CHAPTER

26 Fungal Infections of the Urinary Tract

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Urinary tract infections due to fungi are much less common than those due to bacteria. Among the fungi, relatively few target the urinary tract (Table 26.1). Candida species are responsible for most urinary tract infections.[1] Other opportunistic yeasts, such as Cryptococcus neoformans, involve the urinary tract usually only when widespread disseminated infection has occurred. Mold infections, such as aspergillosis and mucormycosis, rarely spread to the urinary tract, but have disastrous consequences when they do. Finally, the group of geographically restricted endemic mycoses, histoplasmosis, coccidioidomycosis, and blastomycosis, can cause localized lower urinary tract infections, but rarely cause symptomatic upper tract infection.

Candiduria is not a disease, but is usually the initial event triggering the question as to whether a fungal urinary tract infection is present.[2] Most patients who have Candida in their urine do not have a urinary tract infection, but are merely colonized with these yeasts. Diagnostic tests to define whether candiduria reflects colonization or infection are often not helpful, and localization of the site of infection either to the bladder or the kidneys can be difficult. For this reason, much of the literature on urinary tract involvement with Candida species is actually based on candiduria and much less often on specific infections due to these organisms.

CANDIDA

Epidemiology

Candida species are common members of the microbiota of the perineum but are found in urine in less than 1% of healthy persons.[3,4] In hospitalized patients, especially those in the intensive care unit, candiduria is very common presumably because of the multitude of risk factors that allow ingress of organisms into the bladder and subsequent growth of Candida species in the urine.[5–11] A recent point prevalence survey of positive urine cultures obtained from hospitalized patients in hospitals throughout Europe found that Candida species were the third most common microorganism isolated from urine.[5] Although it has been thought that candiduria could serve as a prelude to candidemia, this appears to be uncommon. Investigation of candiduric and candidemic isolates by molecular genotyping failed to show a relationship between the two sites in over half of the patients in one study.[12] In a large prospective surveillance study only 7 of 530 (1.3%) candiduric patients followed for 10 weeks developed candidemia.[13]

The risk factors for candiduria have been better defined than those for either bladder or kidney infection with Candida. This is due to the fact that firm diagnostic criteria for infection have not been defined, but candiduria is easily and simply defined as the growth of Candida species from a urine culture. Prospective surveillance studies and case-controlled studies have shown that increased age, female sex, antibiotic use, urinary drainage devices, prior surgical procedures, and diabetes mellitus are important risk factors for candiduria[6,8,11,13] (Table 26.2).

In the largest multicenter surveillance study, which assessed 861 hospitalized patients, urinary drainage devices, consisting mostly of indwelling urethral catheters, were present in 83%, diabetes in 39%, and urinary tract abnormalities in 37% of patients who had candiduria. Only 11% of patients with candiduria had no obvious risk factor identified.[13] In a multicenter study from Spain assessing candiduria in patients in an intensive care unit (ICU) setting, the independent risk factors associated with candiduria were age over 65 years, female sex, diabetes mellitus, prior antibiotics, mechanical ventilation, parenteral nutrition, and length of hospital stay before admission to the ICU.[6]

Among children, low-birth-weight neonates who are in an ICU are at the highest risk for candiduria and Candida urinary tract infections.[14–16] Fewer data are available for patients in the community than for hospitalized patients. Risk factors appear to be similar to those in hospitalized patients and include diabetes, indwelling catheters, and the use of antibiotics.[11]

Several studies, especially those focused on the ICU population, have noted increased mortality rates in patients who have candiduria when compared to similar patients without candiduria.[6,9,13,17,18] In all of these studies it appeared that Candida urinary tract involvement was not responsible for death but was most likely a marker for seriously ill patients

26.1 Fungi That Cause Urinary Tract Infection

Yeastlike Fungi
- Candida species[a]
- Cryptococcus neoformans
- Saccharomyces cerevisiae
- Trichosporon asahii

Molds
- Aspergillus species
- Mucorales

Endemic Fungi
- Histoplasma capsulatum
- Blastomyces dermatitidis
- Coccidioides species

[a]The vast majority of fungal urinary tract infections are due to Candida species. All of the other fungi listed only rarely cause urinary tract infections.

who died of their underlying illnesses. Treatment of candiduria did not impact mortality rates.[18]

Pathogenesis

Candida species can cause renal infection by either the hematogenous or ascending routes. In contrast, most bacterial upper tract infections are related to ascending infection from the bladder. It is likely that most kidney involvement with Candida occurs by hematogenous seeding from a distant focus but almost all of these infections cause no urinary tract symptoms. Rather, the patient is ill from candidemia or other foci of infection due to Candida. The pathogenesis of hematogenous seeding of Candida to the kidney has been studied extensively in experimental rodents and rabbits given an intravenous bolus of C. albicans.[19] Multiple microabscesses develop throughout the cortex. As the infection progresses, the yeasts penetrate through the glomeruli into the proximal tubules and are shed into the urine. Healthy animals eventually clear the organisms from the kidney, usually within 2 weeks; however, animals given immunosuppressive drugs cannot clear the infection. In agreement with experimental studies, renal microabscesses have been identified at autopsy in most patients who die of invasive candidiasis.

The pathogenesis of ascending infection with Candida has not been studied as extensively as that of hematogenous spread. Not surprisingly, it has been shown that those Candida strains found in the vagina are genetically related to the strains that cause candiduria in women who have indwelling bladder catheters while in the ICU.[20] There is no animal model that replicates the mode of spread that occurs in humans, which is presumably from the perineum into the bladder and then retrograde to the collecting system of the kidney.[21] Creating the milieu in which Candida persist in the bladder has been difficult in experimental animals. Studies from the 1970s showed that rats made diabetic were unable to clear C. albicans inoculated into the bladder, and also that the presence of a concomitant Escherichia coli urinary tract infection allowed retrograde spread of Candida to the kidney.[19] Unfortunately, these experiments have not been repeated nor has use of this model continued. Another model using bladder tissue explants from rabbits confirmed the essential role of adherence to the epithelial cells in colonization of the explants, but could not further explore the pathogenesis of retrograde spread.[22]

Microbiology

C. albicans is the yeast most commonly isolated from urine, accounting for 50% to 70% of isolates. C. glabrata is the second most common yeast found in urine, accounting for about 20% of isolates.[2,13] However, the proportion of urine isolates that are C. glabrata varies with different risk groups. Older adults frequently have C. glabrata isolated from urine, but neonates rarely are colonized or infected with C. glabrata. In patients who have hematologic malignancies, and in kidney transplant recipients, C. glabrata is more commonly isolated, possibly because of increased use of fluconazole in units that care for these patients. In one series of kidney transplant recipients, over half of all urine isolates were C. glabrata and only one third were C. albicans.[23] A study among hospitalized patients who had indwelling bladder catheters found that independent risk factors for C. glabrata candiduria were diabetes, ICU admission, and prior treatment with antibiotics and with fluconazole.[24]

C. parapsilosis, C. tropicalis, and C. krusei are less commonly found in urine although some centers have reported C. tropicalis more often than C. glabrata.[8] In general, there are no distinguishing characteristics of urinary tract infections due to the different Candida species.

Many laboratories do not identify yeast isolates to species level. This is reasonable because most yeasts that are

26.2 Risk Factors for Candiduria[a]

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

[a]Most patients have more than one predisposing factor present.

isolated are merely colonizing the urinary tract. However, knowledge of the species is needed if treatment of infection is required. Almost all isolates of C. albicans, C. tropicalis, and C. parapsilosis are susceptible to fluconazole, the antifungal agent of choice for treating Candida urinary tract infections. However, many isolates of C. glabrata and all isolates of C. krusei are resistant to fluconazole. Additional benefit is obtained when the laboratory performs susceptibility studies for fluconazole by helping the clinician to tailor therapy to the specific infecting organism.

Clinical Manifestations

Most patients with candiduria are asymptomatic, reflecting the fact that most do not have infection. In one large prospective surveillance study of patients with candiduria, fewer than 5% had symptoms suggestive of urinary tract infection.[13] Patients who have had hematogenous spread to the renal parenchyma in the course of candidemia may have fever, hypotension, and other manifestations of sepsis associated with invasive candidiasis. They do not have symptoms suggesting urinary tract infection. In these patients candiduria is a clue to the presence of invasive candidiasis, but the urinary tract is not the primary site of infection or the source of candidemia.

In those patients who do have symptomatic urinary tract infection, symptoms are indistinguishable from those noted with bacterial infections. Cystitis is manifested by dysuria, frequency, urgency, and suprapubic discomfort. Rarely pneumaturia and the passage of particulate matter may be present. Fever is uncommon. Patients who have an indwelling bladder catheter rarely complain of symptoms other than suprapubic discomfort, and if they are in the ICU they often are unable to communicate about symptoms that they might have.

Patients who have pyelonephritis usually have chills, fever, and flank pain. Some patients are afebrile whereas others have predominantly lower tract symptoms, but upper tract infection is noted on imaging studies.[25] Pyelonephritis is more common in diabetics, women, and older adults. Complications of pyelonephritis are uncommon but include emphysematous pyelonephritis, perinephric abscess, and papillary necrosis—all of which are associated with increased morbidity and usually require surgical intervention.[26] Formation of a fungus ball composed of a mass of hyphae and yeast cells in the collecting system is frequently found with pyelonephritis and causes obstruction.[25,27–30] Neonates and infants are especially prone to develop fungus balls.[27,30] If obstruction is present oliguria may occur and candidemia is common. Fungus balls can also form in the bladder and obstruct one or both ureters, causing hydronephrosis.[28]

Diagnosis

The initial task when approaching a patient who has candiduria is to decide if the presence of candiduria represents infection or merely reflects contamination of a urine sample or colonization of the bladder or urinary catheter. Repeating the urine culture to determine if the candiduria disappears tells one that the previous specimen was contaminated and no further diagnostic workup is indicated. If the patient is unable to perform a clean-catch collection of urine, bladder catheterization may be required. In those patients who have an indwelling bladder catheter, the catheter should be replaced and the second urine specimen collected from the newly inserted catheter.

Distinguishing colonization from infection is not simple as there are no standardized criteria that enable one to distinguish the two situations, especially in the setting of an indwelling bladder catheter.[2] Specifically, pyuria and quantitative cultures have not been shown to be definitive markers for the diagnosis of Candida urinary tract infection.[31] In patients who have an indwelling bladder catheter, pyuria is routinely noted and thus is not helpful to differentiate infection from colonization. On the other hand, in patients who do not have an indwelling bladder catheter, the presence of pyuria is helpful. One must be sure that bacteriuria is not present as a cause for pyuria.

Early studies by Wise and colleagues in the 1970s showed broad ranges of colony counts for both colonization and infection.[31,32] For patients who did not have indwelling catheters kidney infection was documented with colony counts in urine as low as 10^4 yeasts per mL. For patients who had indwelling catheters colony counts varied between 2×10^4 to $\geq 10^5$ colony-forming units (CFU) per mL, and the correlation of urine colony counts with biopsy-proved renal infection was poor. In a murine model of renal candidiasis initiated by intravenous inoculation of organisms, urine colony counts varied widely and no specific amount in the urine correlated with the burden of organisms in the kidney.[33]

Identification of casts containing yeasts in the urine is specific for kidney infection.[34] However, the techniques required to evaluate the presence of casts are complicated and time consuming, and this assay is not useful clinically. Finding pseudohyphae in urine may not be indicative of infection, especially because some Candida species, specifically C. glabrata, cannot form pseudohyphae.

Occasionally a patient has symptoms suggesting a urinary tract infection and yeasts are seen on microscopic examination of a urine sample, but the urine culture shows no growth. In this circumstance it is likely the patient has infection with C. glabrata, and the culture plates have not been held long enough for detection of this slowly growing species. Although the standard urine culture techniques used in clinical laboratories detect most Candida species, they can miss C. glabrata strains which may not appear for 48 hours. Asking the lab to culture urine specifically for fungi ensures that plates are kept for at least 5 days, and C. glabrata will then be found.

Imaging procedures including abdominal ultrasound and computed tomography (CT) scan are essential to document obstruction in the bladder, ureters, or renal pelvis.[31] It is important to discover the presence of fungus balls in the bladder or kidneys as surgical intervention is often required

for effective treatment. Perinephric abscess and emphysematous pyelonephritis, although unusual, are serious consequences of upper urinary tract Candida infection and are best detected by CT scan. Cystoscopy is helpful to ascertain the presence and extent of mucosal invasion by Candida.

Treatment

As a general rule asymptomatic patients should not be treated with antifungal agents.[35–38] However, there are two circumstances in which asymptomatic patients should be treated (Table 26.3). One such circumstance is when candiduria likely represents a marker for invasive candidiasis in high-risk patients, especially neutropenics and very low-birth-weight neonates.[35] The other circumstance is when the patient has candiduria and is about to undergo a urologic procedure that is likely to lead to candidemia.[35,39] Asymptomatic candiduria in a kidney transplant recipient does not warrant systemic antifungal treatment unless obstruction is present or the patient develops symptoms suggesting infection.[23]

For many patients simply removing the indwelling bladder catheter will allow the host to clear the candiduria.[2] If catheterization cannot be discontinued, the existing catheter should be removed and a new one inserted. Many times this will eradicate candiduria transiently, but it is highly likely that the organisms will return within a short time period. Relieving obstruction to urine flow in the upper or

26.3 Treatment of *Candida* Fungal Urinary Tract infections

Infection	Preferred Treatment	Comments
Asymptomatic candiduria with no high risk factors	Remove risk factors (bladder catheter, antibiotics)	Antifungal treatment not recommended
Asymptomatic candiduria in low birth weight neonates or neutropenics	Fluconazole, 400 mg (6 mg/kg) daily × 2 weeks	Treat for disseminated candidiasis; for fluconazole-resistant Candida, AmB, 0.5–1.0 mg/kg daily × 2 weeks
Asymptomatic candiduria in patient about to undergo urologic procedure	Fluconazole, 200–400 mg (3–6 mg/kg) daily for a few days periprocedure	For fluconazole-resistant Candida, AmB 0.3–0.6 mg/kg daily for a few days periprocedure
Cystitis	Fluconazole, 200 mg (3 mg/kg) daily × 2 wk	For fluconazole-resistant Candida, AmB, 0.3–0.6 mg/kg daily × 1–7 days OR 5-FC, 25 mg/kg qid × 7–10 days
Pyelonephritis	Fluconazole, 200–400 mg (3–6 mg/kg) daily × 2 wk	For fluconazole-resistant Candida, AmB, 0.5–0.7 mg/kg daily ± 5-FC, 25 mg/kg qid × 2 weeks OR 5-FC alone× 2 weeks
Renal infection—hematogenous spread	Fluconazole, 400 mg (6 mg/kg) daily × 2 wk	Treat for disseminated candidiasis; for fluconazole-resistant Candida, AmB, 0.5–1.0 mg/kg daily × 2 weeks
Prostatitis	Fluconazole, 400 mg (6 mg/kg) daily until resolved	Surgical drainage usually needed in addition to antifungal therapy
Epididymoorchitis	Fluconazole, 400 mg (6 mg/kg) daily until resolved	Surgical drainage usually needed in addition to antifungal therapy
Fungus balls (bladder, ureter, or kidney)	Fluconazole, 200–400 mg (3–6 mg/kg) daily until resolved	Surgical or radiologic intervention almost always required; local instillation of AmB an effective adjunct

AmB, amphotericin B deoxycholate; 5-FC, flucytosine; qid, four times a day.
Modified from Pappa PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:503.

lower urinary tract is essential for the long-term eradication of Candida from the urinary tract. Stopping broad-spectrum antibiotics will help the host clear candiduria without having to resort to antifungal agents.

Patients who have symptoms suggesting cystitis or pyelonephritis, and in whom bacteria as well as Candida are found in the urine culture, should be treated with an antibacterial agent alone to see if this leads to resolution of symptoms. However, many times there is a dual infection and both infections, bacterial and fungal, will require treatment.

Antifungal Agents

When therapy is indicated oral fluconazole is the drug of choice (Table 26.3). A loading dose of 400 mg should be given and then the daily dosage is 200 mg for a total of 14 days.[35,40] Fluconazole achieves high urine levels and effectively treats all Candida species with the exception of those due to C. glabrata, which are relatively or completely fluconazole-resistant, and C. krusei, which are uniformly fluconazole resistant. The dosage of fluconazole is reduced when the creatinine clearance falls to 50 mL per minute (Table 26.4).

26.4 Dosages of Antifungal Agents in Patients with Renal Insufficiency

Antifungal Agent	Creatinine Clearance (mL/min)	Recommended Dosage
Fluconazole	>50	400 mg every 24 hours
	21–50	200 mg every 24 hours
	11–20	200 mg every 48 hours
	Hemodialysis	400 mg after each dialysis
Flucytosine[a]	>50	25 mg/kg every 6 hours
	21–50	25 mg/kg every 12 hours
	11–20	25 mg/kg every 24 hours
	Hemodialysis	25 mg/kg after each dialysis

[a]Flucytosine peak levels should be measured 1–2 hours after dosing and should be <75 ug/mL.

The other available azoles (itraconazole, voriconazole, and posaconazole) and all of the echinocandins (micafungin, anidulafungin, and caspofungin) are not excreted into the urine as active drug, greatly limiting their use for Candida urinary tract infections.[37] It is possible that the tissue concentrations achieved with these agents might be adequate to treat invasive Candida infections of the kidney. However, clinical data are limited and both failures and success have been reported in individual patients.[41–43] It is highly likely that the echinocandins and voriconazole are able to eradicate those Candida organisms that have seeded into the kidney because all of these agents are effective therapy for candidemia and residual infection in the kidney after treatment of candidemia does not seem to be a common problem. However, currently no echinocandins or other azoles are recommended for the treatment of Candida urinary tract infections.

Intravenous amphotericin B deoxycholate has been used for decades as an effective treatment for Candida urinary tract infections.[35] However, because of its well-known toxicity, it is generally reserved for patients who have upper tract infection or documented bladder infection, and not merely colonization with C. glabrata or C. krusei (Table 26.3). The usual dosage is 0.3 to 0.6 mg/kg/d for 5 to 7 days, but even single-dose treatment with 0.3 to 1.0 mg per kg has been shown to be effective.[36,44] Infusion-related side effects that are seen in some patients, even when treated with low dosage amphotericin B deoxycholate, are rigors, fever, nausea, vomiting, and headache. Even a few days of therapy can cause transient renal insufficiency in some patients.

Unfortunately, the lipid formulations of amphotericin B, liposomal amphotericin B, amphotericin B lipid complex, and amphotericin B colloidal dispersion are not effective in treating fungal urinary tract infections.[45] It is postulated that the addition of the lipid component, which decreases nephrotoxicity with these agents, also precludes these drugs from achieving adequate levels in the urinary tract. This has been documented in one patient undergoing nephrectomy.[46]

Oral flucytosine can be used to treat fluconazole-resistant C. glabrata urinary tract infections either in concert with amphotericin B or as the sole agent.[35] Flucytosine is excreted into the urine as active drug in high concentrations. Unfortunately, it is fairly toxic with reversible bone marrow toxicity and hepatotoxicity being common. These adverse effects correlate directly with high serum levels and can be avoided in most patients who have normal renal function by using no more than 25 mg per kg orally every 6 hours for 7 to 10 days. Treatment longer than this is likely to lead to the development of resistance to flucytosine. The risk of toxicity increases greatly with renal dysfunction and the dose must be reduced (Table 26.4).

Local Antifungal Administration

Instillation of amphotericin B into the bladder to treat candiduria is used much less frequently now than previously.[47] Although local instillation will eliminate candiduria the effect is brief and Candida colonization returns in 1 to 2 weeks

in most patients.[48–50] Bladder instillation obviously is not efficacious for patients who have upper tract infection.

The usual daily dosage has been 50 mg amphotericin B deoxycholate per liter of sterile water. An indwelling catheter must be placed for instillation and most often a triple-lumen catheter is used for this purpose. This allows continuous slow infusion of amphotericin B. However, it has been questioned whether this effectively allows the infusate to "wash" the whole bladder or just the local area where the catheter is located. The alternative method for infusing amphotericin B is to administer a bolus of drug several times daily through a standard indwelling catheter, clamp the tube after the administration of drug, and then after about 30 minutes allow the infusate and urine to drain.

Most physicians and patients prefer oral azole therapy rather than bladder instillation, and recent guidelines do not recommend bladder instillation as a therapeutic option.[35] However, there are some specific circumstances in which local administration of amphotericin B can be useful. For example, bladder instillation might be helpful for treating patients who have documented cystitis with C. krusei, or C. glabrata resistant to fluconazole. In some of these patients local infusion of amphotericin B has proved useful.[51] Some have advocated the use of fluconazole bladder infusion (200 mg in 1 liter sterile saline daily) for patients who have renal insufficiency and have failed oral fluconazole therapy and are not candidates for systemic amphotericin B therapy.[52] The other circumstance in which local administration of either fluconazole or amphotericin B is indicated is when a patient has a fungus ball as discussed next.

Treatment of Complications

Patients who have a fungus ball should be treated with systemic antifungal agents, either fluconazole or amphotericin B deoxycholate with or without flucytosine, and surgical or radiologic interventions to relieve obstruction caused by the fungus ball.[35] Nephrostomy tubes placed into the collecting system are usually irrigated with amphotericin B, but fluconazole has also been used in this context.[53] This causes no damage to the kidney but achieves very high local levels of antifungal drug in the fungus ball. Other methods to break up fungus balls include irrigation with saline or streptokinase[54] and debulking the hyphal mass by percutaneous endoscopic disruption.[55,56] Treatment of emphysematous pyelonephritis almost always requires nephrectomy, as is the case with some patients in whom papillary necrosis has occurred following severe Candida pyelonephritis. Perinephric abscess can sometimes be drained without loss of the kidney. For all of these complications of upper tract candidiasis antifungal treatment with either fluconazole or amphotericin B is indicated in concert with surgical management.

Prostatitis

Candida prostatitis presents with symptoms similar to those noted with bacterial prostatitis, but generally patients are not as acutely ill as they can be with bacterial infection. Perineal discomfort, pressure behind the pubis, dysuria, difficulty voiding, and sexual dysfunction are some of the symptoms that may be present.[57–60] The patient may or may not be febrile. Diffuse infection or abscess formation can occur and rarely, emphysematous prostatitis.[61] The prostate is tender on examination and urine obtained after prostatic examination may reveal yeasts. Patients may present with urinary retention, thought to be due to benign prostatic hyperplasia or cancer, only to have Candida infection found on biopsy.

A combination of surgery and antifungal treatment is usually required for effective treatment of Candida prostatitis or prostatic abscess. Fluconazole is recommended as the preferred antifungal agent provided the organism is susceptible.[35] Fluconazole concentrations in prostatic tissue are approximately 30% of serum concentrations.[62] For infections due to C. glabrata or C. krusei that are resistant to fluconazole, amphotericin B is preferred and has been shown to be efficacious.[57] No data are available regarding the penetration of voriconazole, posaconazole, or the echinocandins into prostatic tissue, and their efficacy is unknown.

Epididymoorchitis

Candida epididymoorchitis is uncommon and appears to occur more often in patients who have diabetes and an indwelling catheter or urinary tract instrumentation.[63] A tender scrotal mass usually brings the patient to the physician's attention.[63–66] The presence of candiduria is a clue to the etiology of the epididymoorchitis.[63] Ultrasound or CT scan to assess for abscess formation should be performed. Drainage or orchiectomy is usually required for resolution. Fluconazole, 400 mg daily, is the preferred antifungal agent,[35] but there is experience using amphotericin B with flucytosine.[64,65] Treatment should continue for several weeks and until all signs of infection have resolved.

OTHER YEASTS

Yeasts other than Candida species are an uncommon cause of urinary tract infections. The most common among the non-Candida yeasts is Cryptococcus neoformans, a heavily encapsulated environmental yeast. This fungal infection occurs predominantly in persons who are immunosuppressed but normal hosts also can be infected by C. neoformans. The pathogenesis of infection begins with inhalation of the yeast, which is nonencapsulated in the environment and thus more easily dispersed. The initial infection involves the lungs and usually is asymptomatic. Because of the neurotropism of this organism, meningitis is the most common clinical manifestation.

Widespread disseminated infection, usually with accompanying meningitis, occurs commonly in those who are markedly immunosuppressed, especially patients with AIDS. In autopsy series kidney involvement has been noted in 25% to 50% of AIDS patients, but it is usually asymptomatic.[67] Symptomatic genitourinary tract involvement can occur as one aspect of widely disseminated infection or present as isolated prostatitis or epididymoorchitis.[67–69] Even focal

involvement implies disseminated infection, however, and other sites of infection should always be sought in such patients. The prostate can remain as a reservoir for viable Cryptococcus organisms after other sites of infection are successfully treated leading to subsequent relapse.[70]

The diagnosis of cryptococcosis is established by growth of C. neoformans in culture, by visualization of the encapsulated yeast in tissue sections with special stains, and/or by detection of capsular antigen in serum or body fluids. Treatment is based on whether meningitis is present and on the state of immune suppression in the host. In general, patients who have meningitis and/or disseminated infection should receive initial therapy with amphotericin B and flucytosine and subsequent consolidation and maintenance therapy with fluconazole.[71] In those rare cases that appear to have focal genitourinary tract cryptococcal infection, fluconazole 400 mg daily for at least 6 months is the preferred treatment.[71]

Saccharomyces cerevisiae has been described in a few cases as a cause of urinary tract infection.[72,73] The presentation is the same as that noted with Candida species. If the clinical microbiology laboratory does not identify yeasts isolated from urine to the species level, this organism will not be differentiated from Candida. S. cerevisiae is often resistant to fluconazole, and successful treatment may require amphotericin B.[74]

Trichosporon asahii is an opportunistic yeastlike organism that causes disseminated infection in immunosuppressed hosts, most often in those who have leukemia and are neutropenic. Genitourinary involvement can be related to disseminated infection or in certain settings can occur as an isolated infection. This appears to be the case in kidney transplant recipients who can be merely colonized, develop local fungus ball formation and obstruction, or have progressive invasion of the transplanted kidney without the occurrence of disseminated infection.[75] Treatment of disseminated infection is usually with voriconazole, and treatment of localized infection is voriconazole with surgical relief of obstruction, if present.

ASPERGILLUS AND OTHER MOLDS

Aspergillus and other molds uncommonly involve the urinary tract. In most instances involvement is noted for the first time at autopsy in patients who have widely disseminated infection. However, symptomatic localized urinary tract infections of the kidneys, the prostate, and the epididymis have been reported.[1,76–83] Most commonly these infections are due to Aspergillus species, but infections with the Mucorales, including Rhizopus and Mucor species, and other more rare molds have also been reported.[1] In most cases the patients who have urinary tract mold infections are immunosuppressed due to bone marrow or solid organ transplantation, HIV/AIDS, or neutropenia related to hematologic malignancies.[76,79–83] However, a few patients have been reported who had only diabetes or corticosteroid use as risk factors.[77,78]

The usual pathogenesis in most cases is hematogenous spread to the urinary tract from an initial pulmonary infection. However, primary renal aspergillosis that developed post-lithotripsy in a diabetic patient and localized Aspergillus prostatic abscess related to indwelling bladder catheterization have been reported with no other focus of infection.[77,78]

Kidney involvement is usually manifested by numerous microabscesses and infarcts, and, in some cases, obstruction to the collecting system occurs due to the development of fungus balls.[1] Patients who have obstructing renal lesions present with decreased urine output, flank pain, and fever. Prostatic and epididymal abscesses present with dysuria, frequency, or localized painful scrotal swelling.

Fungus balls or lower tract abscesses can be visualized by CT scan or ultrasound examination. Diagnosis of a mold infection is dependent on tissue biopsy showing invasion by hyphae and culture of the biopsy sample revealing the specific organism. Urine cultures cannot be relied on to yield the organism. Removal of an obstructing fungus ball, and many times nephrectomy, is required to treat mold infections of the kidneys. Surgical drainage of a prostatic abscess and epididymoorchiectomy are usually needed to effectively treat lower tract mold infection. Systemic antifungal therapy, either with amphotericin B or voriconazole for aspergillosis and with amphotericin B for mucormycosis, is necessary in all but exceptional cases in which truly localized infection has been documented. Mortality remains high in patients who have kidney involvement.

ENDEMIC FUNGI

The endemic fungi are those fungi that are restricted to certain geographical areas and that are dimorphic. They exist in the environment as molds, which are the infectious forms. In the body, and in the laboratory at temperatures from 35°C to 37°C, they transform to the yeast phase or in the case of Coccidioides, the spherule phase. The major endemic mycoses are Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides immitis, and Coccidioides posadasii. Paracoccidioides brasiliensis is restricted to South America and Penicillium marneffei to Southeast Asia and will not be discussed further. All of the major endemic mycoses have been reported to infect the genitourinary tract. Infection occurs by the hematogenous route as a sequel to the initial pulmonary infection. There are two major manifestations involving the genitourinary tract. Kidney involvement occurs as one manifestation of widespread disseminated infection with these fungi and is generally asymptomatic, but can be associated with renal insufficiency. The other manifestation is infection of the prostate, epididymis, or testicles presenting either as an isolated finding or as one manifestation of active disseminated infection. In either case, the pathogenesis of infection is via the hematogenous route.

B. dermatitidis has the greatest propensity to cause symptomatic genitourinary tract infection. In patients who have disseminated blastomycosis, involvement of the

genitourinary tract occurs in as many as a third of cases.[1] Kidney involvement is generally asymptomatic and found only at autopsy.[84] In most cases symptomatic infection involves the prostate and less commonly the epididymis or testicles. In some patients, dysuria, hesitancy, and trouble initiating urination are the presenting symptoms of what later is shown to be disseminated blastomycosis.[85] In others, biopsy of a prostatic nodule or a nontender epididymal mass, thought to be cancer, shows granulomas, and B. dermatitidis is seen on histopathologic examination and/or grown from the tissue.[84,86] Every patient who has blastomycosis found to involve the genitourinary tract should have a workup to define the extent of involvement of other organs.

Symptomatic genitourinary tract involvement with histoplasmosis is rare, but autopsy findings document spread to the kidneys not uncommonly in patients who have disseminated histoplasmosis.[87,88] Individual case reports of testicular or prostatic abscesses, epididymitis, and ulcerations of the bladder have been published.[87,89,90] In most of these cases a prostatic nodule or an epididymal or testicular mass, thought to be cancer, is found on biopsy to show granulomas and the small budding yeasts typical of H. capsulatum. In a few cases immune complex glomerulonephritis with H. capsulatum antigen demonstrated in the mesangium has been described.[87,88]

Coccidioidomycosis rarely causes symptomatic urinary tract infection but autopsy series of disseminated coccidioidomycosis have noted kidney involvement in 30% to 40% of cases.[1] Rarely, in the course of severe disseminated coccidioidomycosis, renal insufficiency can be ascribed to kidney involvement. In some patients with disseminated coccidioidomycosis, coccidioiduria can be found with an absence of symptoms. Localized infection, presenting as abscesses or mass lesions of the epididymis, testicles, or prostate, also occurs in patients who have coccidioidomycosis. Sometimes this occurs in the absence of documented disease elsewhere, but in other patients urinary tract involvement is just one manifestation of disseminated infection.[91–93]

Treatment of genitourinary infection due to the endemic mycoses depends on the pathogenesis of the infection. In most cases urinary tract involvement is one manifestation of disseminated disease and systemic therapy with amphotericin B or an azole, as recommended for disseminated infection, is given.[94–96] For those patients who have a focal mass or abscess in the epididymis or testicle, surgical removal has usually been accomplished before the diagnosis is suspected. Although cure has been reported with surgical excision alone,[93] additional treatment with an azole agent is recommended because the pathogenesis of infection is always related to hematogenous dissemination. If biopsy of a prostatic nodule shows infection with one of the endemic mycoses further surgical drainage is generally not necessary, and the infection can be treated successfully with an azole agent.

The specific azole agent to use should be discussed with an infectious diseases consultant. Itraconazole, the azole of choice for histoplasmosis and blastomycosis, does not achieve very high levels in the prostate. However fluconazole, a second-line agent for these infections, achieves excellent prostatic tissue levels.[62] Fluconazole is a first-line agent for coccidioidomycosis and should be used for focal Coccidioides infection of the genitourinary tract. Little is known about the penetration into prostatic tissue by voriconazole or posaconazole, and neither is currently recommended for treatment of the endemic mycoses.

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