Candiduria

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Candiduria is a common finding. Yeasts can be detected in urine that is contaminated during collection, in patients who have bladder colonization, and in patients who have upper urinary tract infection that developed either from retrograde spread from the bladder or hematogenous spread from a distant source. Most patients with candiduria are asymptomatic. The rate of development of complications is not known but appears to be low; candidemia rarely results from asymptomatic candiduria unless obstruction is present or instrumentation of the urinary tract is done. Unfortunately, there are no established diagnostic tests that reliably distinguish infection from colonization. Guidelines for the treatment of candiduria, based almost entirely on anecdotal reports and expert opinions, rather than controlled clinical trials, have been suggested by the Infectious Diseases Society of America. Until reliable methods to distinguish infection from colonization are developed, further treatment trials are unlikely to provide information to guide the clinician in the treatment of candiduria.

Candiduria is often observed in hospitalized patients. Candiduria is neither a symptom nor a sign, and it is clearly not a disease. The finding of yeast (almost always Candida species) in the urine could mean that the patient has pyelonephritis or cystitis. It also could mean that hematogenous seeding of the kidney cortex has occurred in the course of disseminated candidiasis. Finally, and most likely, the presence of candiduria may reflect only colonization of the bladder, perineum, or indwelling urinary catheter. The vast majority of patients with candiduria have no symptoms suggesting the presence of urinary tract infection (UTI) [1]; culture of the urine is done because of unexplained fever, elevated WBC count, or less cogent reasons, such as cloudy or smelly urine. For a surprisingly high number of patients who have had a sample obtained and cultured, the physician does not do a follow-up study to help determine the significance of candiduria [1–3].

PATHOGENESIS

One reason that it is difficult to determine the meaning of candiduria is that the organism appears to have equal propensity to cause disease by either the hematogenous or the ascending route. This situation clearly differs from that associated with UTIs caused by Escherichia coli, the most common uropathogen. The pathogenesis of UTIs due to E. coli is almost always an ascending infection from bladder to the collecting system of the kidney; rarely is hematogenous seeding of the kidney found with E. coli or other gram-negative bacilli that commonly cause UTIs.

The classic model for hematogenous infection of the kidney is Staphylococcus aureus. A positive result of culture of urine for S. aureus always demands follow-up to ensure that the patient does not have bacteremia or endocarditis. Although ascending infections with S. aureus do occur, mostly in patients with prior instrumentation of the genitourinary tract, they are much less common than infections due to hematogenous seeding of the cortex.

The pathogenesis of hematogenous seeding of Candida species to the kidney was well established by studies performed decades ago and has been verified by newer studies [4–7]. Multiple microabscesses develop throughout the cortex; the yeasts penetrate through the glomeruli into the proximal tubules and then are shed into the urine [6]. Although a healthy mouse will eventually clear the infection, immunocompromised animals cannot; more important, the presence of yeast in the urine implies widespread dissemination to many
viscera, a condition that must be treated with an antifungal agent [4].

The pathogenesis of ascending infection with Candida species is not clearly known. No animal model exists for this condition. It is known that obstruction and the presence of stones are important in some patients, but the exact mechanisms of adherence and subsequent growth in the calyx have not been elucidated.

**RISK FACTORS**

A small number of case-controlled studies, several retrospective reviews, and a large prospective surveillance study have evaluated risk factors for candiduria [1–3, 8–10]. Remarkably, each series shows similar risk factors: increased age, female sex, antibiotic use, urinary drainage devices, prior surgical procedures, and diabetes mellitus. In the largest series, only 11% of 861 patients with candiduria were without any known underlying illness, and long-term indwelling urethral catheters or other urinary drainage devices were present in 83% of patients [1].

A recent case-controlled study, in which the control subjects were patients who had Foley catheters in place but who did not have candiduria, compared candiduria due to Candida glabrata with that due to Candida albicans [10]. Candiduria due to either species was associated with female sex, admission to an intensive care unit (ICU), and antibiotic use. C. glabrata was also associated with diabetes mellitus and, not surprisingly, prior use of fluconazole.

**MICROBIOLOGY**

C. albicans has been the yeast most commonly isolated from urine, accounting for 50%–70% of isolates in various studies [1–3]. C. glabrata and Candida tropicalis are the next most common species found in cultures of urine. Candida parapsilosis, a common cause of candidemia in both adults and neonates, is uncommonly isolated from urine of adults [1–3]. C. parapsilosis is found more often in urine from neonates and is usually associated with systemic infection in this population [11]. However, many hospital laboratories do not speciate yeasts that are isolated from urine unless specifically requested to do so. Thus, changes or trends in species causing candiduria cannot easily be tracked.

**DIAGNOSTIC ISSUES**

Unfortunately, no reference standard exists for the diagnosis of UTIs due to Candida species. Although many attempts have been made to clarify this area, it remains a conundrum for the clinician to try to sort out the issues of contamination with normal perineal flora, colonization of bladder or indwelling devices, and true infection of bladder and/or kidney.

Contamination can usually be differentiated from urinary tract colonization or UTI by obtaining and culturing new urine samples to see if yeasts persist. In older women, to eliminate contamination by perineal flora, it is often necessary to obtain the second urine specimen by sterile bladder catheterization. If the second specimen yields no yeasts on culture, it can be assumed that contamination by perineal flora was the cause of candiduria, and no further diagnostic studies are needed.

The diagnosis of bacterial UTIs relies on the findings of pyuria and bacteriuria, usually at a certain minimum number of colony-forming units, in a patient with appropriate symptoms. Guidelines exist for establishing the diagnosis of a bacterial UTI, and the existence of excellent diagnostic tests allows appropriate treatment to be evaluated and become standard practice [12]. However, the diagnosis of a UTI due to Candida species is much more difficult. No studies have unequivocally established the importance of pyuria or quantitative urine cultures for UTI due to Candida.

An important initial observation is that most patients with candiduria are asymptomatic; only 4% of patients in one large multicenter study and 14% in another smaller series had symptoms suggesting a UTI [1, 3]. It seems that this should allow the clinician to make a diagnosis of asymptomatic candiduria for these patients, and, similar to the situation with asymptomatic bacteriuria, no further work-up or treatment should be required. However, an important complicating factor in this easy dismissal of many cases of candiduria is that, frequently, patients with candiduria are in the ICU or a long-term-care setting. They are unable to vocalize symptoms, and many have a long-term indwelling urethral catheter and thus cannot perceive frequency or dysuria.

The presence of pyuria is helpful, but only for patients without a long-term indwelling catheter. Both long-term indwelling catheters and intermittent catheterization are associated with low-grade inflammation and the presence of WBCs in the urine [13]. In addition, as many as 25% of patients with candiduria also have bacteriuria, which could cause pyuria [1].

Quantitation of the number of organisms in the urine to define infection and to distinguish upper UTI from lower UTI has been an alluring concept [14]. Initial attempts were undertaken by investigators in the 1970s in several studies that used renal biopsies to establish renal involvement [15–17]. In patients who did not have long-term indwelling catheters, documented renal infection was found with as few as 10,000–15,000 yeasts/mL and as many as 40,000 yeasts/mL in urine [17]. However, in the presence of long-term indwelling urethral catheters, the colony counts ranged from 20,000 to 100,000 cfu/mL, and there was no correlation with biopsy-proved renal infection. Thus, for a typical patient with an indwelling catheter, clinicians are left with 2 very unhelpful facts. As few as 10,000 cfu/mL may mean infection, and 10,000 to ≥100,000 cfu/mL may mean only colonization. These studies have not been ver-
ified, and it is highly unlikely that biopsy-proved renal infection is a standard that can be set for any study today. Recent data obtained from an experimental animal system of hematogenous renal candidiasis noted that any concentration of Candida species in the urine could reflect renal involvement [7].

Given that pyuria and quantitative cultures of urine have proved to be of little use in separating infection from colonization, other measures have been sought. It had been thought that the presence of pseudohyphae could distinguish yeasts causing infection from those merely colonizing the bladder, but this has been shown to be invalid [9]. Some species, such as C. glabrata, cannot make pseudohyphae, and C. albicans can be induced to form pseudohyphae merely by varying the pH and nutrients in the urine. In the 1970s, it was also thought that antibody-coated yeasts in the urine could be used as a marker for infection. This was shown to be a nonspecific finding present in most urine samples tested [18–20], including those from several patients who were found later at autopsy not to have Candida species in their kidneys [18]. A finding of casts containing yeast is specific for upper UTI with Candida species, but it is a very insensitive test [6, 21].

Thus, no diagnostic test emerges as sensitive, specific, and of practical use. This diagnostic dilemma directly affects a clinician’s decision to treat or not to treat when Candida species are found in the urine and also influences the interpretation of results of such treatment.

OUTCOMES

Part of the decision about whether to treat patients who have Candida species in their urine relates to the possibility of complications developing with untreated infection. Pyelonephritis can occur but is rarely well documented [22]. The risk of acute worsening of renal failure secondary to pyelonephritis is not well established. In the absence of obstruction, there are no data to suggest that upper UTI with Candida species leads to chronic renal failure.

Certain unusual complications of upper UTI— emphymatous pyelonephritis, perinephric abscess, and papillary necrosis—occur more often in persons with diabetes, as do fungus balls that obstruct the ureters [23–28]. Neonates are a special group in that Candida species in the urine usually signals hematogenous spread to the kidneys, and this event frequently is associated with the development of multiple obstructing fungus balls in the collecting system [24].

Candiduria does not herald candidemia in most patients. In a large prospective study, only 7 (1.3%) of 530 patients who had candiduria and were followed for 12 weeks developed candidemia [1]; in another smaller retrospective study, 11 (10.5%) of 105 patients with candiduria developed candidemia [3]. In a treatment trial that specifically enrolled asymptomatic or minimally symptomatic patients with candiduria, none of 316 patients developed candidemia [29]. However, in the presence of obstruction, candidemia can follow candiduria [30, 31]; this observation has led to recommendations to administer prophylactic antifungal agents to patients who are about to undergo urinary tract procedures to relieve obstruction [32].

Thus, the overwhelming body of evidence points to the fact that the presence of candiduria as an isolated observation generally does not portend subsequent invasive disease. This finding should make it less imperative to use antifungal agents to treat patients who have candiduria.

TREATMENT

Given the difficulty of defining precisely the site and source of candiduria and whether yeast in the urine reflects infection or colonization, it is not surprising that controversy exists regarding the appropriate treatment of candiduria [32–37]. First and foremost is the decision as to whether candiduria requires any therapeutic intervention. If treatment is regarded as appropriate, should it involve simply removing an indwelling urinary catheter or should an antifungal agent be given? If an antifungal agent is deemed to be appropriate, the choices include irrigation of the bladder with amphotericin B, intravenous amphotericin B, oral or intravenous fluconazole, or oral fluocytosine. Decisions as to the most appropriate antifungal therapy are based almost entirely on past experience with various therapeutic modalities rather than controlled trials that compared different regimens.

The largest controlled treatment trial of candiduria compared treatment with fluconazole (200 mg daily for 14 days) versus treatment with a placebo and noted an overall 50% response rate with drug versus 29% with placebo [29]. Clearance of funguria was greatest (78%) if the patient received therapy for 14 days and did not have an indwelling urethral catheter. In contrast, 47% of patients who received placebo and who also had their catheter removed had eradication of funguria. Similar clearance rates (35%) with catheter removal alone were noted in a large observational study of funguria [1].

The only other randomized treatment trials were open comparisons of bladder irrigation with amphotericin B and treatment with oral fluconazole [38–40]. A randomized study that compared bladder irrigation with several dosages of amphotericin B, single-dose intravenous amphotericin B, and low-dose fluconazole for treatment of candiduria noted more rapid clearance of funguria with bladder irrigation. However, eradication rates 1 week to 1 month after completion of therapy did not differ among the treatment regimens [39]. A subsequent treatment trial of bladder irrigation with amphotericin B compared with oral fluconazole (100 mg daily for 7 days) also showed higher initial clearance rates with bladder irrigation but similar rates by 1 month later [40].

All of the above treatment trials were flawed for a variety of
reasons. The numbers of patients in each treatment arm were too small to obtain meaningful results, the treatment period was short, and/or the dosage likely too low [38–40]. The follow-up period was too short in all of these trials for a variety of reasons. Follow-up for 7–9 days is too short to establish effectiveness of treatment [38, 39]. In a study of elderly patients [40], there was a 44% rate of withdrawal or death before the study end point occurred at 1 month after treatment. Although the trial was intended to have a 2-month follow-up period, investigators in a large placebo-controlled treatment trial [29] were able to obtain reliable follow-up information only for 2 weeks after treatment.

Perhaps the biggest problem with the few treatment trials that have been done is the populations studied, and this can be traced directly to the inadequacy of diagnostic methods available to investigators. For example, in the blinded placebo-controlled treatment trial of fluconazole, it is likely that most patients had merely bladder colonization. Only asymptomatic or minimally symptomatic patients who had no known urologic obstruction were eligible for enrollment [29]. It is very difficult to establish end points for studies that include patients with complicating factors, such as obstruction or renal insufficiency, and all treatment trials have excluded these high-risk patients. Unfortunately, patients with complicating factors are those for whom identifying the correct therapy is most problematic.

Different problems plague surveillance studies as a method to assess efficacy of treatment regimens. There is no control over the type of patients who are treated, the dosage and duration of treatment, other interventions that might occur, such as surgical procedures, and methods of assessing outcomes. Single-center studies are problematic because they have small numbers of patients, and the findings are frequently not applicable to other centers. Large multicenter surveillance studies overcome these issues but are problematic because there are invariably site-specific differences in the populations enrolled, laboratory techniques used to define candiduria, ability to do appropriate follow-up, and assessment of outcomes.

Despite all of the problems with the existing studies, the Infectious Diseases Society of America has issued guidelines for the treatment of candiduria [32]. It is recommended that the following groups be treated: infants with very low birth weights, patients undergoing genitourinary procedures, patients with neutropenia, renal transplant recipients, and symptomatic patients. The strength of these recommendations is graded IIIB, which means that there is only moderate evidence and that evidence is based on clinical experience, opinions of respected authorities, descriptive studies, or reports of expert committees.

Clearly, patients for whom symptomatic UTI due to Candida species has been diagnosed should be treated with an antifungal agent. The evidence for patients undergoing genitourinary procedures having an increased risk for candidemia is reasonable [30], as is the evidence for candiduria having a higher likelihood of reflecting upper UTI in infants with very low birth weights [11, 24]. Recent data bring into question the validity of the prior assumption that candiduria in a renal transplant recipient implies a high probability of upper UTI [41]. Many experts believe that candiduria in a patient with neutropenia is a marker for disseminated infection and that these patients should be treated for disseminated candidiasis [32]. Evidence for this belief comes from experimental animal studies highlighting the great importance of the kidney as an end organ in immuno-suppressed candidemic mice and from clinical experience with patients with neutropenia who have leukemia.

REMAINING ISSUES AND FUTURE STUDIES

Questions remain regarding the management of candiduria. Whether they can be answered by well-designed studies is yet to be determined. The overriding issue with regard to candiduria is to develop methods to distinguish infection from colonization and to distinguish upper from lower urinary tract involvement. Until this is accomplished, it is unlikely that meaningful treatment trials can be done. Approaches that could be tried include the expanded use of CT or MRI to establish upper UTI. Currently, ultrasound examination, which is easily done, is used for the detection of obstructing fungus balls; it is not clear what additional pathologic abnormalities (e.g., small cortical abscesses) could be assessed by more sophisticated and much more expensive CT and MRI. There is no experience with assays for β-glucan, a cell wall component of Candida species and other fungi, in urine, but it seems unlikely that this type of test will be able to differentiate colonization from infection; these tests are of most benefit on normally sterile body fluids. Bladder washout techniques use irrigation with amphotericin B to eliminate colonization of the bladder [42]; urine samples obtained following this procedure that remain positive for yeast presumably reflect upper UTI. It is doubtful that this technique will be adopted broadly because of the need for placement of a urethral catheter. For individual complicated cases, however, it could be tried.

A second issue of great importance is to determine for specific populations the true risk of developing UTI with Candida. There is probably little to be gained from further studies that encompass a broad sampling of patients in hospital. A noteworthy specific population that would be worthwhile to study is patients with diabetes. From case reports and retrospective reviews, it appears that this group is at higher risk for the complications that can arise from UTIs due to Candida species [23, 26–28], but no cohort has been followed long-term to define the actual risk of these unusual complications. Another group is patients in long-term-care facilities. These patients are frequently treated for candiduria, but no studies have actually determined the incidence of candiduria, explored the natural
history of this finding, or defined the role of the catheter in this setting. Another group for which data on the incidence and natural history of candiduria would be very important is patients in the ICU. The heterogeneity of these patients makes this task difficult, but the greatest need probably exists in this group, who appear to be at high risk for candiduria. Defining the role of urinary tract colonization in relation to candidemia in specific high-risk groups within the ICU setting might prove to be very useful to clinicians. The overriding issue in attempting to study any of these specific groups remains our inability to distinguish infection from colonization.

The third issue is to define better treatment regimens, especially for those patients who have fluconazole-resistant yeasts. To perform controlled, randomized, blinded studies, very stringent inclusion criteria for entry will have to be observed. One can envision a study in which inclusion criteria will encompass no indwelling catheters, urine obtained by straight catheterization, persistent candiduria at an arbitrary minimum number of yeasts per milliliter, such as $\geq 10,000\text{ cfu/mL}$, and symptoms suggesting infection. It will be very difficult to enroll patients into such a restrictive study. Outcome measures of such a trial need to be stringent, and follow-up must be done more effectively than has been accomplished in any study thus far. It is unlikely that eradication of candiduria will be an adequate end point.

Thus, there are roadblocks to studying each of the major issues associated with candiduria. The diagnostic issues override all others and, at this time, effectively render untenable studies assessing risk factors for infection and superiority of various treatment regimens.

Acknowledgments

Potential conflicts of interest. C.A.K.: no conflicts.

References


