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INFECTIONS

Urinary tract infections and *Candida albicans*

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Introduction Urinary tract candidiasis is known as the most frequent nosocomial fungal infection worldwide. *Candida albicans* is the most common cause of nosocomial fungal urinary tract infections; however, a rapid change in the distribution of *Candida* species is undergoing. Simultaneously, the increase of urinary tract candidiasis has led to the appearance of antifungal resistant *Candida* species. In this review, we have an in depth look into *Candida albicans* uropathogenesis and distribution of the three most frequent *Candida* species contributing to urinary tract candidiasis in different countries around the world.

Material and methods For writing this review, Google Scholar –a scholarly search engine– (http://scholar.google.com/) and PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/) were used. The most recently published original articles and reviews of literature relating to the first three *Candida* species causing urinary tract infections in different countries and the pathogenicity of *Candida albicans* were selected and studied.

Results Although some studies show rapid changes in the uropathogenesis of *Candida* species causing urinary tract infections in some countries, *Candida albicans* is still the most important cause of candidal urinary tract infections.

Conclusions Despite the ranking of *Candida albicans* as the dominant species for urinary tract candidiasis, specific changes have occurred in some countries. At this time, it is important to continue the surveillance related to *Candida* species causing urinary tract infections to prevent, control and treat urinary tract candidiasis in future.

Key Words: urinary tract infection ‹› *Candida albicans* ‹› *Candida glabrata* ‹› *Candida tropicalis*

INTRODUCTION

Anatomically, urinary tract infections (UTIs) –whether caused by fungi or bacteria– are categorized into two sections (lower and upper tract infections) which may occur in asymptomatic or symptomatic forms [1, 2].

Our knowledge about the incidence of candidal UTIs is obtained from diverse published reports in different countries worldwide, just like a puzzle which is completed by putting together puzzle pieces. It is important to control the pattern of etiologic microbial agents regularly in order to find new options to manage and prevent the related infections [3].

According to numerous investigations, *Candida* species and in particular, *Candida albicans* (*C.albicans*) are the most remarkable opportunistic pathogenic fungi causing nosocomial UTIs [4–7].

Candida albicans and non–*C.albicans Candida* (NACA) species are considered important parts of microbial normal flora in the oral cavity, alimentary canal and vagina in a vast range of the healthy people. Furthermore, they colonize on the external side of the urethral opening in premenopausal and healthy females. Immune deficiencies may lead to an imbalance between *C.albicans*, NACA yeasts and the other host normal flora. In this condition, the commensal yeasts of *Candida* may convert into opportunistic

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pathogenic microorganisms creating candidal UTIs in the host [5, 6, 8–12].
As shown in Table 1, there is a diverse range of predisposing factors causing UTI candidiasis [1, 2, 4, 6, 8, 11, 13, 14, 15].
The presence of *C.albicans* and NACA species in urine is known as candiduria, which may occur in both asymptomatic and symptomatic UTIs [6, 9].
Despite the high rate of morbidity in UTIs caused by *C.albicans,* the mortality is low. However, the rate of mortality in patients with systemic candidiasis and AIDS is high [6, 16].
Because of the importance of UTIs caused by *C.albicans,* the present paper is aimed to review the different attributes of yeast and related UTIs.

Candida albicans and virulence factors

C.albicans as a diploid dimorphic fungus ranks first for causing systemic candidiasis and fungal nosocomial UTIs worldwide. The shape flexibility, as in switching between yeast and filamentous forms, is one of the most well known pathogenic factors in the dimorphic fungus *C.albicans.* Additionally, there are several attributes such as adhesion, invasion, discharging hydrolytic enzymes, stereotropism (thigmotropism) and biofilm formation which are absolutely considered as pathogenic mechanisms pertaining to *C.albicans* [6, 16–20].

Candida albicans and polymorphism

Morphology of *C.albicans* determines the strategy of fungal colonization and infection. The three forms of *C.albicans* include spheroid–ovoid shape of single–celled budding yeast, loose septate pseudohyphae with an elongated ellipsoid appearance of the hyphae divisions as well as septate truehyphae. In accordance with recorded reports, yeast cells and true hyphae both directly contributed to UTI candidiasis and the pseudohyphal form of *C.albicans* is known as a switch construction of the fungus *in vivo* conditions. Therefore, an obvious morphological evolutionary pathway is seen in the life cycle of *C.albicans* [6, 10, 16, 19].
The filamentous form of *C.albicans* is an invasive morphology of the fungus which is observed in solid tissues, such as the kidneys, and is able to produce a huge amount of proteases. These enzymes are able to hydrolyze, disrupt and progress within the host tissues at an accelerated rate. In contrast, the yeast form of *C.albicans* with slight invasion ability is an effective pathogenic morphology for disseminating in different parts of mucosal membranes and liquid–form structures of the host [6, 16].

Table 1. *The predisposing factors causing UTI candidiasis*

Characteristic	Predisposing factors
UTI Candidiasis	Age, Gender (Women), Antibiotic consumption for a long period, Genetic inheritance, Sex activity, Diabetes, Immiunosuppression, AIDS, Pregnancy, Surgeries, Hypertension, Stone creation, Hospitalization, Indwelling medical devices such as Catheter or Prosthesis, Malnutrition, Low–level individual hygiene, Social behaviors, Unsuitable air conditioning, Peripheral milieu, Surfaces, and the Personnels' hands

Adhesion and invasion

In both life styles, including commensalism and pathogenesis, *C.albicans* utilizes a special set of proteins called adhesins to have successful adherence to the other cells of *C.albicans,* host cells or inanimate surfaces. Therefore, the first and essential factor for colonization of commensal or pathogenic strains of *C.albicans* is a strong attachment to prevent being washed away. Two sets of protein families belonging to *C.albicans,* including Als [agglutinin–like sequence (Als1–7 and Als9)] and Hwp1 (Hypha associated GPI–linked protein) adhesins, mediate the activity of adhesion in the filamentous form of *C.albicans.* Among Als proteins, the Als3 has the key role in adhesion. The aforementioned proteins are the products of *als* and *hwp1* genes, respectively [16, 17].
On the other hand, invasion is a natural mechanism in the hyphal structure of pathogenic strains of *C.albicans.* Generally, there are two complementary invasion processes in which invasins are mediated for invading host cells. These processes are consisted to trigger endocytosis and the Trojan Horse mechanism (hyphal active penetration) [16, 17, 21].
The triggered endocytosis mechanism is mediated by determined proteins on hyphal cells' surfaces called invasins. Invasins in both dead and living fungal cells are able to bind to host cells ligands, including E–cadherin on epithelial cells and N–cadherin on endothelial cells. The most important invasins involve Als3 and Ssa1 proteins. Als3 is an adhesin–invasin protein which is applied for adhesion and invasion in fungal hyphae of *C.albicans.* Furthermore, Ssa1 protein is a member of heat shock protein 70 (HSP70) which acts as an invasin in parallel with Als3 in *C.albicans* hyphal structures. It seems that the triggered endocytosic mechanism is necessary for the early steps of invasion [16, 17, 21].
The second mechanism, known as Trojan Horse (hyphal active penetration), occurs only in living cells to penetrate deeper into tissues. Pathogenic *C.albicans* possesses 10 secreted aspartic protease (Sap) isoen-

zymes. Saps 4–6 strongly mediate invasion mechanism of fungal hyphae via tissue penetration. According to reported data, penetration of *C.albicans* hyphae is facilitated by Saps 4–6 via hydrolyzation of surface proteins to create several openings throughout the host mucosal cells' surfaces. The integrins placed in the outermost layer of host epithelial cells are the main targets of Saps 4–6. Saps 4–6 bind to integrins to provide several gaps on the host cells for penetrating activity. This process, known as Trojan Horse mechanism, may lead to apoptosis of the host epithelial cells via the intralysosomal proteolytic activity of Saps 4–6 [16, 17, 21].

Stereotropism (thigmotropism) and biofilm formation

Direct contact or contact sensing is known as the main factor for inducing hyphal growth, thigmotropism and biofilm formation. Abiotic or biotic solid surfaces stimulate the performance of switching yeast single cells into filamentous hyphae, biofilm formation and invasion. According to different evidences, stereotropism and biofilm formation are known as important factors for pathogenicity in pathogenic strains of *C.albicans* [11, 16].

Candiduria

The presence of *Candida* spp. such as *C.albicans* in the urine is known as candiduria. Candiduria is categorized into asymptomatic (in healthy people or patients) and symptomatic forms. Symptomatic candiduria is seen in patients with cystitis, epididymorchitis, prostatis, pyelonephritis and renal candidiasis. However, asymptomatic candiduria is mostly benign and is not counted as a definite disease. *C.albicans* is one of the most important fungal agents which may lead to candiduria (20% of nosocomial infections). A wide range of reported data shows that *C.albicans* ranks first for causing candiduria among more than 200 *Candida* species [1, 6, 9, 22, 23, 24].
Symptomatic candiduria is normally seen in inpatients and asymptomatic candiduria is observed mostly in outpatients and healthy people. The prevalence of candiduria and the rate of its mortality between intensive care unit (ICU) inpatients is absolutely higher [9, 15, 22, 24, 25, 26].
Catheterization is recognized as the most common risk factor of candidura in ICU patients. There are several reports claiming significant increase in NACA species UTIs and candiduria. Despite it, the prevalence of UTIs and candiduria caused by *C.albicans* dominates NACA species infections. Table 2 shows the distribution of the three most frequent *Candida* species causing candiduria in some countries placed in different continents of America, Europe, Asia, Africa, and Australia respectively [1, 2, 4, 6, 9, 11, 12, 20, 24, 26–39].

Table 2. *Distribution of the first three Candida species in different countries*

USA [4]	51%	40%	8%
Brazil* [9, 12, 27]	42.63%	8.95%	14.05%
Argentina [28]	24.7%	18.7%	44.7%
France [18]	67%	22%	3%
Germany [35]	67.4	13.5	8.9
Poland [13]	46.5%	30.6%	5.7%
Slovakia [36]	61.7	–	6.3
Spain [18]	68%	8%	4%
Turkey [9, 30]	44%	18%	20%
Iran* [31, 32]	48.35%	23.45%	17.85%
India [33]	36.7%	13.76%	22.94%
Korea [37]	49.4%	7.2%	6.5%
China [38]	37.4%	28.9%	27.8%
Egypt [34]	34.5%	29.5%	18 %
Ethiopia [39]	42%	34.2%	15.8%
Ghana [29]	27.7%	35.5%	20.5%
Australia [36]	85.2	27.8	–
Average:	49.1	21.2	14.4

*Mean percentage

Until now, the three most common species among young and adult individuals are reported as *C.albicans, C.glabrata,* and *C.tropicalis,* respectively. However the rate of candiduria caused by *C.parapsilosis* is increasing among neonates [18].
The majority of people with candiduria show no clinical demonstrations or abnormalities. For this reason, the precise costs upon the medical health care society is not determined. On the other hand, the charges relating to candidemia resulted from chronic candiduria are calculated up to circa $39,000 for adult patients and $92,000 for children. Therefore, appropriate diagnostic methods and skillful personnel will help to decrease the unnecessary costs [18].

Candida Cystitis and pyelonephritis

The urinary bladder may also be infected by *Candida* spp. Normally, the urinary bladder is sterile, thus, the presence of *Candida* spp. may lead to Candida cystitis, which is known as a symptomatic lower UTI. Sometimes, Candida cystitis may lead to symptomatic candiduria. Candida cystitis is identified via symptoms of high urination frequency, dysuria and hematuria [18, 24, 25].

Candida pyelonephritis is a severe nosocomial upper UTI which may lead to candidemia and sepsis. The most predominant primary symptoms pertaining to candida pyelonephritis is reported as fever and candiduria [2, 24].

Genitourinary infections: Candidal Balanitis and vulvovaginal candidiasis

Although candidal balanitis (CB) is known as a sexually transmitted disease (STD), the number of studies relating to CB is not significant. Normally, in STDs such as CB (in the male gender) and vulvovaginal candidiasis (VVC) (in the female gender) both sexual partners are involved [6, 18].

VVC is a common fungal infection among 75% of women around the world and is often easy to treat. This infection correlates with individual hygiene, sexual activities and social behaviors [2, 40].

According to different studies (Table 2) in the USA, Brazil, Europe, Asia, north–east Africa (Egypt and Ethiopia) and Australia, the dominant *Candida* species is *Candida albicans*. However, the distribution of common NACA species causing UTIs, including *C.glabrata* and *C.tropicalis,* varies in the aforementioned regions (Table 2). Some studies indicate the increase of VVC by *C.glabrata* among elderly women [18].

The increase of candidiasis has led to the appearance of several antifungal drug resistant strains. Therefore, it is important to control the prevalence of candidal UTIs in determined intervals. CB and VVC are linked to each other and can be recognized by detecting it in one sexual partner [1, 40].

As the morbidity associated with CB and VVC is significantly high, gynecological consultation may lead to decreased incidence of genitourinary candidiasis in some cases. In clinical exams, the physical demonstrations and discharges of VVC are often helpful for an accurate diagnosis. In the case of CB, although the clinical demonstrations are nonspecific, it can be recognized by local erythema, papules and probable pustules together with pruritic signs and burning symptoms. The mortality rate among patients with CB and VVC without serious predisposing factors is low [6, 18].

Diagnosis of candidal UTIs

In the first step of candidal UTI diagnosis, it is important to find out whether the urine sample is contaminated or infected. Thus, there is no definite or standard method for detecting candidal UTIs immediately. However, there is a step–by–step approach for distinguishing candidal UTIs. The first positive urine culture must be repeated to make sure that the results are accurate. A 103–105 CFU/ml urine confirms the presence of candiduria in adults. If there is an accessible predisposing factor, such as a catheter, it must be cultured too. In the case of symptomatic UTIs, treatment is achieved in parallel with diagnosis. So if the administered antibiotics are not effective, it means that an antifungal drug like fluconazole must be administered as soon as possible. Normally, either urine or vaginal samples may be appropriate for diagnosing the infection. In many cases, clinical manifestations are helpful for a definite diagnosis between lower and upper candidal UTIs [18, 24, 25].

Treatment

Today, many types of oral and topical antifungal drugs are commercially available. Depending on candidiasis situations such as candiduria, cystitis, pyelonephritis, CB and VVC, the mycoses therapies differ in antifungal medications [9, 18, 25].

Among a vast range of antifungal drugs, the azole family is the largest one which inhibits lanesterol 14–β–demethylase activity. The enzyme is involved in the ergosterol biosynthesis pathway and its inactivity may lead to disruption of the fungal cell membrane [9].

In the case of candiduria, the application of antifungal therapy is absolutely dependedent on microscopic observations and growth cultures. According to the Infectious Diseases Society of America (IDSA) guidelines, asymptomatic candiduria in patients with no risk factors may be improved either spontaneously or via elimination of indwelling catheters. However, in patients with high risks, the oral use of fluconazole is necessary and unavoidable for preventing invasive candidiasis. Fluconazole is determined as an effective antifungal drug against candiduira caused by *C.albicans* in different age ranges. In the case of asymptomatic candiduria caused by Fluconazole–Resistant NACA (FRNACA) in patients with high risk, amphotericin B is administered. The antifungal therapy for symptomatic candiduria may be performed by fluconazole, but, the use of amphotericin B, with or without flucytosine, is recommended for treating symptomatic candiduria caused by FRNACA species. Either fluconazole or amphotericin B must be used daily for two weeks [9, 18, 24, 25].

Furthermore, the treatment of VVC and CB is successfully reported throughout topical application of azoles such as fluconazole. The treatment of VVC caused by FRNACA species is often achieved via gelatin capsules of vaginal boric acid, amphotericin B,

and/or flucytosine cream. In the case of recurrent VVC, itraconazole together with an oral and topical probiotic including *Lactobacillus acidophilus* is recommended [6, 9, 18, 40].

CONCLUSIONS

UTIs associated with Candida species and particularly *C.albicans* are known as a common multifacotrial nosocomial infections. In parallel with *C.albicans,* the NACA species are responsible for UTIs worldwide. Despite the increase in number of UTIs caused by NACA species, *C.albicans* still ranks first for fungal UTIs (Table 2). According to the outcomes of the present review, the first three important *Candida* species are *C.albicans, C.glabrata,* and *C.tropicalis,* respectively.

Genitourinary tract infections consist of different infections, including asymptomatic and symptomatic candiduria, cystitis, pyelonephritis, CB and VVC. Although there are different therapeutics and antifungal drugs against *Candida* species, the type of risk factors in patients is determinant.

The changes in the pattern of *Candida* species causing UTIs around the world show an urgent need for continuous and chained surveillance.

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