Diagnosis and Management of Fungal Urinary Tract Infection

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KEYWORDS

• Candida • Fungal urinary tract infection • Fungus ball • Cystitis • Pyelonephritis • Fluconazole • Amphotericin B • Flucytosine

KEY POINTS

- Most patients with candiduria are asymptomatic. Candidemia rarely results from asymptomatic candiduria.
- The most common risk factors for candiduria are increased age, female sex, antibiotic use, urinary drainage devices, prior surgical procedures, and diabetes mellitus.
- Treatment is indicated only for the following groups with asymptomatic candiduria: very low birth weight infants, patients undergoing urinary tract procedures, and neutropenic patients. The vast majority of patients should not be treated.
- Patients who have symptoms of urinary tract infection should be treated. The treatment of choice is oral fluconazole. Amphotericin B and fluctyosine are less desirable alternatives, and there is little role for amphotericin B bladder irrigation.
- Other antifungal agents, such as voriconazole, posaconazole, and the echinocandins, cannot be recommended for *Candida* urinary tract infections because very little active drug is found in the urine.

INTRODUCTION

When the terms funguria or fungal urinary tract infection are used, most physicians are referring to candiduria and urinary tract infections due to *Candida* species. Other fungi, including yeasts, such as *Cryptococcus neoformans* and *Trichosporon asahii*, and molds, such as *Aspergillus* species and members of the Mucorales, can involve the kidney during the course of disseminated infection, but rarely cause symptoms referable to the urinary tract.[1,2] Among the major dimorphic fungi, *Blastomyces dermatitidis* not uncommonly causes symptomatic prostatic infection, and both *B dermatitidis* and *Histoplasma capsulatum* can cause epididymo-orchitis, but typical urinary tract infections are not seen. *Candida* species appear to be unique in their ability to both colonize and cause invasive disease in the urinary tract.[3] This overview focuses only on candiduria and *Candida* urinary tract infection because they are common and many times present perplexing management issues.

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Infect Dis Clin N Am 28 (2014) 61–74
http://dx.doi.org/10.1016/j.idc.2013.09.004 **id.theclinics.com**
0891-5520/14/$ – see front matter Published by Elsevier Inc.

EPIDEMIOLOGY

Candida species normally inhabit the gastrointestinal tract, the genital tract, and the skin of humans. Urine rarely yields *Candida* species in persons who do not have specific risk factors allowing the organism to gain ingress into and colonize the bladder mucosa. Hospitalized patients, especially those in the intensive care unit (ICU) acquire many risk factors during hospitalization, and candiduria is a common finding. A 1-day, point-prevalence survey of urine cultures obtained from hospitalized patients in hospitals throughout Europe found that *Candida* species were the third most common organism isolated from urine after *Escherichia coli* and *Enterococcus* species.[4]

A large multicenter surveillance study assessed 861 hospitalized patients with candiduria and found several very common risk factors, including urinary drainage devices in 83%, diabetes in 39%, and urinary tract abnormalities in 37%.[5] In an ICU setting, a multicenter study from Spain noted the following independent risk factors for candiduria: age older than 65 years, female sex, diabetes mellitus, prior antibiotics, mechanical ventilation, parenteral nutrition, and length of hospital stay.[6] Although studies are few, risk factors for candiduria for those in the community are similar to those in hospitalized patients, namely diabetes, indwelling urinary catheters, and antibiotics (**Box 1**).[7]

Although there often is concern that candiduria will lead to candidemia, this is uncommon in the absence of obstruction or urinary tract instrumentation. In the large prospective surveillance study noted previously, only 7 (1.3%) of 530 candiduric patients who were followed for 10 weeks developed candidemia.[5] Similarly, in an ICU setting from France, only 5 of 233 patients who had candiduria developed candidemia due to the same species 2 to 15 days later.[8] In another study from Brazil, comparison by genotyping of paired candiduric and candidemic isolates from individual patients showed no relationship in more than half of the patients.[9]

Several studies in ICU populations have reported that patients who have candiduria have increased mortality rates when compared with similar patients without candiduria.[6,8] In none of these studies was it shown that candiduria led to candidemia, which then caused the death of the patient. Others have documented the trend to increasing mortality in non-ICU hospitalized patients with candiduria[10,11] and have also reported that treatment had no effect on mortality rates.[10] It seems likely that candiduria is a marker for a seriously ill patient who requires indwelling devices for monitoring and treating underlying illnesses.

Box 1
Risk factors predisposing to candiduria[a]

- Older age
- Female sex
- Diabetes mellitus
- Antibiotic use
- Urinary tract obstruction
- Urinary tract surgery/instrumentation
- Urinary drainage device

[a] Most patients have several predisposing factors.

PATHOGENESIS

Candida species cause urinary tract infection by either the hematogenous or ascending routes. Most kidney infection occurs by hematogenous seeding during an episode of candidemia, but this event is usually asymptomatic with regard to urinary tract symptoms. Many studies in experimental animals have found that multiple microabscesses develop throughout the cortex after intravenous administration of *Candida albicans*.[12] The organisms penetrate through the glomeruli into the proximal tubules, and then are shed into the urine.[13] Most animals were able to clear *Candida* from the kidney within several weeks. Autopsy studies note renal cortical microabscesses in most patients who die with invasive candidiasis.[14]

The pathogenesis of ascending infection with *Candida* has not been studied in depth.[15] *Candida* strains found in the vagina are genetically related to the strains that cause candiduria in women with indwelling bladder catheters.[16] Presumably spread from the perineum into the bladder leads to colonization, and then retrograde spread occurs into the collecting system of the kidney.[12] The presence of an indwelling catheter allows for biofilm formation and persistence of the organism.[15] This has been shown for several species of *Candida*, but appears to be less likely with *Candida glabrata*.[12,17] Formation of fungus balls is a complication that leads to obstruction and great difficulty in eradicating the organism. The pathogenesis of fungus ball formation likely is tied to biofilm formation, allowing persistence of the organism.[15]

MICROBIOLOGICAL ASPECTS

There are no distinguishing characteristics of urinary tract infections because of the different *Candida* species. Most infections are due to *C albicans*; overall, this species accounts for 50% to 70% of isolates.[4–6,18] *C glabrata* is the second most common cause of urinary tract infections in most series,[18] but *Candida tropicalis* is the second most common species in some centers.[9,19] *Candida parapsilosis, Candida krusei*, and other unusual *Candida* species are less commonly found in urine (**Table 1**).

Certain types of patients have a higher risk of developing *C glabrata* urinary tract infection. These include patients with hematological malignancies and transplant recipients. In the largest prospective series of kidney transplant recipients who had *Candida* urinary tract infections, approximately 50% of all isolates were *C glabrata* and 30% were *C albicans*.[20] A study among hospitalized patients who had indwelling

Table 1
***Candida* species causing candiduria and urinary tract infections**

Species	Comments
Candida albicans	Most common colonizing and infecting species (50%–70% in most series); most strains fluconazole susceptible
Candida glabrata	Second or third most common species (10%–35%, depends on geography); most common in older adults, uncommon in children; most strains fluconazole resistant
Candida tropicalis	Second or third most common species (10%–35%, depends on geography); most strains fluconazole susceptible
Candida parapsilosis	Uncommon in urine (1%–7%); common cause of central line–associated candidemia and neonatal candidiasis; most strains fluconazole susceptible
Candida krusei	Uncommon in urine (1%–2%); innately fluconazole resistant

bladder catheters found that independent risk factors for *C glabrata* candiduria were diabetes, ICU admission, and prior treatment with antibiotics and with fluconazole.[21] *C glabrata* has a distinct age distribution for both candidemia and urinary tract colonization and infection. It is most common in older adults and very uncommon in neonates and young children.[22,23]

DIAGNOSIS

General Principles

The most difficult task when faced with a patient with candiduria is deciding whether this finding represents a contaminated urine sample, an organism colonizing the bladder and/or catheter, or an infection of the upper or lower urinary tract. Additionally, candiduria may be a manifestation of candidemia rather than just a cardinal sign of a urinary tract infection. There are not sensitive diagnostic criteria available to help one sort through these different possibilities, and clinical judgment must be relied on in many circumstances.

Approach to the Patient With Candiduria

The initial task is to decide if the presence of candiduria represents contamination of the sample (**Box 2**).[24] It is wise to first repeat the culture, being certain that a clean-catch midstream urine has been obtained. If the second sample does not yield

Box 2
Approach to the patient with candiduria

- Asymptomatic patient
  - Repeat clean-catch urine culture to be sure not a contaminant
    - If cannot obtain clean-catch urine, obtain urine by catheterization
  - Candida grows on repeat culture: correct predisposing factors (stop antibiotics, remove catheter)
    - Repeat urine culture after correct predisposing factors
  - Culture remains positive: obtain ultrasound to look for obstruction
    - No obstruction: observe and do not treat
    - Obstruction present: urology consultation
      - Treat with fluconazole if procedure performed to correct obstruction
- Lower urinary tract symptoms: dysuria, frequency, urgency
  - Culture urine for bacteria: if present, treat with appropriate antibiotic
  - No bacteriuria or persistent symptoms after treatment with antibiotic: obtain ultrasound to look for obstruction and treat with fluconazole
    - Obstruction present: urology consultation
- Upper urinary tract symptoms: fever, flank pain
  - Culture urine for bacteria: if present, treat with appropriate antibiotic
  - No bacteriuria or persistent symptoms after treatment with antibiotic: obtain ultrasound to look for obstruction and treat with fluconazole
    - Obstruction present: urology consultation
    - Obtain blood cultures to look for candidemia

organisms, then candiduria reflected contamination only and no further workup need be done. If the patient is unable to perform a clean-catch midstream urine collection, sterile bladder catheterization should be performed to obtain a sample.

In patients who have candiduria and who have an indwelling urinary catheter, the catheter should be discontinued, if feasible, and then a second sample obtained several days later to see if the candiduria has disappeared. If so, no further studies need be done. In patients in whom a catheter is required, the catheter should be replaced and a urine sample collected through the new catheter. If candiduria disappears, the first sample merely reflected colonization and no further workup is needed.

Many patients will have persistent candiduria, and in these patients, the problem is to define whether they have bladder colonization, cystitis, or upper tract infection. Clinical manifestations sometimes can be useful in establishing whether the patient has a *Candida* urinary tract infection. Laboratory studies also are of some help, but there are overlapping findings in patients who have colonization with no need for treatment and those with a urinary tract infection who do need to be treated.

Clinical Manifestations

Most patients with candiduria are asymptomatic.[5] Hematogenous spread to the renal cortex is usually an asymptomatic event, although these patients usually have symptoms related to candidemia. Thus, fever, hypotension, and signs of sepsis can be found in these patients, but they do not have symptoms referable to the urinary tract. In these patients, diagnosis and treatment are aimed at the bloodstream infection, and the finding of candiduria is incidental.

Patients who have ascending *Candida* urinary tract infection have symptoms that are no different from those noted with bacterial infections. Patients with cystitis have urgency, frequency, dysuria, and suprapubic discomfort. Some will complain of pneumaturia, and a few may notice that they have passed particulate matter. Systemic symptoms and signs of infection are usually absent.

Patients who have *Candida* pyelonephritis usually manifest chills, fever, and flank pain.[25] Symptoms of lower tract infection, including dysuria and frequency, are frequently also present. Although some patients have an acute febrile illness, others do not appear acutely ill, but on imaging studies will be found to have upper tract involvement. Pyelonephritis is more often seen in diabetic patients, in older adults, and in women.

Severe, but uncommon, complications of pyelonephritis include emphysematous pyelonephritis, perinephric abscess, and papillary necrosis, all of which are associated with increased morbidity and usually require surgical intervention.[14] If a fungus ball, which is a mass of hyphae and yeast cells, forms in the collecting system, the patient may become oliguric and have increasing flank pain. Fungus balls that form in the bladder can remain asymptomatic until they cause obstruction of ureters and/or urethra.

Patients who have an indwelling bladder catheter do not have dysuria or frequency and usually complain of few symptoms,[26] and patients in the ICU often are unable to communicate about any symptoms that they might have. Both of these circumstances make differentiation of infection versus colonization especially difficult.

Laboratory Studies

Urinalysis and culture of urine are the obvious initial laboratory studies that should be performed. Unfortunately, neither provides much help in distinguishing colonization from infection. Pyuria is present in patients who have a *Candida* urinary tract infection. If the patient does not have an indwelling bladder catheter, pyuria is helpful in

differentiating colonization from infection. However, pyuria is routinely found in patients who have an indwelling bladder catheter, so that it becomes a less useful clue to infection in this population. Unfortunately, candiduria occurs most often in patients with indwelling urinary catheters, and it is in these patients that the physician is most often faced with decisions about colonization versus infection.

Studies in the 1970s showed that quantitative cultures for *Candida*, in contrast to those for bacteria, did not separate into distinct zones defining infection and colonization.[24,27] Among patients without indwelling urinary catheters, kidney involvement was documented with urine colony counts from 10^4 to greater than 10^5 yeasts/mL. For patients who had indwelling catheters, colony counts in the same range (between 2×10^4 to $>10^5$ colony-forming units/mL) did not correlate with biopsy-proven kidney infection. In an experimental murine model in which *Candida* was given as an intravenous bolus, colony counts in the urine did not correlate with the number of organisms found in the kidney.[28]

The techniques routinely used in most clinical microbiology laboratories for the detection of bacteria are adequate for detecting yeasts in urine. However, *C glabrata* grows slowly, and the tiny colonies may not appear until after incubated for 48 hours. Almost all laboratories discard routine urine culture plates after 24 hours, and may well miss growth of *C glabrata*. The laboratory should be told that a *C glabrata* urinary tract infection is suspected and asked to hold the culture plates for 72 hours to look for slowly growing colonies. In addition, sending a urine sample for fungal culture, which routinely is held for several weeks, can be helpful.

Most clinical microbiology laboratories do not identify yeast isolates obtained from the urine to species level. This is both a cost-saving and time-saving measure based on the fact that most yeasts isolated from urine are only colonizers, which should not be treated. However, if a patient is thought to have a *Candida* urinary tract infection, knowledge of the species is crucial because many isolates of *C glabrata* and all isolates of *C krusei* are resistant to fluconazole, the standard treatment.

Antifungal susceptibility studies should be performed if *C glabrata* is isolated. In a minority of cases, the organism may be susceptible and fluconazole can be used; in many cases, however, the organism will be resistant, and other options will need to be explored. Most isolates of *C albicans, Candida parapsilosis*, and *Candida tropicalis* are susceptible to fluconazole, but resistance has been reported, and susceptibility testing should be sought for these species, as well as other unusual *Candida* species, if treatment is anticipated.

Other laboratory studies are not very helpful in defining whether a patient has a *Candida* urinary tract infection. Inflammatory markers are usually within normal limits; white blood cell count and percentage of neutrophils are not usually elevated. Serum creatinine is important to define kidney function and dosages of antifungal agents if treatment is needed.

Imaging Studies

Ultrasonography is the preferred initial study because of its simplicity and ready availability. It is valuable for documenting hydronephrosis, and in *Candida* pyelonephritis may show focal hypoechoic lesions in the kidney. Obstruction due to fungus balls at any level in the urinary tract can be delineated with ultrasonography.[23,29,30] It is essential to look for obstruction, as antifungal treatment is rarely successful if obstruction is not relieved.

Computed tomography urograms are helpful in demonstrating the cause of hydronephrosis, the presence of a perinephric abscess or fungus ball, and can evaluate the excretory function of the kidney (**Fig. 1**).

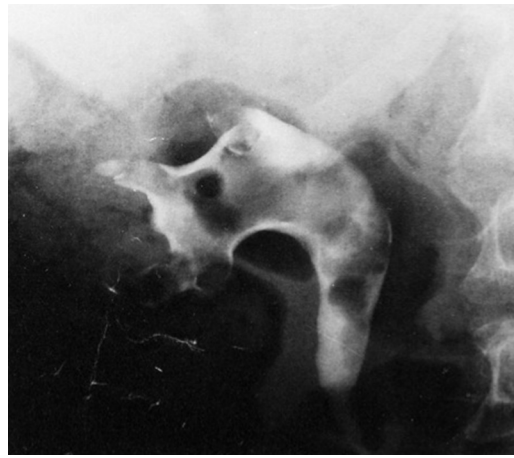

Fig. 1. Hydronephrosis and several fungus balls visualized as round masses excluding dye in excretory urogram of a patient with pyelonephritis due to *Candida albican*s.

TREATMENT

General Principles

Several concepts should be kept in mind when treating *Candida* urinary tract infections (**Box 3**). Asymptomatic candiduria should not be treated except in certain specific circumstances noted later in this article. Treatment must take into account the antifungal susceptibilities of the infecting species as well as the ability of the antifungal agent to achieve adequate concentrations in the urine. Fortunately, the most common species is *C albicans*, and most strains are susceptible to fluconazole, which is excreted into the urine as active drug.

The presence of indwelling urinary catheters makes eradication of candiduria very difficult. Often, simply removing the catheter without administering antifungal drugs and doing a follow-up urine culture will show that the host has been able to clear the organism from the urine.[5]

Equally important to remember is that if obstruction to urine flow is present anywhere in the genitourinary tract, antifungal agents will likely be ineffective in treating *Candida* urinary tract infection. Thus, an ultrasound study looking for obstruction should be done if the patient has persistent candiduria.

Box 3
General principles in the treatment of *Candida* urinary tract infections

- Asymptomatic candiduria should not be treated with antifungal agents, except in certain populations at risk for candidemia
- Antifungal susceptibilities and concentrations of antifungal agents in the urine are important factors in choosing the appropriate antifungal agent for *Candida* urinary tract infections
- Persistence of indwelling urinary catheters will likely prevent eradication of *Candida* with antifungal drugs
- Failure to relieve obstruction in the urinary tract will render antifungal therapy ineffective

Because bacteriuria is common in patients who have candiduria, treating the bacterial infection first is recommended. Many times the patient's symptoms clear with antibacterial therapy, and antifungal therapy is not needed. However, other patients require therapy for both bacteria and fungi to become asymptomatic.

Asymptomatic Candiduria

There are only a few circumstances in which asymptomatic candiduria should be treated (**Table 2**).[31,32] If a patient with candiduria is about to undergo a urological procedure, antifungal therapy should be given in the periprocedure period to prevent candidemia.[33,34] Asymptomatic candiduria also should be treated in patients who are neutropenic.[31] Symptoms may be minimal because of the neutropenia, and in this population, there is a high likelihood that candiduria reflects upper tract infection as a result of candidemia. Another patient population in which candiduria should always be treated is very low birth weight neonates. In these infants, candiduria is often a marker for invasive candidiasis and upper tract infection.[23,31]

Symptomatic Urinary Tract Infection

For patients who have persistent candiduria and symptoms of cystitis, treatment with oral fluconazole should be given (**Table 3**). The recommended dose is 400 mg initially, followed by 200 mg daily for 14 days based on the results of a multicenter, randomized, blinded, placebo-controlled trial.[31,35] Lower doses given for only a few days are discouraged, as *Candida* urinary tract infections should be viewed as complicated infections, requiring higher doses and longer treatment durations.

For patients who have persistent candiduria and whose symptoms suggest pyelonephritis, fluconazole is also the treatment of choice. The recommended dosage is 200 to 400 mg daily for 2 weeks.[31] Imaging of the urinary tract should be considered essential in any patient undergoing treatment for *Candida* pyelonephritis to evaluate for obstruction and the presence of complications, such as fungus ball formation, perinephric abscess, or emphysematous pyelonephritis.

Treatment of Complications

The most common complication is relapse of infection or failure to clear the infection after a course of fluconazole. If the patient has recurrent cystitis, imaging, urodynamic voiding studies, and cystoscopy should be performed. Prostatic abscess, bladder fungus ball, and chronic bladder changes due to long-standing infection all can contribute to relapse or failure to clear the infection. An extended course of fluconazole for susceptible organisms is indicated in these circumstances.

Table 2
When to treat asymptomatic candiduria

Patient Group	Comments
Patients undergoing a urological procedure	Risk of candidemia high following urinary tract instrumentation; treat with fluconazole immediately before and right after procedure
Neutropenic patients	High likelihood that candiduria represents candidemia with seeding to kidneys
Very low birth weight neonates	High likelihood that candiduria represents candidemia; high propensity to form renal fungus balls when candidemic

Table 3
Treatment of *Candida* urinary tract infections, with dosages for adult patients with normal kidney function

Indication	First-Line Treatment	Alternative Options for Resistant *Candida* Species
Asymptomatic candiduria in very low birth weight neonates or neutropenic patients	Treat for disseminated candidiasis: fluconazole, 400 mg qd × 2 wk	AmB, 0.5–1.0 mg/kg/d × 2 wk
Asymptomatic candiduria in patient about to undergo urological procedure	Fluconazole, 200–400 mg qd periprocedure	AmB, 0.3–0.6 mg/kg/d periprocedure
Cystitis	Fluconazole, 200 mg qd × 2 wk	AmB, 0.3–0.6 mg/kg/d × 1–7 d; 5-FC, 25 mg/kg tid × 7–10 d
Pyelonephritis	Fluconazole, 200–400 mg qd × 2 wk	AmB, 0.5–0.7 mg/kg/d × 2 wk; 5-FC, 25 mg/kg tid × 2 wk; or both AmB and 5-FC × 2 wk
Renal infection—hematogenous spread	Treat for disseminated candidiasis: fluconazole, 400 mg qd × 2 wk	AmB, 0.5–1.0 mg/kg/d × 2 wk
Fungus ball (bladder, ureter, or kidney)	Fluconazole, 200–400 mg qd until resolved; surgical removal	Local instillation of AmB an effective adjunct

Abbreviations: 5-FC, flucytosine; AmB, amphotericin B deoxycholate; qd, every day; tid, 3 times a day.

In patients who have upper tract *Candida* infection, obstruction is often found, and placement of a percutaneous nephrostomy tube or a ureteral stent may be required. This should be followed by a longer course of therapy with fluconazole, if the organism is susceptible.

The rare complications of emphysematous pyelonephritis and papillary necrosis almost always require nephrectomy. Drainage of a perinephric abscess is essential and is usually accomplished by interventional radiological techniques.

Patients in whom a fungus ball has been found should be treated with oral fluconazole and surgical or radiological interventions to relieve obstruction.[31] Nephrostomy tubes can be irrigated with amphotericin B deoxycholate to achieve high local concentrations. Given through this route, amphotericin B is not absorbed and is not nephrotoxic. Fluconazole also has been infused locally through nephrostomy tubes.[36] Local infusion is generally an interim procedure until the fungus ball can be removed by surgical or interventional radiological techniques.[37,38] It is imperative to maintain antifungal treatment when the fungus ball is being removed to prevent fungemia.

Special Problem of C glabrata Infection

C glabrata urinary tract infections, which are common in older adults, are often refractory to treatment. Removal of catheters, discontinuance of antibiotics, and relief of obstruction are essential. A higher dosage of fluconazole (800 mg daily) may provide adequate urine concentrations to eradicate this more azole-resistant organism. However, if the organism is totally resistant, then this approach will not succeed, and in

patients with renal failure, the urine fluconazole concentrations may be too low to be effective.

An oral alternative is flucytosine, which is active against almost all strains of *C glabrata*.[31] Unfortunately, success rates are low, and adverse effects can be serious. Patients treated with this agent must be monitored carefully. Amphotericin B is probably the most effective agent, but requires placement of an intravenous catheter, and the drug's many side effects have to be dealt with.[31]

Echinocandins, which do not achieve adequate urine concentrations, have been tried; failure is the usual outcome, but success has been reported in a few cases.[39–42] Voriconazole and posaconazole, although active against *C glabrata*, do not achieve urine concentrations adequate to treat urinary tract infections. In some cases of recalcitrant cystitis, local irrigation of amphotericin B has been helpful in the short run, but definitive eradication remains elusive for many patients.

Antifungal Agents

Oral fluconazole is the agent of choice for treatment of *Candida* urinary tract infections.[31] It is effective for both upper and lower tract infections. Fluconazole achieves high urine levels, and most *Candida* species are susceptible to this agent. The exceptions are *C glabrata*, which is often fluconazole resistant, and *C krusei,* which is uniformly fluconazole resistant. The dosage of fluconazole should be reduced in patients who have reduced creatinine clearance (**Table 4**).

Fluconazole's urinary excretion is unique among azoles; all of the other azole agents, itraconazole, posaconazole, and voriconazole, are metabolized in the liver, and urinary excretion of active drug is either minimal or nil. As a result, none are recommended for treatment of *Candida* urinary tract infections.

Intravenous amphotericin B deoxycholate is effective in treating *Candida* urinary tract infections, but is generally reserved for instances in which fluconazole has proven to be ineffective. However, it is the treatment of choice for urinary tract infections caused by *C glabrata* or *C krusei*. The recommended dosage is 0.3 to 0.6 mg/kg per day for 5 to 7 days, but even single-dose treatment with 0.3 to 1.0 mg/kg has been shown to be effective.[43]

The lipid formulations of amphotericin B were introduced to reduce nephrotoxicity. It appears that they do not achieve adequate concentrations in the urine, and failures have been reported when these formulations have been used to treat *Candida* urinary

Table 4
Fluconazole and flucytosine dosing for *Candida* urinary tract infections in patients with reduced kidney function

Creatinine Clearance	Dosage
Fluconazole	
>50 mL/min	400 mg q 24 h
21–50 mL/min	200 mg q 24 h
<20 mL/min	200 mg q 48 h
Flucytosine	
>50 mL/min	25 mg/kg tid
21–50 mL/min	25 mg/kg bid
<20 mL/min	25 mg/kg qd

Abbreviations: bid, twice a day; q, every; qd, every day; tid, 3 times a day.

tract infections.[44] Thus, lipid formulations are not recommended for urinary tract infections.

Flucytosine has a limited but sometimes valuable role in treating fluconazole-resistant *C glabrata* urinary tract infections. This agent achieves high concentrations in the urine and is active against many isolates of *C glabrata*. *C krusei* is not susceptible to flucytosine. Flucytosine is often combined with amphotericin B. It can be used as a single agent, but resistance develops quickly.[31,32] Although the dosage recommended is 25 mg/kg 4 times daily for 7 to 10 days for cystitis and 14 days for upper tract infection,[31] this dosage is likely to cause bone marrow toxicity. For this reason, a lower dosage of 25 mg/kg 3 times daily is preferred. If there is renal dysfunction, the dosage should be decreased further (see **Table 4**).

None of the echinocandins are excreted into the urine as active drug, limiting their use for the treatment of urinary tract infections. However, there are reports of patients in whom caspofungin has been given to treat infection due to a fluconazole-resistant organism. Some reports note success and others document failure.[39–42] When these agents have been efficacious, it is generally in a patient in whom hematogenous dissemination to the kidney has occurred with candidemia. In these cases, it is possible that tissue concentrations in the kidney, rather than urine concentrations, are adequate and are most important for eradication.

Local Bladder Antifungal Infusion

Several trials have compared local bladder instillation of amphotericin B deoxycholate versus oral fluconazole for the treatment of candiduria.[45–47] Local instillation was effective in eliminating the organism from the bladder, but the effect was short-lived.

The usual daily dosage is 50 mg amphotericin B deoxycholate in 1 L sterile water, and instillation is done through an indwelling triple-lumen urinary catheter. An alternative method is the instillation of 100 mL of this solution several times daily through a regular indwelling catheter. The catheter is then clamped for 30 minutes, allowing the drug to remain in the bladder, and then unclamped.

Fluconazole bladder infusion has been used in patients with cystitis who have renal insufficiency and perhaps for that reason have failed oral fluconazole therapy.[48] The dose used was 200 mg in 1 L sterile saline daily.

Guidelines and commentaries on the management of urinary tract candidiasis do not recommend bladder instillation of antifungal agents,[31,49,50] but there are a few situations in which it can be helpful. For example, local infusion of amphotericin B can be used as adjunctive treatment for *C glabrata* or *C krusei* cystitis.

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