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TOPIC PAPER

Candida urinary tract infections in adults

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Abstract
Candiduria is commonly seen in hospitalized patients and most of the patients are asymptomatic, but it may be due to cystitis, pyelonephritis, prostatitis, epididymo-orchitis or disseminated candidiasis. Major risk factors are diabetes mellitus, indwelling urinary catheters, use of broad-spectrum antibiotics, urinary obstruction, and admission to intensive care units. *Candida* urinary tract infections can be caused by hematogenous spread following candidemia, or retrograde route via the urethra. The presence of *Candida* species in urine in asymptomatic patients does not warrant antifungal therapy except neutropenic patients, very low-birth-weight infants and patients undergoing urologic procedures. Fluconazole is the treatment of choice for symptomatic infections, it achieves high urinary levels. The other azole antifungals and echinocandins do not reach sufficient urine levels. Amphotericin B deoxycholate is the alternative antifungal agent if fluconazole can not be used because of resistance, allergy or failure.

Keywords Candiduria · Funguria · Candida · Candida urinary tract infection · Fluconazole · Amphotericin B

Introduction

Candida species are the most prevalent organisms among fungal urinary tract infections (UTIs). *Candida* UTIs are mostly seen in hospitalized patients, although they are less common in the community setting. Colonization or contamination is usually the most common cause in a patient with candiduria. It is important to distinguish whether this finding is just colonization or originated from a real *Candida* UTI. Unfortunately, there are no clearly established rules or guidelines for the diagnosis of *Candida* UTIs and also distinguishing infection from colonization. Antifungal therapy is generally not recommended in asymptomatic patients. It is sufficient to correct the underlying risk factors or, if possible, to remove or replace the catheter in patients with indwelling urinary catheters. A limited number of antifungal drugs can reach the desired concentrations in the urine.

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Epidemiology and risk factors

Candida spp. account for 1% of urine cultures positive for any pathogen in hospital laboratories (0.2% of all cultures evaluated) [1]. In a prospective multicenter study, the incidence of candiduria was found as 22% in critically ill patients admitted to medical intensive care units (ICU) for more than 7 days [2]. In the same study, in-hospital mortality was significantly higher in patients with candiduria compared to those without candiduria (48.8% vs 36.6%, $p < 0.001$). In a European multicenter survey on nosocomial urinary tract infections, *Candida* spp. are found to be one of the five most common isolated micro-organisms (12.9%, third rank) [3]. In another study evaluating the cultures of 1408 catheterized in-patients, *Candida* spp. were the second leading pathogen causing catheter-associated urinary tract infection or asymptomatic colonization [4]. Interestingly in a study from Australia, *Candida* spp. were the most common pathogen responsible for ICU-acquired positive urine cultures and illness severity was a risk factor for candiduria in the study population [5]. When we look at the renal transplant patients, the incidence of the candiduria is around 3.4–11% and usually most of them clinically asymptomatic [6, 7]. The occurrence of candiduria in chronically catheterized patients with spinal cord injury was found to be 17% (17 of 100 patients), and the presence of indwelling

urinary catheters (urethral or suprapubic) was significantly associated with candiduria; only one person on intermittent catheterization developed candiduria [8]. In a recent study, the incidence of candiduria in 400 clean-catch midstream urine specimens collected from type 2 diabetes patients was found as 10% and interestingly 87.5% of the patients were females [9]. Studies evaluating epidemiology of candiduria in different patient populations are summerized in Table 1.

In the case of candiduria, most physicians find it difficult to decide whether it is colonization or an infection that requires treatment because it is commonly seen in the normal microbial flora of the urogenital system and skin of healthy people. Candiduria is usually accepted as colonization or contamination by most of the physicians, but it may be the only sign of the invasive candidiasis. Outcomes of the 530 candiduria patients were evaluated in a multicenter prospective study by Kauffman et al. [10] and there were only 7 patients (1.3%) developed invasive candidiasis during the 10 weeks of follow-up. The authors concluded that candiduria was not a useful predictor for candidemia or disseminated candidiasis in their study patients. In another multicenter study performed in 24 French ICUs, candiduria and candidemia are evaluated prospectively [11]. Among the followed patients eighteen developed both ICU-acquired candidemia and candiduria, representing 31.6% of 57 candidemia patients and 7.7% of 233 candiduric patients. Interestingly, candiduria preceded candidemia in only 5 of 233 candiduric patients (2.1%) and candiduria was due to the same isolates in each case. In a retrospective study evaluating development of candidemia in candiduria in candiduric non-catheterized, nonintensive care unit patients with hematologic malignancies, the incidence of candidemia was 4% (1 of 24 patients) at 4 weeks of follow-up [12]. The risk of developing candidemia after candiduria, and also the molecular relatedness between isolates was evaluated in a 5-year period prospective study; 8% of the patients with candidemia had detected concomitant candiduria but in only 2.8% of candidemia patients had genetically similar *Candida* spp. in both blood and urine [13]. In a case–control study, Binelli et al. [14] found a significant association between candiduria and candidaemia, but the *Candida* isolates from urine and blood were different for 52% of the patients. In a nested case–control study performed by Safdar et al. [15] in 192 renal transplant patients with candiduria, candidemia was observed in 10 of them (5%). In a prospective multicenter cohort study, Blumberg et al. [16] found a positive predictive value of 2.7% for the development of candidemia in a patient with candiduria, and candiduria was not associated with an increased risk of subsequently developing bloodstream infection. Simpson et al. [17] compared morbidity and mortality in in-patients with asymptomatic funguria between those treated and those observed for funguria, they found that 2.7% of patients progressed invasive fungal infection and treatment for asymptomatic funguria in hospitalized adults did not impact morbidity or mortality. Candiduria itself is not a good predictor for candidemia or disseminated candidiasis, but some patient characteristics were evaluated in a study to differentiate patients with candiduria from those with concomitant candidemia. Wang et al. [18]. found that hospitalizations greater than 12 days, central venous catheter, parenteral nutrition, hematological and gynecological malignancy, and receipt of beta-lactam/

Table 1 Studies evaluating epidemiology of candiduria in different patient populations

Study	Study population and description	Definition of candiduria (cfu/ml)[a]	Frequency of Candiduria
Colodner et al. [1]	Prevalence of candiduria in urine samples from both community and hospitalized patients	$\geq 10^4$ women $\geq 5\times10^3$ men	0.2% of all samples 1% of culture positive samples
Padawer et al. [4]	Prevalence of catheter-associated candiduria in hospitalized patients	$\geq 10^4$	19.49%
Alvarez-Lerma et al. [2]	Incidence of candiduria in intensive care unit patients hospitalized > 7 days	$\geq 10^4$	22%
Bougnoux et al. [11]	Incidence, of nosocomial candiduria in intensive care unit patients	$\geq 10^{4b}$	27.4/1000 admissions
Delgado et al. [6]	Incidence of candiduria in renal transplant recipients	$\geq 5\times10^4$	3.4%
Denis et al. [7]	Incidence of candiduria in renal transplant recipients	$\geq 10^3$	2.3/100 person-year 4%
Safdar et al. [15]	Incidence of candiduria in renal transplant recipients	$\geq 10^3$	11%
Goetz et al. [8]	Occurance rate of candiduria in chronically catheterized patients with spinal cord injury	Not defined	17%
Esmailzadeh et al. [9]	Prevalence of candiduria in type 2 diabetes patients	$\geq 10^3$ $\geq 10^4$	10% 7%

[a]cfu/ml: colony forming unit per mililiter of urine

[b]Quantitative urine cultures were available in 61% of patients, and 86% of them had *Candida* growth of $\geq 10^4$ cfu/ml

beta-lactamase inhibitors are predictors for increased risk of candidemia in patients with candiduria

When we evaluate the *Candida* spp. causing candiduria, *C. albicans* is the most common and it is followed by *C. glabrata*, *C. tropicalis*, and *C. parapsilosis* [4, 10, 11, 19, 20]. Previous treatment with azole antifungals is an independent risk factor for isolation of non-albicans *Candida* spp. *C. glabrata* has a special significance because it may be resistant to fluconazole or may be susceptible to higher dosages of fluconazole [21]. Particularly in renal transplantation patients, *C. glabrata* seems more prevalent than other isolates [6, 7]. *C. parapsilosis* frequently causes candiduria in neonates and pediatric patients. *C. kruzei* is intrinsically resistant to fluconazole and *C. lusitaniae* may also develop intrinsically resistance to Amphotericin B (AmB). In some of the candiduria cases, more than one species of *Candida* may be isolated at the same specimen. *Candida auris* is an emerging isolate with its nosocomial dissemination in hospital wards and its multiple antifungal drug resistance [22].

Risk factors for the development of candiduria and *Candida* UTIs have been evaluated in many studies, and important risk factors are summarized in Table 2. *Candida* spp. are usually isolated from individuals characterized by prolonged or frequent antimicrobial use, diabetes mellitus, urinary indwelling catheters [2, 4, 8, 10, 11, 23]. Broad-spectrum antibiotics suppress the gastrointestinal and genital flora and cause *Candida* colonization predisposing to candiduria. The indwelling catheters breach the physiological and microbiologic barriers and ease the entry of microorganisms including *Candida* spp. [24]. ICU admission is another important risk factor for candiduria, probably because of high antimicrobial exposure [2, 11]. It is clearly shown that *Candida* spp. were more frequently isolated in ICU- than in non-ICU acquired UTIs [5, 25]. Urinary tract abnormalities causing obstruction or incomplete emptying of the bladder are also important risk factors [10]. Candiduria is usually more prevalent in females because of the shorter urethra and a high likelihood of vulvo-vestibular colonization with *Candida* [18, 26]. Colodner et al. [1] compared the risk factors between hospital and community-acquired candiduria: younger age, pregnancy, and bedridden patients were more prevalent in community-acquired candiduria.

Table 2 Risk factors for candida urinary tract infections [2–5, 8, 10, 11, 18, 20, 23, 26]

Diabetes mellitus
Urinary indwelling catheters
Antibiotics
Urinary tract abnormalities making obstruction or incomplete emptying of the bladder
ICU admission
Urinary tract surgery
Obstructive uropathy/lithiasis
Advanced age (> 65)
Renal transplantation
Female sex
Major abdominal surgery
Total parenteral nutrition
Mechanical ventilation
Immunosuppression
Malignancy

Clinical manifestations

Presence of *Candida* in urine may be due to:

- Contamination of the urine sample
- Colonisation of the bladder or urinary catheters
- Urinary tract infection
    - Cystitis
    - Pyelonephritis
    - Renal candidiasis, arising from hematogenous dissemination
    - Fungus ball (bladder or pelvicalyceal)
- Manifestation of candidemia without urinary tract infection
- *Candida* prostatitis
- *Candida* epididymo-orchitis
- Emphysematous pyelonephritis or cystitis (extremely rare conditions in adults)

There are two main mechanisms for the invasion of the urinary tract by *Candida* spp; one is hematogenous dissemination to kidneys (antegrade infection), and the other is ascending route through urethra and bladder (retrograde infection) [24]. The ascending infection of the upper urinary tract is rare and the risk increases with obstruction, diabetes mellitus or reflux [24, 27]. Patients with candiduria are usually asymptomatic because most of them do not have true *Candida* UTIs. In a prospective observational multicenter study, only 2–4% of the patients with funguria had dysuria, frequency, urgency, flank pain, or hematuria suggesting UTIs [10]. Even in renal transplant patients with candiduria most of them are asymptomatic; dysuria and suprapubic pain were seen in 6% and 4% of patients, respectively [28]. Compared to nosocomial candiduria significantly more patients with community-acquired candiduria may present with abdominal pain or dysuria (54% vs 11%, respectively) [1]. Most of the candiduric patients with the urinary indwelling catheters are asymptomatic and, clinical features are usually not specific in symptomatic ones. Moreover, fever and leukocytosis in candiduric ICU patients may be due to several other causes.

The symptomatic patients with lower UTIs may present with dysuria, urgency, frequency and suprapubic pain, which are indistinguishable from bacterial UTIs. Patients who have *Candida* pyelonephritis presents with fever, flank pain and dysuria [20]. As we discussed before, the risk of development of candidemia in asymptomatic candiduric patients is low, but the presence of urinary tract obstruction or surgical intervention significantly increases the risk of upper urinary tract infection and candidemia [29–32]. Ang et al. [32] retrospectively evaluated 26 cases of candidemia associated with urinary tract source and, they found that 88% had urinary abnormalities, 73% had urinary tract obstruction and 83% had undergone urinary tract procedures before the onset of candidemia. Beck et al. [33] reported 2 patients with liver cirrhosis who underwent ureteroscopy and holmium laser lithotripsy and developed life-threatening fungal sepsis, both patients had indwelling ureteral stents and negative preoperative urine cultures. Again, candiduria can be seen in a patient with candidemia or disseminated candidiasis, but the urinary tract is usually not the source for the candidaemia [14]. Hematogenous seeding of renal parenchyma can occur during candidemia but these patients usually do not have typical urinary tract symptoms but other systemic findings [20]. Fungus balls may cause obstruction and present with flank pain, hematuria, urinary retention and even may present with urosepsis [34–36].

Candida prostatitis and epididymo-orchitis may clinically present with similar symptoms to bacterial infections [37]. Epididymo-orchitis is an uncommon manifestation of *Candida* UTIs, patients are usually elderly, and have risk factors for candiduria such as diabetes mellitus, bladder instrumentation, urinary outflow obstruction, previous broad-spectrum antibiotic therapy, or HIV infection [38]. *Candida* epididymo-orchitis may present like bacterial infections but tends to be bilateral and comes with more prolonged symptoms ranging from 5 days to 5 months. *Candida* prostatitis can cause lower urinary tract symptoms, mimic prostate cancer, co-exist with prostate cancer, sexual dysfunction, and rarely presents with acute abscess [37, 39].

Laboratory testing and imaging studies

Definition of candiduria is not standardized and in most of the studies, it is accepted as at least one culture of urine that yielded $\geq 1\times10^3$ to $>1\times10^4$ *Candida* colonies/ml in different study populations and risk groups (ICU, nosocomial, community-acquired, diabetic, renal transplantation, hematological malignancy, with or without urinary catheters, etc.) [1–4, 6, 7, 9, 10, 12, 15, 40]. It seems that the growth of at least one culture of urine that yielded $\geq 1\times10^3$ colonies/ml usually accepted as candiduria in most of the studies. The *Candida* colony counts in urine culture also do not help to differentiate the contamination, colonization, or infection. In many studies fungal–bacterial coinfection and colonization are not uncommon [4]. The detection of budding yeast, hyphae, or pseudohyphae in direct examination of urine samples may be a clue for candiduria, but again this findings usually do not change the approach of physicians to their patients. In a study evaluating 146 catheter-associated candiduria patients, *Candida* spp. were visible in the urine sediment of 41 patients (28%), and 48 patients (33%) had leukocytes in their urine samples [4]. In another study evaluating candiduric patients who are mostly asymptomatic, the presence of yeasts in urine samples was noted as high as 60% and the presence of pyuria was 55% [10]. Like the presence of fungal elements in urinalysis, pyuria is also not a good sign of UTIs in candiduric patients [37, 41]. The presence of pyuria may suggest *Candida* UTIs in candiduric patients without urinary indwelling catheters, but in asymptomatic patients with urinary indwelling catheters, pyuria is usually a nonspecific finding.

Candiduria is the most common laboratory finding of *Candida* epididymo-orchitis. Pyuria and yeast in urine microscopy are also common but usually nonspecific findings. Blood cultures (in cases with systemic symptoms), early urology consultation, and scrotal ultrasonography are usually recommended to detect abscess formation, dissemination, and other complications [38]. In cases of *Candida* prostatitis, post-massage urine culture is usually recommended, and even a comparison of *Candida* colony counts in the urine cultures collected before and after prostatic massage is very useful [37, 42]. *Candida* prostatitis with negative urine culture is not uncommon, in such cases transurethral or transrectal drainage or biopsy is the most helpful diagnostic approach [39].

Ultrasonography is usually the first choice imaging study in *Candida* UTIs, and computed tomography is preferred in selected patients [37]. Imaging studies can be used to detect pyelonephritis, renal or perinephric abscesses, obstruction at any level in the urinary tract, fungus balls, and to evaluate prostate and epididymis. Excretory urography or retrograde pyelography can be used to diagnose fungus balls. Upper urinary tract fungus balls (*Candida* bezoars) may cause obstruction with imaging features of the simultaneous presence of a low-density filling defect, calcified areas, and gas bubbles [43]. Imaging studies are also indicated in patients not responding to antifungal treatment to evaluate complicating factors. Patients with persistent candiduria should be evaluated for urinary retention by postvoid residual test [26].

Therapeutic approach

Therapeutic approaches to asymptomatic and symptomatic patients with candiduria are summerized in Tables 3 and 4. In patients with asymptomatic candiduria, it is usually

recommended to exclude contamination first [20, 26, 27, 37, 44]. Contamination can be ruled out by repeating the urine culture 1 or 2 days later in patients without urinary indwelling catheters. In elderly women and patients who can not provide a clean-catch urine sample, a second sample can be taken by catheterization. If the repeat cultures

Table 3 Summary of the treatment approaches in patients with asymptomatic candiduria

Conditions	Antifungal treatment	Recommendations
Detection of candiduria in an asymptomatic non-catheterized patient	No	Repeating urine culture 1–2 days later to rule out contamination
Asymptomatic patients with candiduria and urinary indwelling catheters	No	Change catheter Repeat urine culture on next day
Persistence of candiduria after changing catheter in an asymptomatic patient	No	Evaluate and remove predisposing factors: Remove catheter if possible Control blood sugar Treat obstruction Stop antibiotics Urinary system imaging may be considered
Asymptomatic candiduria patients without any known risk factors	No	Follow with urine cultures Most of them resolve within weeks to months
Asymptomatic candiduria in renal transplant recipients	No	Try to remove predisposing factors Antifungal treatment is not recommended
Asymptomatic candiduria patients with high risk of developing candidemia	Yes	Neutropenic patients Patients exposed to urological manipulations Very low-birth-weight infants (< 1500 g)
Asymptomatic candiduria in patients undergoing urological manipulations	Yes	Fluconazole 400 mg daily, or 6 mg/kg or deoxycholate Amphotericin B 0.3–0.6 mg/kg daily, several days before and after the procedure

Table 4 Summary of the treatment approaches in patients with symptomatic urinary tract infections caused by *Candida* species

Conditions	Treatment recommendations
Symptomatic urinary tract infections	Fluconazole is usually the drug of choice Deoxycholate Amphotericin B is recommended in fluconazole resistance Flucytosine is an alternative, not available in many countries Removal of indwelling catheters is recommended if possible Amphotericin B irrigation in selected patients
Candida cystitis	Oral fluconazole, 400 mg loading, 200 mg (3 mg/kg) daily for 14 days In case of fluconazole resistance: Deoxycholate Amphotericin B, 0.3–0.6 mg/kg daily for 1–7 days Oral flucytosine, 25 mg/kg 4 times daily for 7–10 days Amphotericin B bladder irrigation (the procedure is described in the text)
Ascending *Candida* pyelonephritis	Fluconazole 400–800 mg loading, then 200–400 mg daily (3–6 mg/kg), for 14 days In case of fluconazole resistance: Deoxycholate Amphotericin B 0.3–0.6 mg/kg daily for 1–7 days ± flucytosine
Candida fungus ball	Surgery Systemic antifungal agents like in cystitis or pyelonephritis Amphotericin B irrigation from nephrostomy tubes as described in the text
Candida prostatitis	Surgery and systemic antifungals Deoxycholate Amphotericin B is mostly used in case reports Fluconazole can also be used
Candida epididymo-orchitis	Surgery and systemic antifungals: Fluconazole or Amphotericin B (see text for details based on case reports)
Symptomatic *Candida* urinary tract infections in pregnancy	Deoxycholate Amphotericin B is the drug of choice Fluconazole may cause congenital anomalies and spontaneous abortion, it is not recommended Flucytosine was shown to be teratogenic in rats

are negative for *Candida* spp. then it is accepted as contamination. In asymptomatic patients with urinary indwelling catheters, repeat culture should be done the next day after changing the catheter. If the repeat culture is negative additional diagnostic or therapeutic approaches are not recommended. Persistence of candiduria in asymptomatic patients requires the assessment of predisposing factors. The elimination of predisposing factors such as removal of the bladder catheter is usually sufficient for treatment and antifungal agents are not recommended [10]. Asymptomatic patients without any known risk factors should be followed with urine cultures, candiduria will resolve in most of them within weeks to months without antifungal treatment [10, 21, 40]. Treatment with antifungal agents in asymptomatic candiduria is recommended only in patients at high risk of developing candidemia; these are neutropenic patients, patients exposed to urological manipulations, and very low-birth-weight infants (< 1500 g). For the patients undergoing urologic procedures, fluconazole (400 mg daily, or 6 mg/kg) is usually recommended for several days before and after the procedure [21].

Treatment of asymptomatic candiduria in renal transplant recipients is also not recommended, treatment in such patients does not appear to result in improved outcomes [15]. Unnecessary antifungal treatment increases the risk of antifungal resistance and adverse drug events. Unfortunately, overtreatment of asymptomatic candiduria is frequently seen in daily clinical practice. Jacobs et al. [45] found that approximately half of the candiduric in-hospital patients were inappropriately managed in accordance with guidelines, and such patients also had an increased incidence of re-hospitalization. Asymptomatic outpatients with persistent candiduria who have underlying risk factors, again removal of the predisposing factors (controlling blood sugar, removal of bladder catheter, treatment of obstruction or urological abnormality, discontinuation of antibiotics) is usually sufficient and no antifungal treatment is not needed [44].

Both in hospitalized and outpatient asymptomatic candiduric patients who also have predisposing conditions (indwelling urinary catheter, diabetes mellitus, etc.), many studies showed that antifungal treatment did not reduce morbidity or mortality, and did not increase the resolution rate of candiduria [10, 15, 17, 40]. In patients with solid evidence of renal involvement or systemic dissemination, treatment can be considered [44]. Imaging of urinary system, evaluation of risk factors for invasive candidiasis, blood cultures, and culture of other non-sterile body sites and ophthalmologic examination are some recommended procedures [26, 44]. The presence of *Candida* colonization at multiple body sites (urine, respiratory secretions, oral, rectal, inguinal) may be an important clue for invasive candidiasis. The *Candida* score and colonization index are used to discriminate *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients, and multiple body site colonization is an important parameter of these methods [46–48]. In severely ill febrile non-neutropenic ICU patients empirical antifungal treatment can be recommended if they have risk factors for invasive candidiasis (such as the growth of *Candida* in multiple nonsterile body sites and no other explanation of fever [21].

For the treatment of symptomatic *Candida* UTIs fluconazole is usually the drug of choice because of its well tolerability, high oral bioavailability, and excretion to urine in high amounts by the kidneys reaching 10–20 times of the serum concentrations [20, 21, 26, 40, 44]. Approximately 80% of a fluconazole dose is eliminated as unchanged drug in the urine. Some of the major disadvantages of fluconazole are drug–drug interactions, liver toxicity, prolongation of QT interval and resistance with some *Candida* isolates such as *C. glabrata* and *C. krusei*. In case of *C. glabrata* growth, antifungal susceptibility tests should be requested if possible, high-dose (800 mg/day) fluconazole treatment may be successful, but AmB should be used if the isolate is resistant to fluconazole [20, 21, 49]. Other azole antifungals are not excreted into the urine as an active drug (itraconazole concentration < 1%, voriconazole concentration < 5%, posaconazole concentration < 1%) and they are not useful for the treatment of cystitis [44]. Urine elimination of isavuconazole is also negligible, and this agent is also unlikely to be useful for the treatment of urinary tract infections [50]. On the other hand posaconazole and voriconazole can concentrate well in kidney tissue and they may be effective in *Candida* renal parenchymal infections [44]. Echinocandins (caspofungin, anidulafungin, and micafungin) are also not recommended in the first-line treatment of urinary tract infections, all three exhibit low concentrations (< 2% of the dose) of unchanged drug in human urine, but they may reach high concentrations in renal parenchyma [51]. There are a limited number of case reports showing the success of echinocandins in the salvage treatment of complicated urinary tract infections [52–54]. Urinary system penetration of antifungal agents are simply summerized in Table 5.

Renal excretion of lipid formulated AmB preparations are also low compared to deoxycholate AmB, Infectious Diseases Society of America (IDSA) recommends deoxycholate AmB but not lipid formulations for the treatment of *Candida* UTI [21, 51]. Side effects (nephrotoxicity, chills, fever, dyspnea, hypokalemia) and low tolerability by the patients is a major problem with deoxycholate AmB. Deoxycholate AmB irrigation is an alternative treatment in patients with cystitis and urinary fungus ball (50 mg amphotericin B deoxycholate in 1 l sterile water, and instillation is done through an indwelling triple-lumen urinary catheter, for 5 days). It is usually preferred in patients who can not be treated with systemic antifungals due to intolerance, drug side effects or infection with resistant organisms. Deoxycholate AmB

Table 5 Urinary system penetration of antifungal agents

Antifungal agent	Urine concentration of active drug and use in lower urinary tract infections	Renal parenchymal concentration
Deoxycholate Amphotericin B	Good Recommended	Good Recommended in ascending *Candida* pyelonephritis
Lipid formulated Amphotericin B	Poor Not recommended	Good[a]
Fluconazole	Good Recommended	Good Recommended in ascending *Candida* pyelonephritis
Other azole antifungals: Voriconazole, Posaconazole, Isavuconazole, and Itraconazole	Poor Not recommended	Good[a]
Echinocandins: Caspofungin, Anidulafungin, and Mycofungin	Poor Not recommended	Good[a]
Flucytosine	Good Recommended	Good Recommended in ascending *Candida* pyelonephritis

[a]The renal parenchymal concentrations of these agents are also good, they are currently not recommended in ascending *Candida* pyelonephritis. However some case reports suggest that they may be successful in the treatment of renal parenchymal *Candida* infection following candidemia

can be applied as continuous irrigation into the bladder via a triple-lumen urinary catheter or as intermittent irrigation (the drug is administered to the bladder with a single lumen catheter, 4–6 times per day and clamping is performed for 30–60 min each time, a solution of drug containing 50 mg amphotericin B deoxycholate in 1 l of sterile water will be prepared, 100 ml of this solution will be used in each intermittent irrigation) [20, 21, 49, 55, 56]. Flucytosine is used orally but it is not available in many countries, it can be used for the treatment of cystitis or pyelonephritis. Major disadvantages are the risk of development of resistance when used alone for more than a week and side effects like hepatotoxicity and bone marrow toxicity [44].

Oral fluconazole is the drug of choice for the treatment of *Candida* cysititis usually for a duration of 14 days (400 mg loading dose, 200 mg (3 mg/kg) daily), removal of indwelling bladder catheter is usually recommended if feasible. Oral flucytosine (25 mg/kg 4 times daily for 7–10 days) and parenteral deoxycholate AmB (0.3–0.6 mg/kg daily for 1–7 days) is usually the alternative drugs. For the treatment of ascending *Candida* pyelonephritis fluconazole is again the drug of choice and should be given for 2 weeks 400–800 mg loading dose, then 200–400 mg daily (3–6 mg/kg). Removal or replacement of nephrostomy tubes or stents, if it is possible, is also recommended. For the treatment of urinary fungus balls, surgical intervention and systemic antifungal treatment are usually recommended until it resolves, in patients with nephrostomy tubes irrigation with AmB can also be added. In a study, fluconazole irrigation of bladder is also shown to be successful in the treatment of renal fungal ball [57]. The combination of surgical intervention and systemic antifungal is the recommended approach in the treatment of *Candida* prostatitis. Deoxycholate AmB is the most commonly used antifungal agent, and fluconazole can also be used [39, 44]. The treatment of *Candida* epididymo-orchitis is mostly based on case reports, surgical intervention in conjunction with fluconazole is usually the recommended treatment. Jenkin et al. recommended surgery and 2 weeks of fluconazole therapy postoperatively, if surgical intervention is not performed they recommend a 6-week course of systemic antifungal therapy. AmB with or without flucytosine may be used alternatively if fluconazole resistance is likely or determined [38, 44].

If candidemia is detected in a patient with candiduria, the hemodynamic status of the patient should be evaluated and the history of azole exposure should be questioned. Fluconazole can be given if the patient is hemodynamically stable, not septic and has no history of recent azole exposure. If the patient is septic or has recently exposed to azole antifungals the drug of choice is echinocandins. If the patient is stable and the isolate is susceptible to fluconazole, we can replace echinocandin with fluconazole on the fifth day of treatment [21].

Candiduria in a pregnant woman should be evaluated carefully. Vaginal candidiasis is more common in pregnant women than in non-pregnant women [58]. Therefore, the possibility of contamination of the urine sample by vaginal secretions should be considered in pregnant women. In the literature, we have hardly found any information about the incidence or epidemiology of *Candida* UTIs in pregnant women. A very limited number of antifungal agents can be used safely in pregnant women with invasive or disseminated *Candida* infections. AmB is considered the antifungal of choice in pregnancy for invasive fungal infections [21, 59]. Fluconazole may cause congenital anomalies and spontaneous abortion when used in pregnancy and its use in pregnancy is not recommended. Voriconazole is also teratogenic and its use is contraindicated in pregnancy. Echinocandins (caspofungin, anidulafungin, and micafungin) revealed embryotoxic effects in animal studies and are not

considered safe during pregnancy. Flucytosine was shown to be teratogenic in rats [59].

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