

Urinary tract infections (UTIs) or genital tract infections (GTIs)? It's the diagnostics that count

Harnwegsinfektionen (HWI) oder Genitaltraktinfektionen (GTI)? Diagnostik: Darauf kommt es an

Abstract

Urinary tract infections (UTIs) and genital tract infections (GTIs) are both very common infectious diseases. Thus, accuracy and rapidity in recognition and treatment of sexually transmitted urogenital tract infections (ST-UGTIs) is a major concern in global public health systems. The application of reliable, accurate diagnostic tools is the key to definite detection, identification and treatment. This literature review focused on different characteristics of UGTIs in patients and the importance of diagnostic methodologies.

The articles published and indexed from 1980 through October 2018 in the databases of PubMed and MEDLINE, as well as the Google Scholar web search engine, were collected and studied. MeSH keywords of "Sexual intercourse", "Urinary Tract Infections", "Genital Tract Infections" and "Toll-Like Receptors" were used for searching articles. Then, the proper articles (original and review articles) were subjected to a very rigorous selection process.

The clinical symptoms and signs or asymptomatic properties of UTIs and GTIs are similar and often overlap. In many cases, the lack of suitable diagnostic techniques leads to misdiagnosed/undignosed GTIs and overdiagnosed UTIs. The outcome of poor diagnostics is failure of definite identification and treatment.

The application of advanced techniques comprising PCR, microarray and next-generation sequencing promises to be more effective, together with the use of the microbial pattern of the individual's UGT to provide reliable detection, identification and definite treatment. This will be an option in the near future.

Keywords: sexual intercourse, urinary tract infections, genital tract infections, toll-like receptors

Zusammenfassung

Infektionen des Harntrakts (HWI) und des Genitaltrakts (GTI) sind beides infektiöse Erkrankungen. Deshalb ist die Genauigkeit und Schnelligkeit der Erkennung und Behandlung sexuell übertragener Infektionen des Urogenitaltrakts (SÜ-UGT) entscheidend. Die Verwendung geeigneter Diagnosetools ist der Schlüssel zur eindeutigen Erkennung, Identifizierung und Behandlung. Die Literaturrecherche konzentrierte sich auf verschiedene Merkmale von SÜ-UGTs und die Bedeutung diagnostischer Methoden.

Veröffentlichungen (Originalbeiträge und Reviews) wurden im Zeitraum von 1980 bis Oktober 2018 in den Datenbanken PubMed, MEDLINE und Google Scholar anhand der Schlüsselwörter „Sexual intercourse“, „Urinary Tract Infections“, „Genital Tract Infections“ und „Toll-Like Receptors“ gesammelt, sorgfältig ausgewählt und ausgewertet.

HWI und GTI überlappen sich häufig entweder auf Grund der ähnlichen klinischen Symptomatik oder wegen asymptomatischen Verlaufs. In vielen Fällen führt das Fehlen geeigneter Diagnosemethoden zu falsch

Payam Behzadi¹
Elham Behzadi¹
Edyta Agnieszka
Pawlak-Adamska²

1 Department of Microbiology,
College of Basic Sciences,
Shahr-e-Qods Branch, Islamic
Azad University, Tehran, Iran

2 Department of Experimental
Therapy, Hirsfeld Institute of
Immunology and
Experimental Therapy,
Wrocław, Poland

diagnostizierten oder nicht erkannten GTI und überdiagnostizierten HWI. Das Ergebnis einer unzureichenden Diagnostik führt zum Versagen der eindeutigen Identifizierung und Behandlung.

Die Anwendung moderner Techniken wie PCR, Microarray und Next-Generation-Sequenzierung wird in Verbindung mit der Identifizierung der mikrobiellen individuellen Besiedlung des UGT eine qualitativ hochwertige Erkennung und Behandlung ermöglichen.

Schlüsselwörter: Geschlechtsverkehr, sexuell übertragene Infektionen des Urogenitaltrakts, Harnwegsinfektionen, Genitaltraktinfektionen, Toll-like Rezeptoren

Introduction

Urinary tract infections (UTIs) are the second most common infectious diseases worldwide. UTIs involve a wide range of clinical manifestations, including acute, chronic, uncomplicated, complicated, asymptomatic, symptomatic and recurrent. The infections may affect the lower and/or the upper parts of urinary tract. There are different types of microbial pathogens, such as Gram-negative bacteria (e.g., uropathogenic *Escherichia coli* [UPEC]), Gram-positive bacteria (e.g., *Staphylococcus saprophyticus*) and yeasts (e.g., *Candida albicans*), which may cause UTIs in their hosts. Urogenital tract infections (UGTIs) include the prevalent infectious diseases of the genital tract, urinary tract and sexually transmitted urogenital tract infections (ST-UTIs), which have become a major concern in public health systems [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12].

UTIs such as cystitis (lower UTIs) and pyelonephritis (upper UTIs) in healthy hosts with no history of UTIs are recognized as uncomplicated UTIs. In contrast, complicated UTIs are normally seen in the elderly and catheterized patients. Although there is a wide range of predisposing factors which may lead to the occurrence of UTIs, the uncomplicated cases are mostly known as ST-UTIs. UTIs and GTIs sometimes occur together, and the GTIs are often ignored or misdiagnosed. In other words, there are many patients who suffer from UGTIs, but the GTIs are reported as UTIs. Thus, the misdiagnosis/underdiagnosis of GTIs and overdiagnosis of UTIs is a serious error, leading to incorrect treatment and spread of infections. Furthermore, asymptomatic UGTIs can be considered another significant problem in public health systems [8], [13], [14], [15], [16], [17], [18], [19].

Based on the high frequency of UGTIs and the severe consequences of misdiagnosis, this literature review focused on different characteristics of UGTIs in patients and the importance of diagnostic methodologies.

Methods

The articles published and indexed from 1980 through October 2018 in the databases of PubMed and MEDLINE as well as the Google Scholar web search engine were collected and studied. The MeSH keywords “sexual intercourse”, “Urinary Tract Infections”, “Genital Tract Infec-

tions” and “Toll-Like Receptors” were used for searching articles. Then, the proper articles (original and review articles) were selected very rigorously.

Results and discussion

Sexual intercourse, UTIs, and GTIs

Adolescence results in physical and emotional maturity. This process may lead to special social and intimate relationships between young people and adults. Sexual intercourse experimentation is one of the most important needs among teenagers, young adults, and adults. Uncertain and uncontrolled sexual activities and sexual intercourse may lead to serious health problems and the occurrence of UGTIs. Venereal diseases (VD) and ST-UGTIs occur through anal, oral and vaginal sexual activities. Cystitis and rarely pyelonephritis caused by UPEC are known as frequent UTIs in sexually active women. As previous studies have shown [16], [18], [19], [20], [21], the number of misdiagnosed/undiagnosed GTIs and overdiagnosed UTIs among sexual active women is extremely high. According to reports from the Centers for Disease Control and Prevention (CDC) [18], about 19 million cases are added annually to the population of patients with STIs. Because of the damaging epidemiological consequences of STIs, performing early diagnosis and definite treatment are imperative. The major problem is that in UGTIs, there is no distinct border between GTIs and UTIs. According to the literature [16], [20], [21], in up to 50% of patients with UTIs, GTIs were also recognized (UGTIs). Moreover, there are several symptoms common to the early stages of both GTIs and UTIs. However, many UGTIs are clinically asymptomatic. Sometimes, important pathogenic bacteria, such as *Gardnerella vaginalis*, *Ureaplasma* spp. and *Mycoplasma hominis*, are actually members of the UT's normal flora but act as pathogenic microorganisms in the etiology of UGTIs (in some cases, *Ureaplasma* spp. and *Mycoplasma hominis* are known as UGT commensal bacteria). Thus, possessing an up-to-date microbiota pattern from UGTs for differentiating pathogenic microorganisms from commensal strains helps us to estimate the real status of UGTIs among populations. There are different types of GTIs which have close similarities with UTIs. Table 1 describes these infections and their characteristics [1], [5], [12], [16], [17],

Table 1: Urogenital tract infections (UGTIs), microbial causative agents and related clinical properties and manifestations

UGTI	Microbial Agent	Clinical properties and manifestations
Bacteriuria	Uropathogenic <i>Escherichia coli</i> (UPEC) and other enteric bacteria (such as <i>Klebsiella</i> spp., <i>Proteus</i> spp., <i>Providencia stuartii</i> (<i>P. stuartii</i>), <i>Morganella morganii</i> (<i>M. morganii</i>), <i>Staphylococcus</i> spp. (e.g. <i>S. saprophyticus</i> , <i>S. aureus</i>), Group B Streptococci (GBS), <i>Enterococcus</i> spp., <i>Pseudomonas aeruginosa</i> (<i>P. aeruginosa</i>), <i>Gardnerella vaginalis</i> (<i>G. vaginalis</i>)	Asymptomatic (>10 ⁵ microbial cfu/ml urine): In chronic form may lead to serious UTIs Symptomatic: Dysuria, pyuria, urgency in urination, cystitis, epididymitis, orchiepididymitis, nephritis, prostatitis, pyelitis, pyelonephritis
Candiduria	<i>Candida</i> spp.	Asymptomatic: It is not recognized as an infectious sign Symptomatic: Dysuria, urgency in urination, pyuria, cystitis, epididymitis, orchiepididymitis, nephritis, prostatitis, pyelitis, pyelonephritis
Candidal balanitis	<i>Candida</i> spp.	Frequent urination, dysuria, vaginal discharge, pain in suprapubic area
Cystitis	UPEC and other enteric bacteria (such as <i>Klebsiella</i> spp., <i>Proteus</i> spp., <i>Morganella</i> spp., <i>Citrobacter</i> spp., <i>Enterobacter</i> spp.), <i>P. aeruginosa</i> , <i>Staphylococcus</i> spp., <i>Enterococcus</i> spp., <i>Streptococcus</i> spp., <i>Acinetobacter</i> spp., <i>Candida</i> spp.	Urination with pain, frequent urination, pyuria, hematuria, bacteriuria, candiduria, urethritis, vaginitis, pain in suprapubic area, pelvic inflammatory disease, bladder cancer, (prostitis in men)
Epididymitis and orchiepididymitis	UPEC and other enteric bacteria (such as <i>Klebsiella</i> spp., <i>Proteus</i> spp., <i>P. stuartii</i> , <i>M. morganii</i>), <i>Chlamydia trachomatis</i> (<i>C. trachomatis</i>), <i>Neisseria gonorrhoeae</i> (<i>N. gonorrhoeae</i>), <i>C. albicans</i>	Urethral discharge, pain and inflammation in scrotum (in men)
Prostatitis	UPEC and other enteric bacteria (such as <i>Klebsiella</i> spp., <i>Proteus</i> spp., <i>Enterobacter</i> spp., <i>Serratia</i> spp.), <i>P. aeruginosa</i> , <i>Enterococcus</i> spp., <i>C. trachomatis</i> , <i>N. gonorrhoeae</i> , <i>Candida</i> spp., <i>Staphylococcus</i> spp., <i>Streptococcus</i> spp., <i>Mycoplasma genitalium</i> (<i>M. genitalium</i>), <i>Trichomonas vaginalis</i> (<i>T. vaginalis</i>), <i>Ureaplasma urealyticum</i> (<i>U. urealyticum</i>)	Dysuria, urethral discharge, cystitis, epididymitis, orchiepididymitis, pelvic inflammatory disease, prostate cancer,
Pyelonephritis	UPEC and other enteric bacteria (such as <i>Klebsiella</i> spp., <i>Proteus</i> spp., <i>Enterobacter</i> spp.), <i>Staphylococcus</i> spp., <i>Enterococcus</i> spp., <i>P. aeruginosa</i> , <i>U. urealyticum</i> , <i>Mycoplasma hominis</i> (<i>M. hominis</i>), <i>T. vaginalis</i>	Pain during urination, frequent urination, hematuria, pyuria, bacteriuria, candiduria, pelvic inflammatory disease, cystitis, , pain in flank, fever, chills
Urethritis	UPEC in bisexual, homosexual and heterosexual partners (with anal sex) and other enteric bacteria (such as <i>Klebsiella</i> spp., <i>Proteus</i> spp.), <i>C. trachomatis</i> , <i>M. genitalium</i> , <i>N. gonorrhoeae</i> , <i>T. vaginalis</i> , <i>U. urealyticum</i> , HSV	Urethral discharge, Dysuria, Pyuria, Pain and inflammation in testicles and scrotum in Men
Urosepsis	UPEC and other enteric bacteria (such as <i>Klebsiella</i> spp., <i>Proteus</i> spp., <i>Enterobacter</i> spp., <i>Serratia</i> spp.), <i>Enterococcus</i> spp., <i>Staphylococcus</i> spp., <i>P. aeruginosa</i>	Dysuria, urethral discharge, bacteremia, oliguria, sepsis, cystitis, pyelonephritis, ureterolithiasis, pelvic inflammatory disease, pain and inflammation in testicles and scrotum in men
Vulvovaginitis	UPEC, <i>Candida</i> spp., <i>T. vaginalis</i> , <i>M. genitalium</i> , <i>C. trachomatis</i> , <i>N. gonorrhoeae</i> , HSV	Dysuria, pyuria, bacteriuria/candiduria, vaginal discharge, painful coitus in women
Cervicitis	UPEC, <i>C. trachomatis</i> , <i>N. gonorrhoeae</i> , Herpes simplex virus (HSV), <i>Salmonella</i> spp., <i>Mycobacterium</i> spp., <i>T. vaginalis</i> , <i>M. genitalium</i>	[Mucopurulent discharge, cervical bleeding, pelvic inflammatory disease, vulvovaginitis, infertility, (regarding bacterial infections)], [different types of cervical lesions, cervical ulcers, erythema (regarding viral infections)] in women
Chlamydia	<i>C. trachomatis</i>	In men: Non-gonococcal urethritis, dysuria, penile discharge, testicle pain, infertility, urethritis, epididymitis, urethral discharge In women: Pelvic inflammatory disease, dysuria, vaginal discharge, irregular vaginal bleeding, ectopic pregnancy, infertility, metritis, urethritis, cervicitis, urethral discharge
Gonorrhoea	<i>N. gonorrhoeae</i>	In men: Urethritis, dysuria, penile discharge, testicle pain, infertility, epididymitis, proctitis, cystitis, urethral discharge In women: Dysuria, vaginal discharge, irregular vaginal bleeding, urethral discharge, pelvic inflammatory disease, abdominal pain (usually lower part) ectopic pregnancy, infertility
Trichomoniasis	<i>T. vaginalis</i>	In men: Dysuria, urethral discharge, epididymitis, prostatitis, urethritis, infertility In women: dysuria, urethral discharge, yeasty vaginal discharge with amine odor, strawberry cervix (irregular bleeding), perineal itching, infertility, pelvic inflammatory disease, ectopic pregnancy

[19], [22], [23], [24], [20], [21], [25], [26], [27], [28], [29], [30], [31], [32], [33], [34], [35], [36], [37], [38], [39], [40], [41], [42], [43], [44], [45].

Risk factors for UGTIs

A wide range of predisposing factors contributes to multifactorial ST-UGTIs. The most commonly reported risk factors which predispose people to ST-UGTIs are: early sexual activity, frequency of coition, frequency of voiding before and after coition, sexual intercourse with different sex partners (separately or concurrently), sexual abuse, rape, sexual intercourse with addicted partners, sexual intercourse with sex workers, sexual intercourse with online dating friends, sexual intercourse with a new sex partner within less than 2 months, history of previous GTIs or UTIs, immune deficiencies, sexual intercourse with gay, lesbian or bisexual partners, low socioeconomic status, depression, anxiety, low educational status, poor personal hygiene, poor access to condoms and other contraceptive devices, use of spermicidal diaphragms (spermicidal agents also kill lactobacilli), poor access to qualified healthcare systems, high rate of family disruption, and mental disorders. In addition, the increase and spread of multidrug-resistant pathogens and expanded spectrum beta lactamase (ESBL)-producing bacteria have a considerable impact on UGTIs. However, some studies suggest an interesting methodology for overcoming the problem of ESBL-producing enterobacteriaceae by individualized therapy. In other words, the profiles of susceptibilities, severities and types of UGTIs and the characteristics of patients differ from one patient to the next. These properties open promising approaches to providing accurate and definite treatment for UGTIs [22], [23], [24], [46], [47], [48], [49].

Important TLRs (toll-like receptors) in UGTIs

Despite the presence of strong barriers made of urothelial cells in human UGT, uropathogenic microorganisms such as UPEC can breach these barriers. Upon the entrance of UPEC into UGT, the innate immune responses are activated by the expression of certain toll-like receptors (TLRs) within the urothelial cells of bladder and kidneys. TLR expression activates a cascade of different immune system components including chemokines, interferons, interleukins, antimicrobial peptides, and proinflammatory cytokines. The innate immune system responds upon the occurrence of by UPEC entrance, attachment and invasion. The bacterial attachment on the urothelial cells is achieved by the virulence factors of FimH adhesins located on the top of type I fimbriae. The attachment of UPEC cells on the urothelium cells normally leads to expression of TLRs, secretion of interleukin (IL)-6 and the function of programmed cell death (apoptosis; genome fragmentation), where apoptosis may prevent the process of bacterial invasion into the UT epithelial cells and act as a mechanism of immediate bacterial elimination. The

UPEC cells are normally recognized by TLRs 4 and 5. According to several surveys [42], [50], [51], the molecules of TLR4 are expressed by bladder and kidney urothelial cells, while TLR5 molecules are expressed via bladder urothelial cells. The attachment of bacterial lipopolysaccharides (LPS) or P fimbriae to CD14 and glycoprotein molecules (situated on uroplakins/cell membrane of bladder and kidney urothelial cells), respectively, results in TLR4 expression, while the bacterial flagella units (flagellins) activate the expression of TLR5 molecules in bladder urothelial cells. Activation of TLR4 may trigger IL-8 and IL-6 secretion. IL-8 and IL-6 cytokines contribute to neutrophil recruitment and secretion of mucosal antibody of IgA *in situ*, respectively. In addition to UPEC as an important microbial causative agent of UGTIs, fungi such as *C. albicans* are important pathogens that cause UGTIs. Interestingly, *C. albicans* is able to stimulate the innate immune responses via different types of TLRs, including TLR2/6 (zymosan) and TLR4 (neutrophil activation and secretion of mucosal antibody of IgA). The relationship between microbial causative agents of UGTIs and TLRs are shown in Figure 1 and Table 2 [2], [3], [42], [50], [51], [52], [53], [54], [55], [56], [57], [58], [59], [60], [61], [62], [63], [64], [65], [66], [67], [68].

Epidemiology of UGTIs

Patients with UTIs are referred to 7,000,000 medical practices and 1,000,000 emergency departments worldwide. In addition to patients with UTIs, the patients with GTIs are also referred to these medical centers. In accordance with CDC reports, about 20,000,000 patients with STIs are recognized as new cases annually. There are several clinical manifestations common to both GTIs and UTIs (in particular lower UTIs). At the same time, there are several types of UGTIs which are asymptomatic. In addition to these important problems, knowledge about microbial load and population is critical for the detection and identification of pathogenic agents of UGTIs. Healthy people have UGT microbiota with their own UGT microbial patterns. In patients with UGTIs, the microbial ecosystem becomes unbalanced, leading to the occurrence of UGTIs. In the near future, knowing the microbial patterns of healthy UGT and UGTIs will be an invaluable and effective biodiagnostic tool. That is why a large proportion of patients with GTIs undergo wrong treatments and are undiagnosed or misdiagnosed. Today, we know that the reports regarding UTIs and GTIs are neither accurate nor correct. It seems that the reported percentage of patients with UTIs (about 50%) or GTIs (up to 50%) is biased. Overdiagnosis and underdiagnosis have occurred relating to the rates of UTIs and GTIs, respectively. The use of advanced molecular and pan-genomic diagnostic methods, such as polymerase chain reaction (PCR) and DNA microarray, is more appropriate than traditional microbiological diagnostic tests. In addition, the application of sequencing technologies, e.g., 16s rRNA sequencing, is recommended for viable but non-culturable microorganisms. Normally, the PCR technique is applied to detect

Table 2: The relationship between toll-like receptor (TLR) induction and microbial causative agents of UGTIs in humans

Microbial agent	TLR	Ligands
Non-motile enteric bacteria	TLRs1-2 TLRs2-10	Triacylated lipoproteins
	TLR4	Lipopolysaccharide (LPS), Type I fimbriae, Type P fimbriae, Heat Shock Proteins (HSPs)60,70,90
Uropathogenic <i>Escherichia coli</i> (UPEC)	TLRs1-2 TLRs2-10	Triacylated lipoproteins
	TLR4	LPS, Type I fimbriae, Type P fimbriae, HSPs60,70,90
	TLR5	Flagellins
Other motile enteric bacteria	TLRs1-2 TLRs2-10	Triacylated lipoproteins
	TLR4	LPS, Type I fimbriae, Type P fimbriae, HSPs60,70,90
	TLR5	Flagellins
<i>Acinetobacter</i> spp.	TLR2	OmpA
	TLR4	LPS
<i>Mycobacterium</i> spp.	TLRs1-2	Triacylated lipoproteins
	TLR4	HSPs60,70,90
<i>Salmonella</i> spp.	TLRS 1-2/2-6	Lipoproteins
	TLR4	LPS
	TLR5	Flagellins
<i>Mycoplasma</i> spp. and <i>ureaplasma</i> spp.	TLRs1-2 TLRs2-10	Triacylated lipoproteins
	TLRs2-6 TLRs1-10 TLRs10-10	Diacylated lipoproteins
<i>Candida</i> spp.	TLRs2-6	Zymosan
	TLR4	HSPs60, 70, 90, mannan
<i>Staphylococcus</i> spp.	TLRs2-6	Lipoteichoic acid, Gram-positive bacterial peptidoglycans
<i>Streptococcus</i> spp. and <i>enterococcus</i> spp.	TLRs2-6	Lipoteichoic acid, Gram-positive bacterial peptidoglycans
	TLR4	HSPs60, 70, 90
<i>Chlamydia trachomatis</i>	TLRs 1-2	Outer membrane proteins, Peptidoglycan, HSP60, Elementary bodies
	TLR3	dsRNA
	TLR4	LPS, HSP60
<i>Neisseria gonorrhoea</i>	TLRs1-2	Porins
	TLR4	HSPs60,70,90
<i>Trichomonas vaginalis</i>	TLR2	Induced by the host's urogenital epithelial cells
	TLR4	Induced by the host's urogenital epithelial cells
	TLR9	Induced by the host's urogenital epithelial cells
<i>Pseudomonas aeruginosa</i>	TLRs1-2 TLRs2-10	Triacylated lipoproteins
	TLR4	HSPs60,70,90
	TLR5	Flagellins
<i>Gardnerella vaginalis</i>	TLR2	Secretion of tumor necrosis factor (TNF)- α by the host's urogenital epithelial cells induced by <i>G. vaginalis</i>
	TLR4	Secretion of tumor necrosis factor (TNF)- α by the host's urogenital epithelial cells induced by <i>G. vaginalis</i>
Herpes simplex virus (HSV)	TLR2	HSV Glycoproteins
	TLR3	HSV dsRNA molecules
	TLR9	Viral unmethylated CpG motifs of genomic DNA molecules

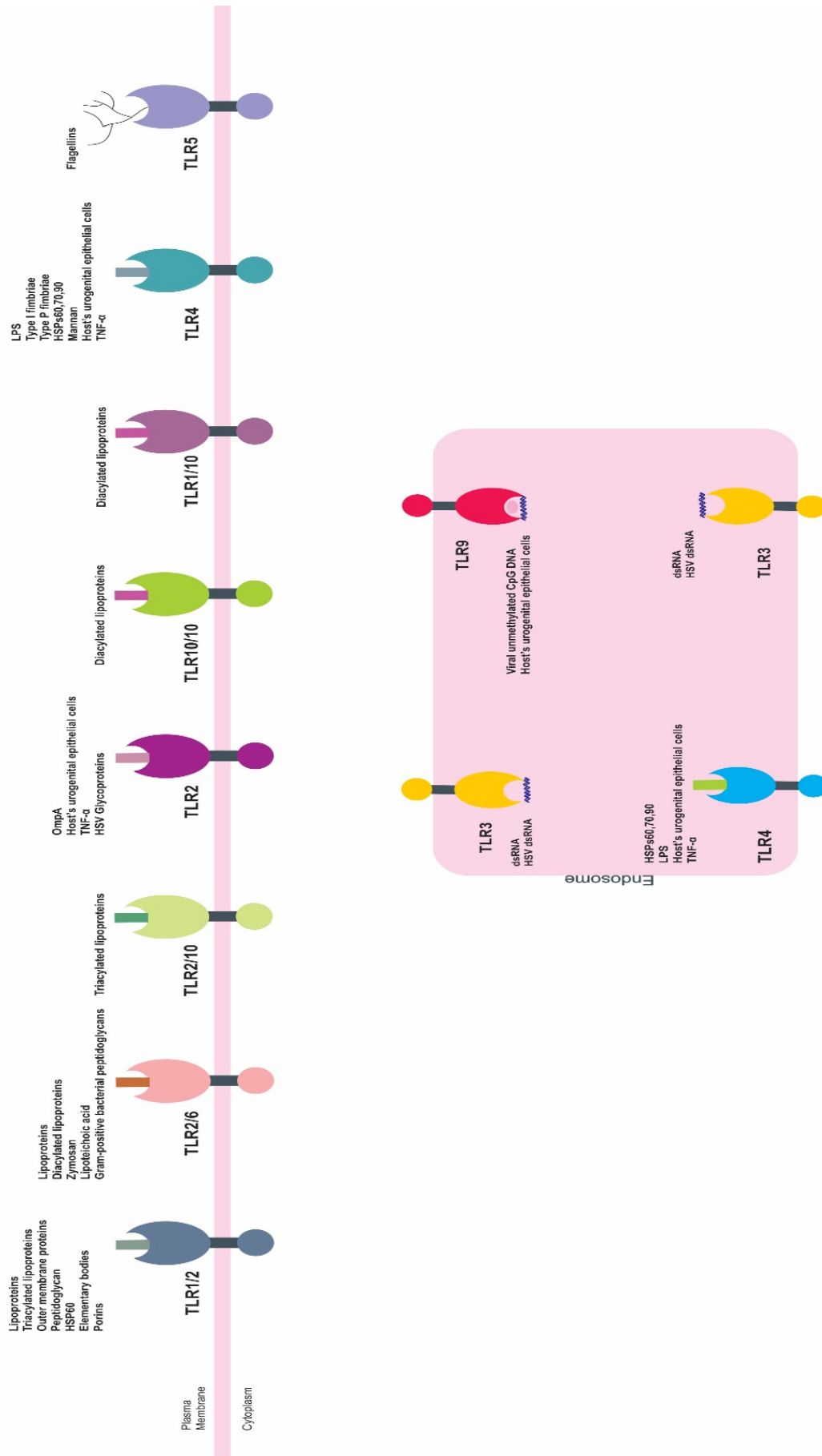


Figure 1: The situation, arrangement and relationship between pathogen-associated molecular patterns (PAMPs) and TLRs in UGTIs

and identify a limited number of genes and samples, while the DNA microarray technique is applied for large numbers of genes and samples. Using 16s rRNA sequencing technologies has offered us an opportunity to detect and identify those microorganisms which do not grow on lab culture media. On the other hand, some recommendations for urogenital pathogen cutoffs of colony forming units (cfu/ml) may lead to incorrect diagnosis. The guideline of the European Association of Urology (EAU) (cited in [30]) suggests a cutoff of $\geq 10^3$ to $\geq 10^5$ cfu/ml for women and $\geq 10^4$ cfu/ml for men as the standard critical number of uropathogenic microorganisms in midstream urine samples regarding bacteriuria. These cutoffs are completely dependent on the UGT microbial patterns. Thus, by employing state-of-the-art microbiological diagnostic methods, it will be possible to obtain a much more accurate interpretation of the results. Thus, the gold standard methodologies of microbiological techniques should be complemented by advanced molecular, pan-genomic and sequencing technologies. As mentioned above, PCR assays are cost-effective, fast, sensitive and specific for a limited number of genes and samples, but DNA microarray is preferable to reach an accurate, inexpensive, fast, flexible, reliable, sensitive and specific diagnosis given a large number of genes and specimens. 16s rRNA sequencing technology can provide a complete microbial pattern of the patient's UGT microbiota. Thus, the patient's anamnesis, clinical manifestations, diagnostic characteristics and application of appropriate diagnostic methods enable reliable detection and identification necessary for definite, appropriate treatment [1], [2], [9], [10], [12], [16], [17], [24], [30], [44], [45], [69], [70], [71].

UGTIs categorizations

As Table 1 depicts, there is a wide range of microorganisms which cause different types of UGTIs. Despite considerably overlaps in UTIs and GTIs, an appropriate screening methodology for accurate clinical diagnosis and definite qualified treatment would facilitate differentiating UTIs from GTIs. As mentioned above, patient's anamnesis, physical examinations, clinical syndromes, diagnostic tools, and regional lab information regarding local infections and the related pathogens are significant items for the detection and identification of UGTIs. Clinical characteristics, manifestations, signs and symptoms such as pyuria, dysuria, frequent urination, urgent urination, hematuria, pain in the flank and suprapubic region, fever and chills are common in both GTIs and UTIs. Moreover, penile discharge in men and vaginal discharge in women may occur in UTIs, but not always. In contrast to UTIs, GTIs are often recognized by genital tract discharges. Therefore, the type of clinical diagnostic tools determines the quality of UGTI recognition [1], [4], [10], [12], [16], [17], [19], [24], [30], [31], [44], [45], [70].

UGT microbiota

Today, a wide spectrum of possibilities and insights are available regarding UGT microbiota. The use of different molecular, nucleic-acid-based, pan-genomic and next-generation technologies enables improves the quality of information about human UGT microbiota. Indeed by the beginning of the human microbiome (microbial genomic treasure) project, the knowledge has greatly increased about an individual's UGT microbiotic profile. At present, we know that the UGT has its own microbiota and it differs not only between men and women but also from person to person. There are many viable but non-culturable microorganisms which can be identified throughout advanced molecular tools, sequencing techniques and microarray technologies. The useful UGT microbiota guarantee the health of the UGT, and any changes in the microbial pattern of UGT microbiota leads to imbalance and the occurrence of UGTIs. In the near future, the microbial pattern of UGTs will become invaluable biomarkers. It seems that human UGT microbiota also differ in different geographical regions; moreover, the effect of an individual's behaviors on his/her UGT microbiota is detectable. For example, the microbial patterns of UGTs in individuals who have frequent sexual intercourse with different partners are more variable than in people with normal sexual activities. Each sex partner shares his/her UGT microbiota with the other. As reported previously, the use of sex toys by women may result in a decrease of the vaginal population of *Lactobacillus* spp. and increase in *G. vaginalis*. In toto, the reduction of the *Lactobacillus* population may provide a favorable environment for pathogenic microorganisms. This means that *Lactobacillus* spp. are sentinel biobarriers which stabilize the UGT environment and keep it healthy. *Lactobacillus* spp. prevent the occurrence of ST-UGTIs in women. Previous reports show that *Lactobacillus crispatus* in a healthy vaginal environment traps viral particles of HIV in cervicovaginal mucus, and eliminates pathogenic bacteria of *N. gonorrhoeae* and UPEC. The presence of *lactobacilli* prevents recurrent UGTIs in susceptible women. Furthermore, bactericidal effects of *lactobacilli* on *C. trachomatis* is reported. *C. trachomatis* is the major bacterial causative agent of STIs around the world. In some cases, such as the occurrence of trichomoniasis, the presence of *T. vaginalis* is correlated with the presence of *Mycoplasma* spp., e.g., *M. hominis*, and the reduction of *L. crispatus* populations ([1], [3], [9], [44], [45], [70], [71]). Despite the variation of microbial patterns of UGTs at different ages in both men and women, there are great similarities in their microbial patterns of UGTs within a certain age range (similar microbial patterns in age ranges of 24–50 years [70], [72], and 39–86 years (in men) [70], [73], 22–51 years old [70], [72], and 26–90 years old (in women) [70], [73]). Table 3 depicts the total populations of UGT microbiota in both men and women [44], [45], [70].

For patients with asymptomatic UGTIs, several studies have found that determining their microbial patterns can

Table 3: The population of UGT microbiota in healthy men and women

	Men	Women
Urogenital microbial normal flora	<i>Aerococcus</i> , <i>Anaerococcus</i> , <i>Atopobium</i> , <i>Corynebacterium</i> , <i>Enterococcus</i> , <i>Escherichia</i> , <i>Fingoldia</i> , <i>Gardnerella</i> , <i>Gemella</i> , <i>Klebsiella</i> , <i>Lactobacillus</i> , <i>Mycoplasma</i> , <i>Prevotella</i> , <i>Sneathia</i> , <i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Ureaplasma</i> , <i>Veillonella</i>	<i>Actinobacteria</i> , <i>Actinobaculum</i> , <i>Actinomyces</i> , <i>Aerococcus</i> , <i>Allisonella</i> , <i>Alloscardovia</i> , <i>Anaerococcus</i> , <i>Anoxybacillus</i> , <i>Arthrobacter</i> , <i>Atopobium</i> , <i>Bacteroidetes</i> , <i>Bifidobacterium</i> , <i>Burkholderia</i> , <i>Corynebacterium</i> , <i>Dialister</i> , <i>Enterobacteriaceae</i> , <i>Enterococcus</i> , <i>Escherichia</i> , <i>Fingoldia</i> , <i>Gardnerella</i> , <i>Klebsiella</i> , <i>Lactobacillus</i> , <i>Peptoniphilus</i> , <i>Prevotella</i> , <i>Ralstonia</i> , <i>Rhodanobacter</i> , <i>Shigella</i> , <i>Sneathia</i> , <i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Trueperella</i> , <i>Veillonella</i>

offer a solution. For example, in the presence of asymptomatic UGTIs caused by *C. trachomatis*, the population of useful bacteria such as *Lactobacilli* decreases in the cervicovagina, while the population of anaerobic bacteria such as *G. vaginalis* increases [44], [45], [70].

This shows that the application of accurate, rapid, sensitive and specific diagnostic tools and technologies definitely has a direct effect on our ability to detect and identify UGTIs. Therefore, knowledge about the quality and the influence of relevant diagnostic techniques is imperative. Some common and important diagnostic methods are discussed as below.

Laboratory diagnostics

In parallel with clinical signs and symptoms, physical tests and patient's history, the use of appropriate laboratory diagnostic tools is necessary. It is clear that a clean mid-stream urine sample, penile discharges and vaginal discharges, bleeding and lesions are required to provide an accurate and definite diagnosis. Dipsticks, microscopic observations, microbiological cultivation, test strips, biomarkers, flow cytometry, mass spectrometry, infrared spectroscopy, isothermal microcalorimetry, biosensors, nucleic-acid-based techniques (including PCR), microarray, and sequencing technologies are some of the modern diagnostic techniques and microbial biomarkers. Of course, the use of appropriate diagnostic tools enables us to detect UGTIs with minimal biases [1], [4], [6], [7], [12], [16], [30], [31], [45], [69], [70], [71]. In the following text, these techniques are described in brief.

Dipstick tests are common diagnostic methods for the detection and identification of uropathogenic bacteria, including UPEC and other enteric bacteria. These assays are known as screening tests for UGTIs to recognize inflammations in the UGT and bacteriuria by detecting leukocyte esterase enzyme (produced by leukocytes) and nitrite (produced by enteric bacteria) in the urine samples. The results of these techniques can help us to confirm or exclude the presence of UGTIs. The sensitivity and specificity of dipstick assays are reported as 77% and 70%, respectively. It is clear that negative results from dipstick tests should be processed for further assessment, including microscopic observation, Gram staining and microbiological cultivation. The negative results can be interpreted as an alert for asymptomatic bacteriuria or GTIs [1], [12], [16], [31], [69].

Microscopic observation is usually performed together with Gram staining procedures. These methods are other elements of screening tests for recognition of UGTIs. It is important to check clinical samples as early as possible, because the number of leukocytes decreases at lab temperature over time (an approximately 40% decrease within 2 hours). Pyuria (identified as 5 leukocytes in a high-power microscopic field) is considered for UGTIs. The morning urine samples are preferred for a narrower diagnosis. The microscopic examination of the sample must be done in parallel with other complementary assays for detection and identification of UGTIs. Pyuria is an important alert for GTIs, if the other results have excluded UTIs [1], [4], [16], [18], [69].

Microbiological cultivation is a gold standard for bacteriuria (within 24 hours). The use of different important culture media, including blood agar and MacConkey agar, is useful. Cultivation is an important tool for detecting and identifying different types of culturable pathogens. The results may show multimicrobial infectious diseases of UGTIs. However, this technique has its limitation regarding sample contamination, viable but non-culturable microorganisms, patients' skills in sampling, anatomical problems and disorders. Positive results of non-invasive and invasive specimens are recognized as 10^4 – 10^5 and 10^2 cfuU/ml, respectively [1], [4], [12], [16], [30], [31], [69].

The test strip is a kind of ELISA based on paper containing antibodies against microbial causative agents of UGTIs. The test strip covers the weak points of dipstick specificity. For detecting and identifying microbial causative agents of UGTIs, this assay is easy to do, effective, and inexpensive [69].

There is a wide range of biomarkers (immunomarkers) which can be used for recognition of UGTIs. For instance, C-reactive protein (CRP), interleukins, cytokines, chemokines, TLRs, antibodies and others are appropriate for the detection and identification of UGTIs [16], [47], [69].

Flow cytometry is a technique based on laser illumination and tracing the scattered beam. The results are obtained by measuring scattered light beams. In this method, the urine is directly checked for pathogenic microorganisms, red blood cells (RBCs) and white blood cells (WBC). The sensitivity and specificity of flow cytometry is around 90% and 65%, respectively. This technique can be used as a single screening tool for recognition of UGTIs, but the

cutoff of cfu/ml is individually determined for different microbial species and patient categories [1], [69].

Mass spectrophotometry is another routine technique for directly testing urine samples. Matrix-assisted laser desorption ionization time-of-flight mass spectrophotometry (MALDI TOF MS) can be used to identify Gram-negative and Gram-positive bacteria. The sensitivity and specificity of this technique are high for Gram-negative bacteria [69]. Thus, this technique is useful for UGTIs caused by Gram-negative bacteria.

The electromagnetic excitation and light scattering technique of infrared spectroscopy works on cultured samples of bacterial cells. The sensitivity and specificity of infrared spectroscopy for Gram-positive bacteria is 100%. This methodology is useful for determining multi-drug resistant (MDR) bacteria [69] and detection of UGTIs.

The isothermal microcalorimetry technique is a quick-time method for detection and identification of microbial agents of UGTIs. There is a specific cfu/ml limit for each microbial agent. Despite some advantages of isothermal microcalorimetry assay, this tool is dependent on cultivation [69].

The assays based on biosensors are effective, rapid, and have high specificity and sensitivity. This method is useful for directly testing urine samples. Biosensor-based technologies have limits for microbial cfu/ml; hence, it varies for different microbial species. The importance of this technique lies in its ability to differentiate between live and dead microbial cells. Biosensors are also able to detect MDR microbial species. The biosensor-based techniques must be set up for each microbial species [69]. Therefore, it seems that this technology may be useful for reliable detection and identification of UGTIs.

Today, there are wide ranges of nucleic-acid-based techniques including PCR, microarray and next-generation sequencing technologies. Given culturable microorganisms with a limited number of clinical samples, the molecular tool PCR is recommended. But in the case of large numbers of genes and samples, the use of an advanced pan-genomic technology such as microarray is unavoidable. Simultaneously, there are vast populations of microorganisms which are viable but non-culturable; these groups of microorganisms are recognized only through sequencing techniques, e.g., the 16s rRNA sequencing method. To have a real and accurate microbial pattern of related microorganisms including microbiota and pathogens, the employment of different technologies are recommended. In toto, the determination of microbial patterns to detect and identify microbial causative agents of UGTIs will be unavoidable in the near future. Thus, microbial biomarkers are our new options to provide high quality detection and identification of UGTIs [2], [3], [9], [10], [16], [17], [45], [68], [69], [70], [71].

Conclusion

UGTIs are one of the most common infectious diseases, which affects millions of people around the world. Despite

the global concerns about UGTIs both in terms of costs and public health systems, there are many problems associated with the UGTI detection, identification and definite treatment. Although familiarity with the clinical manifestations of UGTIs, the related predisposing factors, patient's private history, the application of gold standard and routine diagnostic methods is needed for successful detection, identification and definite treatment, there is still a dramatic lack of accuracy in the detection, identification and definite treatment of UGTIs. In recent years, advanced diagnostic techniques have become accessible but the level of diagnostic biases is high. Depending on the obtained microbial patterns for an individual's UGT, the application of advanced techniques comprising PCR, microarray and next-generation sequencing will be more effective together with the microbial pattern of an individual's UGT in providing quality detection, identification and definite treatment.

Notes

Conflicts of interest

The authors declare no conflicts of interest.

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Corresponding author:

Payam Behzadi
Department of Microbiology, College of Basic Sciences,
Shahr-e-Qods Branch, Islamic Azad University, Fath
Highway, Shahr-e-Qods, End of Shahid Kalhor Blvd, Post
Box: 37541-374, Tehran-Iran
behzadipayam@yahoo.com

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