic groups	Examples of antibiotics
Inhibitor of cell wall synthesis	Knowing the fact that eukaryotic cells do not have cell walls, we found that this structure is critical for the life and survival of bacterial species. A drug that targets cell walls can therefore selectively kill or inhibit bacterial growth.	Beta-lactam antibiotics (penicillins)	Amoxyclav Ampicillin Carbencillin Piperacillin
		Beta-lactam antibiotics (cephalosporins)	Cefadroxil Cefuroxime Ceftriaxone Ceftazidime Cefepime Cefpirome
		Monobactams	Aztreonam
		Carbapenems	Imipenem Meropenem
Inhibitor of nucleic acids	DNA and RNA contain cell's genetic information and intelligence to carry out all the activities. DNA replication followed by cell division is an important factor for new bacterial cell formation. Some of the antibiotics attack this characteristic and prevent DNA formation; hence these antibiotics are called bactericidal.	Quinolones	Nalidixic acid
		Fluroquinolones	Ciprofloxacin Levofloxacin Norfloxacin
		Furanes	Nitrofurantoin
Inhibitor of protein synthesis	It targets bacterial protein synthesis by binding to either the 30S or 50S subunits of the intracellular ribosomes. This results in the disruption of normal cell metabolism of bacteria and consequently leads to inhibition of its growth and multiplication.	Aminoglycosides	Amikacin Tobramycin Gentamicin
Inhibitor of metabolic processes	For DNA synthesis, cell needs folate; unlike mammals, bacteria manufacture their own folate. Some antibiotics work in such a way that they inhibit folate synthesis and hence cell replication stops.	Sulfonamides	Cotrimoxazole
Inhibitor of membrane function	Cell membranes are important barriers that segregate and regulate the intracellular and extracellular flow of substances. Any disruption or damage to this structure can lead to leakage of important solutes essential for the cell's survival.	Polymyxins	Polymyxin B

to speed up the recovery process as an alternative to antibiotics (figure 2). Staying hydrated, that is, drinking plenty of water and avoiding drinks that irritate the urinary bladder (such as alcohol and caffeinated drinks) can help in preventing and treating UTIs. Water helps in removing waste from the body, while retaining essential nutrients and electrolytes needed by the body. Drinking enough water dilutes the urine and speeds up its way through the system, making it harder for bacteria to get an access to the urinary organs and to cause an infection.[50 51]

Figure 2 Alternative methods used to treat minor urinary tract infections.

Similarly, taking probiotics (beneficial bacteria) may help to keep the urinary tract healthy and free from any pathogenic bacteria. Lactobacilli, a group of probiotics, help to treat UTIs as they prevent bacterial adhesion to the urinary tract cells. The acidic urine pH due to lactobacilli makes it difficult for bacteria to survive. They also produce hydrogen peroxide in the urine, which is a strong antibacterial agent.[52] A study conducted by Falagas *et al*[53] suggested that probiotics have a good safety profile and can be used for preventing recurrent UTIs in females. In a similar study, Grin *et al*[54] demonstrated the role of probiotic strains of *Lactobacillus* in combating recurrent UTIs in women.

The role of cranberries has been discussed by many researchers in preventing and treating UTIs. In one such study, Shin[55] revealed that cranberries can decrease bacterial adherence to uroepithelial cells, thereby decreasing the incidence of UTIs. In a similar study, Wan *et al*[56] showed that cranberry juice may help in reducing the incidence of repeated episodes of UTIs in uncircumcised boys. They also revealed the beneficial effects of cranberry juice against the growth of Gram-negative bacterial pathogens.[56] However, a study conducted by Jepson *et al*[57] unveiled that cranberry juice does not have any significant benefit in preventing UTIs and may be unsuitable for long-term consumption. They also suggested that the effectiveness of cranberry was almost similar to antibiotics for women and children.[57]

Montorsi *et al*[58] demonstrated the effectiveness of cranberries, *Lactobacillus rhamnosus* and vitamin C in treating recurrent UTIs in females. Similarly, Hickling and Nitti[59] revealed that ascorbic acid, a form of vitamin C, is often recommended to prevent recurrent UTIs by acidification of the urine. However, some in vitro studies showed its bacteriostatic effect in the urine. They found that it reduces the urinary nitrites to reactive

Table 3 Presence of beta-lactamase and quninolone-resistant genes among uropathogens

S. no.	Antibiotic resistance genes studied	Age group	Study area	Isolates studied (n)	Reference
1.	Bla TEM, Bla SHV, Bla CTX-M, QnrA, QnrB and QnrS	–	Kolkata	73	Tripathi *et al*[68]
2.	Bla CTX-M, Bla TEM, Bla SHV and Bla AmpC	–	Aligarh	160	Gupta *et al*[70]
3.	Qnr A, B, D, S and aac (6′)-Ib-cr	–	Puducherry	642	Yugendran and Harish[71]
4.	Bla TEM and bla CTX-M	–	Tripura	150	Dasgupta *et al*[72]
5.	Bla NDM-5 and Bla CTX-M	18–49 years	Sikkim	241	Gajamer *et al*[73]
6.	Bla SHV, Bla TEM and Bla CTX-M	–	Central India	78	Bajpai *et al*[74]
7.	Bla TEM, Bla CTX-M and Bla SHV	≥18 years	Bhubaneswar	112	Jena *et al*[75]
8.	Bla TEM, Bla CTX-M and Bla SHV	21–50	Assam	85	Kumar *et al*[76]
9.	Bla TEM, Bla CTX-M and Bla SHV	1–89 years	Tamil Nadu	100	Nandagopal *et al*[77]
10.	Bla TEM, Bla CTX-M and Bla SHV	≤18 years	Kerala	523	Nisha *et al*[78]
11.	QnrA1, *B1*, *S1* and Qep, Qnr C, D and aac (6′)-Ib-cr	1 month–88 years	Varanasi	365	Banerjee and Anupurba[79]
12.	QnrA, QnrB, QnrS, OqxAB, QnrC, aac (6′)-Ib-cr, QepA, Bla TEM and Bla CTX-M	–	Kolkata	81	Basu and Mukherjee[80]
13.	Bla TEM, Bla SHV, Bla CTX-M, QnrA, QnrB, QnrS, QepA, OqxA and OqxB	–	Tehran, Iran	247	Goudarzi *et al*[81]
14.	Bla TEM, Bla SHV, Bla CTX-M, QnrA, QnrB and QnrS	–	Spain	382	Briales *et al*[82]
15.	Bla TEM, Bla SHV, Bla CTX-M, QnrA, QnrB, QnrS and QepA, aac (6′)-Ib-cr	–	Sari, Iran	225	Tayebi *et al*[83]
16.	Bla TEM, Bla SHV, Bla CTX-M, QnrA, QnrB and QnrS	children younger than 12 years	Hamadan, Iran	120	Sedighi *et al*[84]
17.	Bla TEM, Bla SHV, Bla CTX-M	≥1 year	Sri Lanka	74	Tillekeratne *et al*[85]
18.	Bla TEM, Bla SHV, Bla CTX-M, Qnr and aac (6′)-Ib	17–88 years	Rome, Italy	195	Longhi *et al*[86]
19.	QnrA, QnrB, QnrS, aac (6′)-Ib, QepA, Bla TEM, Bla SHV and Bla CTX–M	children younger than 12 years	China	292	Han *et al*[87]
20.	QnrA, QnrB and QnrS	3–85 years	Zanjan and Qazvin, Iran	200	Rezazadeh *et al*[88]
21.	QnrA, QnrB, QnrS, aac (6′)-Ib, QepA, Bla TEM, Bla SHV and Bla CTX–M	–	Madrid, Spain	191	Ríos *et al*[89]
22.	Bla TEM, Bla SHV and Bla CTX-M	11 months - 75 years	Iran	245	Seyedjavadi *et al*[90]
23.	Bla CTX-M	0–16 years, and >16 years.	Istanbul	219	Nazik *et al*[91]
24.	Bla TEM, Bla SHV, Bla CTX-M 1, Bla CTX-M 9, QnrA, QnrB and QnrS	–	Korea	111	Kim *et al*[92]
25.	aac (6)-Ib, QnrB, QnrS, OqxA and OqxB	10–85 years	Kerman, Iran	200	Hashemizadeh *et al*[93]
26.	aac (6′)Ib, OqxA, OqxB, QnrA, QnrB, QnrS and QepA, Bla TEM, Bla SHV, and Bla CTX-M	9 months–75 years	Tehran, Iran	290	Goudarzi and Fazeli[94]
27.	Bla SHV, Bla CTX-M and Bla TEM, QnrA, QnrB, QnrC, QnrD, QnrS, aac (6′)- Ib-cr, OqxAB and QepA	1–93 years	Azerbaijan and Iran	219	Azargun *et al*[95]

–, not given.

nitrogen oxides instead of lowering the urinary pH.[60 61] Similarly, Nseir *et al*[62] examined the association of serum levels of vitamin D with the recurrent UTIs among premenopausal women and found that vitamin D deficiency can lead to recurrence of UTIs in premenopausal women. Also, Caretto *et al*[52] suggested in a review that vitamin D enhances the production of cathelicidin in the urinary tract, thereby combating microbial invasion.

Mostly, UTIs occur when bacteria from the rectum or faeces gets access to the urethra due to the shorter distance between the urethra and the rectum. Badran *et al* demonstrated the role of personal hygiene habits and sexual behaviour in preventing UTIs among pregnant women.[63] Persad *et al*[64] also suggested that women who wipe from back to front has a greater risk of developing UTI than those who wipe from front to back.

Non-antibiotic prevention methods lack strong evidence to be administered as routine management options and as an alternative to antibiotics. More randomised controlled trials and further evaluation are required before they can be recommended as an alternative to antibiotics.

ANTIBIOTIC RESISTANCE AMONG UROPATHOGENS

Antimicrobial resistance is considered to be a global menace of the time, and uropathogenic bacteria are also showing same trends worldwide. Reckless use of antibiotic drugs is the main cause for the development of resistance. In their study, Sahm *et al*[65] showed that resistance rates against drugs in the USA were 39% to ampicillin, nearly 16% to cephalothin, 18.6% to cotrimoxazole and 3.7% to ciprofloxacin. Another study that was based on observation in Pune, India, showed that resistance of Gram-negative bacteria was 98% to ampicillin, 94% to norfloxacin, 79% to cotrimoxazole and 14.7% to nitrofurantoin. These data showed that antibiotic resistance among uropathogens has increased drastically over the years.[66]

Antibiotic resistance trends, with respect to *E. coli*, which is the major contributor to UTIs, were studied in the USA over the period between 2003 and 2012, and the results showed that *E. coli* resistance to nitofurantoin changes slightly from 0.7% to 0.9%, and for ciprofloxacin, there was significant change from 3.6% to 11.8%, whereas 17.2% to 22.2% change

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Self-assessment questions

1. Females are more prone to urinary tract infections (UTIs) due to shorter urethra as compared with males. True/false.
2. Vaginal microflora consists of which bacteria?
   A. *E. coli*.
   B. *Klebsiella*.
   C. *Lactobacillus*.
   D. *Staphylococcus.*
3. The most common risk factor for nosocomial UTIs is
   A. Use of spermicides.
   B. Urinary catheter.
   C. Pregnancy.
4. Heat produced by growing micro-organisms is recorded in isothermal microcalorimetry for their detection. True/false.
5. Aptamers were screened through which technique?
   A. Systematic evolution of ligands by exponential enrichment.
   B. PCR.
   C. ELISA.
   D. Isothermal microcalorimetry.

Main messages

- Diagnostic failures lead to improper use of antibiotics, delay in treatment and low survival rate in case of bacterial infections.
- Rapid diagnostic techniques should be followed for early diagnosis of the pathogens.
- Emergence of antibiotic resistance among uropathogens is of great concern, so antibiotics should not be immediately prescribed in case of minor uncomplicated urinary tract infections.

Current research questions

- Can non-antibiotic treatment for minor uncomplicated urinary tract infections be used to avoid antibiotic resistance?
- Is there a need to upgrade the pathogen detection methods in clinics for early and accurate diagnosis of the disease?
- Can antimicrobial stewardship programmes be helpful in promoting the appropriate use of antimicrobials in low-income countries?

in resistance was observed for trimethoprim/sulfamethoxazole. The data indicate that there were increasing trends in resistance in *E. coli* to ciprofloxacin and trimethoprim/sulfamethoxazole especially among young females.[67]

The emergence of extended-spectrum beta-lactamases (ESBLs) among Gram-negative bacteria is of a huge challenge and increases the incidence of UTIs, thus making it more difficult to treat. There are several reports on community-onset UTIs linked with ESBL-positive *E. coli*. Bacterial resistance against beta-lactam and quinolone group of drugs is mainly acquired by intraspecies or interspecies exchange of transferable plasmid that encodes antibiotic resistant genes, *viz.*, blaCTX-M, blaTEM, blaSHV, Qnr A, Qnr B and Qnr S.[68 69] Various studies conducted by researchers on the presence of beta-lactamase and quninolone-resistant genes among uropathogens are given in table 3.

Antibiotic resistance shows dynamic trends for uropathogens, and it is suggested that more studies should be conducted to track and stop this trend. Individual clinicians should study these patterns and prescribe antibiotics based on antibiotic clinical therapy-based guidelines.

CONCLUSION

Infections of the urinary tract can be asymptomatic, acute or chronic and complicated or uncomplicated. The clinical indications of UTIs rely on the part of the urinary tract associated, causative organisms, intensity of the infection and the patient's immune system's response to it. Identification of the causing micro-organism is critically important as it lowers the cost and toxicity of the antibiotic therapy and also narrows the possibility of arising issue of antimicrobial resistance. Rapid diagnostic techniques should be followed for early diagnosis and appropriate treatment of the pathogens. Minor uncomplicated UTIs should be treated with other methods rather than an immediate prescription of antibiotics. Further, antimicrobial stewardship programmes should be encouraged to promote appropriate use of antibiotics to minimise the development of antimicrobial resistance for UTIs.

Acknowledgements The authors thank Guru Nanak Dev University, Amritsar for providing necessary infrastructure to carry out the research work. University Grants Commission for providing financial assistance under University with Potential for Excellence scheme and DRS SAP programmes.

Contributors The study draft was designed by RajiK. Acquisition of data was done by RajaK. Analysis and interpretation of the data was done by RajiK and RajaK. Both authors contributed in writing, revising the manuscript critically and approving the final manuscript.

Funding This study was funded by University Grants Commission (UGC-UPE fellowship).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Rajinder Kaur http://orcid.org/0000-0002-7857-9919

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Answers

1. True
2. (C) *Lactobacillus*.
3. (B) Urinary catheter.
4. True.
5. (A) Systematic evolution of ligands by exponential enrichment.