Predictors and Outcomes of Candiduria in Renal Transplant Recipients

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Background. The epidemiology of candiduria in renal transplantation is unknown.

Methods. We performed a nested case-control study to evaluate the epidemiology of candiduria in renal transplant recipients at the University of Wisconsin (Madison) over an 8-year period.

Results. Renal transplantations were performed on 1738 patients during this period, 192 of whom had 276 episodes of candiduria. *Candida glabrata,* which was recovered from 98 (51%) of 192 case patients, was the most common pathogen identified. Most case patients were asymptomatic. Independent predictors of candiduria were female sex (odds ratio [OR], 12.5; 95% confidence interval [CI], 6.7–23.0), intensive care unit admission (OR, 8.8; 95% CI, 2.3–35.0), antibiotic use during the month before candiduria (OR, 3.8; 95% CI, 1.7–8.3), presence of an indwelling bladder catheter (OR, 4.4; 95% CI, 2.1–9.4), diabetes (OR, 2.2; 95% CI, 1.3–3.9), neurogenic bladder (OR, 7.6; 95% CI, 2.1–27), and malnutrition (OR, 2.4; 95% CI, 1.3–4.4). Log-rank testing of Kaplan-Meier curves revealed that 60-day, 90-day, and cumulative survival rates were significantly different between case and control patients; there was no difference in the survival rate during the first 30 days after transplantation. A variety of regimens were used for treatment; 119 case patients (62%) underwent removal of the indwelling bladder catheter within 1 week after diagnosis of candiduria. Candiduria cleared in 148 case patients (77%). Treatment of candiduria was not associated with an improved survival rate.

Conclusions. Candiduria occurs commonly in renal transplant recipients. Risk factors for candiduria in such persons are similar to those in hospitalized patients who have not received a transplant. Candiduria is associated with reduced survival rates among persons who have undergone renal transplantation; this is likely a marker for severity of illness. Treatment of asymptomatic candiduria in renal transplant recipients does not appear to result in improved outcome.

Major advances in transplantation techniques and understanding of transplant biology have greatly improved survival rates among renal transplant recipients. Each year, ~15,000 renal transplants are performed in the United States, with a 5-year survival rate of >80% [1]. However, infection, particularly infection of the renal allograft, continues to present a major challenge. Among fungi, *Candida* species are the most common causes of infection in persons who have undergone renal transplantation. Although such infections are usually asymptomatic, they can lead to pyelonephritis and disseminated infection [2, 3]. The epidemiology of candiduria in the renal transplant population has not been characterized. We performed a nested case-control study to determine predictors of candiduria and a retrospective cohort study to determine outcomes of candiduria in renal transplant recipients.

METHODS

Data collection and study definitions. We used data from a prospectively maintained transplant database to identify patients who underwent renal transplantation at the University of Wisconsin Hospital (Madison) between 1 January 1994 and 31 December 2001 (n = 1738), all of whom had at least 1 urine culture performed. Case patients were renal transplant recipients who had at least 1 urine culture that yielded ⩾1000 cfu/mL of yeast. Control patients were renal transplant recipients without candiduria who were randomly selected from the database and matched with case patients according to year of transplantation. All control pa-

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tients had at least 1 urine culture negative for *Candida* species within 2 months of the cultures performed for matched case patients. All case and control patients were observed longitudinally at our institution.

Collected data included demographic characteristics, patient signs and symptoms, and information pertaining to transplantation, candiduria, and outcome. Relevant definitions and routine operative- and perioperative-care protocols for renal transplant recipients are shown in table 1.

Statistical analysis. Univariate logistic regression analyses of potential risk factors for candiduria were used to estimate ORs and 95% CIs. Backward elimination was used to select a parsimonious multivariate logistic regression model based on Aikaike's information criterion [5]. Analyses were conducted using SAS software, version 8.1 (SAS). Separate analyses of risk factors for *Candida albicans* and *Candida glabrata* infections were performed similarly.

The life table method and log-rank testing of Kaplan-Meier curves were used to determine the survival rate after transplantation. A Cox proportional hazards model was constructed to assess the role of candiduria as an independent predictor of survival. In addition, the survival rate among case patients was stratified by treatment status to assess differences in the survival rate associated with treatment of candiduria.

RESULTS

Incidence. Of the 1738 patients at the University of Wisconsin who underwent renal transplantation between 1 January 1994 and 31 December 2001, candiduria occurred in 192 (11%). The mean number ($\pm$ SD) of episodes of candiduria per case patient was 1.43 $\pm$ 0.70, for a total of 276 episodes. The first episode occurred a median of 54 days after transplantation (range, 0–2922 days).

Demographic and clinical characteristics. Demographic characteristics and clinical features of case and control patients are summarized in table 2. A total of 218 case and control patients (57%) were female. The median age at the time of transplantation was 47 years for both cases and controls. Most study subjects were white (84% of cases and 91% of controls). African-American subjects accounted for 8% of cases and 6% of controls. A total of 64% of the entire study population (141 cases and 103 controls) received a renal transplant from a cadaveric donor, 27% (43 cases and 61 controls) received a trans-

Table 1. Definitions and routine perioperative- and operative-care protocols in a study of candiduria in persons who received a renal transplant at the University of Wisconsin during 1994–2001.

Term or protocol	Definition or summary
Term	
Candiduria	Presence of >1000 cfu/mL of *Candida* species in the urine
Recurrence of candiduria	Initial clearance followed by a second urine culture positive for *Candida* species within 30 days after the initial culture
Persistence of candiduria	At least 2 consecutive urine cultures positive for *Candida* species
Clearance of candiduria	A second urine culture without evidence of *Candida* species
Candidemia	*Candida* species in the peripheral blood
Renal candidiasis	Parenchymal infection of the kidney caused by *Candida* species, determined on the basis of histopathologic examination or imaging and a urine or tissue culture positive for *Candida* species
Protocol	
Routine operative and perioperative care	An extravesicular Liche technique [4] was used for anastomosis of the donor ureter to the recipient bladder and an intraopertive intraureteral stent placed. Before removal of the stent at 6 weeks, a 500-mg prophylactic dose of oral ciprofloxacin was given. Perioperatively, 1 dose of cefazolin (1 g iv) was given. Bladder irrigation with gentamicin solution was also done. Perioperative fluconazole is not routinely used at our institution. The initial immunosuppressive protocol consisted of mycophenolate, methylprednisolone, and alemtuzumab in recent years. In earlier years, tacrolimus, cyclosporine, and/or azathioprine were used. Acute cellular graft rejection was treated with intravenous methylprednisolone, increased doses of calcineurin inhibitors, and, if necessary, antilymphocyte globulin (thymoglobulin) or OKT3 monoclonal antibody. Renal ultrasonography was performed if obstruction was suspected.
Candida speciation[a]	At our institution, *Candida* isolates detected in the urine are speciated at any colony count for all clean-catch and straight-catheter specimens. All *Candida* isolates associated with a colony count >100,000 cfu/mL are speciated. Cultures are not set up for to test for the presence of fungi on Sabouraud's media.

[a] The cultures for which speciation was not done were excluded from the analysis of risk factors for *Candida glabrata* and *Candida albicans*.

Table 2. Demographic and clinical characteristics of case and control patients who underwent renal transplantation at the University of Wisconsin (Madison) during 1994–2001.

Characteristic	Cases (n = 192)	Controls (n = 192)
Sex		
Male	44 (23)	122 (64)
Female	148 (77)	70 (36)
Age at time of transplantation, years		
Median ± SD	47 ± 12	47.2 ± 15
Range	15–74	0.5–77
Race		
White	162 (84)	175 (91)
Black	16 (8)	12 (6)
Other (Asian, Native American, Hispanic, or unknown)	14 (7)	5 (3)
Transplant donor		
Cadaveric	141 (73)	103 (54)
Living, related	43 (22)	61 (32)
Living, unrelated	8 (4)	28 (15)
Comorbid condition before transplantation		
Diabetes	91 (47)	62 (32)
Hypertension	143 (74)	186 (97)
Glomerulonephritis	45 (23)	57 (30)
Coronary vascular disease	101 (53)	80 (42)
Peripheral vascular disease	73 (38)	46 (24)
Neurogenic bladder	30 (16)	4 (2)
Other active infections	139 (72)	117 (61)
Episodes of candiduria per patient, mean no. ± SD	1.43 ± 0.70	…
Time to first episode of candiduria after transplantation, median days (range)	54 (0–2922)	…
Symptom/sign	89 (46)	34 (18)
Fever	48 (25)	10 (5)
Allograft pain	26 (14)	10 (5)
Suprapubic pain	8 (4)	5 (3)
Dysuria	11 (6)	3 (2)
Pyuria	25 (13)	3 (2)
Hematuria	30 (16)	19 (10)
Concurrent bacteriuria	77 (40)	…
Presence of a ureteral stent ⩽1 month before candiduria diagnosis	91 (47)	110 (57)
Presence of an indwelling bladder catheter[a]		
At the time of candiduria diagnosis	67 (35)	19 (10)
⩽1 Month before candiduria diagnosis	111 (58)	88 (46)
Candidemia	10 (5)	0
Antibiotic use		
At the time of candiduria diagnosis	159 (83)	134 (70)
Within 1 month before candiduria diagnosis	166 (86)	143 (74)

NOTE. Data are no. (%) of patients, unless otherwise indicated.

[a] Including nephrostomy tubes and ileoconduits.

plant from a living related donor, and 9% (8 cases and 28 controls) received a transplant from a living unrelated donor.

Clinical spectrum of disease in case patients. Fever was present in only 25% of cases, and symptoms referable to the genitourinary tract were reported in <20% (table 2). Fifty-four percent of cases were asymptomatic.

Microbiological data. The mean *Candida* colony count (±SEM) was 47,739 ± 2448 cfu/mL. *C. glabrata* was responsible for the majority (146 [53%]) of the 276 episodes, followed by *C. albicans* (96 [35%]). Cultures with ⩾100,000 cfu/mL were associated with 87 episodes (32%; table 3). The concomitant identification of bacteriuria was common (123 episodes [45%]).

Table 3. Results of microbiological analysis of candiduria for renal transplant recipients at the University of Wisconsin (Madison) who had at least 1 urine culture that yielded ⩾1000 cfu/mL of yeast, 1994–2001.

Isolate(s) recovered	No. (%) of candiduria episodes (n = 276)
Candida species[a]	
C. albicans	96 (35)
C. glabrata	146 (53)
C. parapsilosis	10 (4)
C. krusei	1 (<1)
C. tropicalis	4 (1)
Non-*Candida* species[b]	14 (5)

NOTE. A total of 87 episodes (32%) were associated with a colony count of >100,000 cfu/mL.

[a] Two species were recovered in 5 episodes (2%).

[b] Includes *Saccharomyces* and unspeciated isolates.

The most common urine collection method was midstream urine sampling (178 episodes [64%]), indwelling bladder catheter sampling (68 [25%]), single or intermittent catheter sampling (18 [7%]), nephrostomy tube sampling (7 [3%]), and ileal conduit sampling (5 [2%]). Urinalysis suggested that the majority of specimens (153 [55%]) were of predefined adequate quality (i.e., they contained ⩽2 epithelial cells/mL). Results of risk factor analyses were similar regardless of urinalysis quality. We did not identify a preponderance of poor-quality urinalyses in women or in association with certain collection methods.

Candidemia was observed in 10 case patients (5%). All 10 cases had intravascular catheters, and most were in the intensive care unit (ICU). *C. glabrata* was responsible for candidemia in 6. Three of the 10 cases died, but the deaths were not attributed to candidemia (2 died from unknown causes, and 1 died from disseminated *Aspergillus* infection).

Univariate risk factor analysis. Candiduria was more common among females, occurring in 114 (77%) of 148 and 25 (36%) of 70 female case and control patients, respectively. The comorbid illnesses most strongly associated with candiduria in case patients were diabetes (in 91 [47%]; OR, 1.9; $P = .003$), peripheral vascular disease (in 73 [38%]; OR, 1.9; $P = .005$), and cardiovascular disease (in 101 [53%]; OR, 1.5; $P = .036$) (table 4). Other underlying infections, which occurred in 139 case patients (72%; OR, 1.7; $P = .018$), were also more common in this group, with recurrent bacterial urinary tract infections occurring in 77 (40%; OR, 4.0; $P < .001$). Other common infections included respiratory tract infection (in 19 cases [10%]), intra-abdominal infection (in 25 [13%]), and primary blood stream infection (in 28 [15%]). A total of 169 case patients (88%) were undergoing dialysis at the time of transplantation (OR, 2.0; $P = .015$). Several associated conditions, including malignancy and neutropenia, that were reported as being common in other patient population studies [2] were not found more commonly in the current cohort.

Urologic abnormalities, which were found in 69 case patients (36%), were significantly associated with candiduria (OR, 1.9; $P = .004$). The most common abnormality, observed in 30 cases (16%), was a neurogenic bladder associated with long-standing diabetic neuropathy (OR, 9.1; $P < .001$). Few study subjects had nephrolithiasis (11 cases [6%] and 4 controls [2%]), and no bladder or renal fungal balls were identified. Twenty-two percent of the study population had an indwelling urinary catheter that was either a Foley catheter, a nephrostomy tube, or an ileal conduit at the time of sample collection (67 cases [35%] and 19 controls [10%]), and 52% of the subjects (111 cases [58%] and 88 controls [46%]) had a urinary catheter placed within 30 days before the candiduria episode (table 2). Ureteral stents were common in both cases and controls (91 [47%] and 110 [57%], respectively; OR, 0.7; $P = .053$) (table 4). Urinary catheters stayed in place for a mean of 8.8 days (range, 1–31 days).

Other nosocomial or iatrogenic factors identified more commonly in the candiduria cohort included antibiotic use before (166 cases [87%]; OR, 2.2; $P = .004$) or at the time of candiduria (OR, 2.1; $P = .003$), presence of a central venous catheter (134 [70%]; OR, 1.9; $P = .003$), receipt of parenteral nutrition (18 [9%]; OR, 9.8; $P = .002$), and admission to the ICU (38 [20%]; OR, 15.5; $P < .001$). Antibiotic therapies included trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* pneumonia prophylaxis, ciprofloxacin before stent removal, and specific treatment for bacterial infections. Agents from multiple antibiotic classes were used, and no one antibiotic class was more likely to be associated with candiduria.

Multivariate risk factor analyses. In the final multivariable models (table 4), female sex (OR, 12.5; 95% CI, 6.7–23.0), ICU admission (OR, 8.8; 95% CI, 2.3–35.0), antibiotic use in the month before candiduria (OR, 3.8; 95% CI, 1.7–8.3), presence of an indwelling bladder catheter (OR, 4.4; 95% CI, 2.1–9.4), diabetes (OR, 2.2; 95% CI, 1.3–3.9), neurogenic bladder (OR, 7.6; 95% CI, 2.1–27), and malnutrition (OR, 2.4; 95% CI, 1.3–4.4) were independent predictors of candiduria. The presence of a ureteral stent was associated with a decreased likelihood of candiduria (OR, 0.2; 95% CI, 0.1–0.4).

Risk factors for* C. albicans *and* C. glabrata *infections. We identified risk factors separately for *C. albicans* and *C. glabrata* infections. Independent predictors for *C. albicans* candiduria were female sex (OR, 9.0; $P < .01$), diabetes (OR, 3.0; $P = .004$), neurogenic bladder (OR, 10.5; $P = .002$), malnutrition (OR, 2.8; $P = .015$), antibiotic use in the 1 month before candiduria (OR, 6.6; $P < .001$), presence of an indwelling catheter (OR, 4.3; $P = .003$), presence of a ureteral stent (OR, 0.1;

Table 4. Univariate and multivariate analyses of predictors of candiduria in case and control patients who received a renal transplant at the University of Wisconsin (Madison) during 1994–2001.

Variable	No. (%) of patients with candiduria		Univariate analysis		Multivariate analysis	
	Cases (n = 192)	Controls (n = 192)	OR (95% CI)	P	OR (95% CI)	P
Female sex	148 (77)	70 (36)	5.9 (3.8–9.2)	<.001	12.5 (6.7–23)	<.001
Diabetes	91 (47)	62 (32)	1.9 (1.2–2.9)	.003	2.2 (1.3–3.9)	.006
Glomerulonephritis	45 (23)	57 (30)	0.7 (0.4–1.1)	.14	…	
Cardiovascular disease	101 (53)	80 (42)	1.5 (1.0–2.3)	.036	…	
Peripheral vascular disease	73 (38)	46 (24)	1.9 (1.2–2.9)	.005	…	
Malignancy	17 (9)	10 (5)	1.8 (0.8–3.9)	.17	…	
Urologic abnormality	69 (36)	48 (25)	1.9 (1.2–3.0)	.004	…	
Neurogenic bladder	30 (16)	4 (2)	9.1 (3.1–26)	<.001	7.6 (2.1–27)	.002
Nephrolithiasis	11 (6)	4 (2)	2.9 (0.9–9.1)	.077	2.9 (0.7–12)	.15
Malnutrition	95 (49)	47 (25)	3.0 (1.9–4.6)	<.001	2.4 (1.3–4.4)	.006
Dialysis	169 (88)	151 (79)	2.0 (1.1–3.5)	.015	1.9 (0.9–4.0)	.10
Other active infection	139 (72)	117 (61)	1.7 (1.1–2.6)	.018	…	
Detection of cytomegalovirus IgG	34 (18)	20 (10)	1.7 (0.9–3.0)	.077	…	
Hepatobiliary disease	28 (15)	18 (9)	1.6 (0.9–3.1)	.12	…	
Antibiotic use						
1 Month before candiduria diagnosis	166 (86)	143 (74)	2.2 (1.3–3.7)	.004	3.8 (1.7–8.3)	.001
At the time of candiduria diagnosis	159 (83)	134 (70)	2.1 (1.3–3.4)	.003	…	
Presence of an indwelling bladder catheter						
At the time of candiduria diagnosis	67 (35)	19 (10)	4.8 (2.7–8.3)	<.001	4.4 (2.1–9.4)	<.001
1 Month before candiduria diagnosis	111 (58)	88 (46)	1.6 (1.1–2.4)	.019	…	
Ureteral stent	91 (47)	110 (57)	0.7 (0.4–1.0)	.053	0.2 (0.1–0.4)	<.001
Intensive care unit admission	38 (20)	3 (2)	15.5 (4.7–51)	<.001	8.8 (2.3–35)	.002
Total parenteral nutrition use	18 (9)	2 (1)	9.8 (2.2–43)	.002	…	
Recurrent urinary tract infection	77 (40)	28 (15)	4.0 (2.4–6.6)	<.001	…	
Presence of a central venous catheter	134 (70)	105 (55)	1.9 (1.2–2.9)	.003	…	

P < .001), and ICU admission (OR, 7.4; P = .018). For *C. glabrata,* the results were similar.

Fluconazole use before the first episode of candiduria occurred for 6 case patients (3%) with *C. albicans* candiduria and for 17 (9%) with *C. glabrata* candiduria. Use of fluconazole was more common during subsequent episodes of candiduria, increasing to 40% (8 episodes) and 33% (5 episodes) for *C. albicans* candiduria and to 21% (6 episodes) and 43% (9 episodes) for *C. glabrata* candiduria during the second and third episodes, respectively. In the subgroup analysis, however, fluconazole use was not an independent factor for isolation of either organism.

Outcome. We compared survival rates after transplantation between cases and controls at 30 days, 60 days, 90 days, and cumulatively. Overall, 64 subjects died (16 controls [8%] and 48 cases [25%]). Nine cases and none of the controls died during the hospitalization in which candiduria occurred. The remaining deaths occurred in outpatient settings. The most common cause of death among the cases was bacterial infection (in 16 [33%]), whereas the most common cause of death among the controls was malignancy (in 4 [25%]). It is important to acknowledge that the cause of death was not available for the majority of controls. The single fungal infection–associated death was due to invasive aspergillosis. The 30-day survival rate was 99.4% among cases and 100% among controls (P = .32, by the log-rank test), the 60-day survival rate was 97.4% among cases and 100% among controls (P = .02, by the log-rank test), and the 90-day survival rate was 96% among cases and 100% among controls (P = .005, by the log-rank test) (figure 1).

To determine whether candiduria was an independent predictor of death, we performed multivariable Cox proportional hazards modeling using the cumulative survival rate from the time of transplantation as the outcome and the presence of candiduria as the main exposure variable. We adjusted for covariates that might be expected to influence the survival rate from the time of transplantation and to predispose subjects to candiduria, such as ICU admission, receipt of total parenteral nutrition, and presence of urologic abnormalities. The final model revealed that cases were 3 times as likely as controls to die (hazard ratio, 3.0; P < .05).

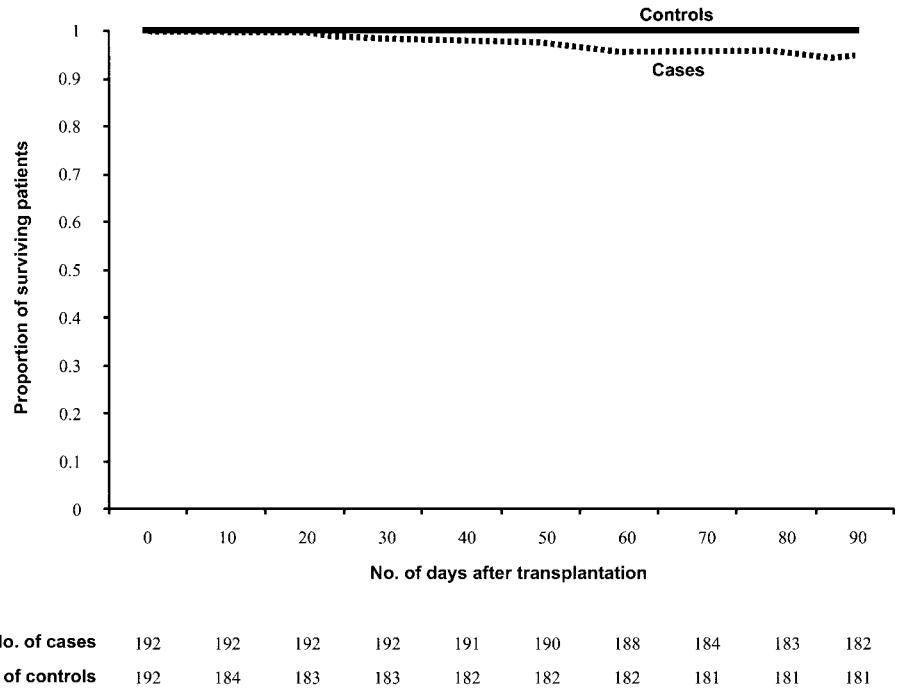

Figure 1. Survival rate after transplantation among case and control patients who received a renal transplant at the University of Wisconsin (Madison) during 1994–2001. The log-rank test revealed a statistically significant difference in the survival rate between the groups at 90 and 60 days after transplantation ($P = .005$ and $P = .009$, respectively) but not at 30 days after transplantation ($P = .32$).

Case patient outcome, by treatment. Of the 192 case patients with candiduria, 97 were and 95 were not treated. Sixteen cases (17%) died in the group that did not receive treatment, and 32 (33%) died in the group that received treatment. Comparison of the cumulative survival rate from the time of transplantation between patients who received treatment for candiduria and those who did not revealed a statistically significant difference ($P = .007$, by the log-rank test; figure 2). In a multivariable Cox proportional hazards model that included ICU admission, treatment was not a statistically significant independent predictor of death. Fifty-nine (61%) of 97 cases were treated with fluconazole, and 58 (60%) were treated with amphotericin B bladder irrigation (table 5). The indwelling bladder catheter was removed from 22% of cases (10 of 45 for whom data were available) on the day on which candiduria was diagnosed. Overall, 119 cases (62%) with candiduria had indwelling catheters removed within 1 week after receiving the candiduria diagnosis. The small number of cases who received any single therapy precluded statistical evaluation of the superiority of treatment.

DISCUSSION

Urinary tract infections are the most common infections that occur after renal transplantation [6]. A substantial proportion of these infections are caused by fungi [7], yet the incidence of candiduria among recipients of renal transplants has not been well defined. We found that 11% of all renal transplant recipients developed at least 1 episode of candiduria. This is similar to the incidence of candiduria reported for hospitalized patients who have not received a transplant [8–10].

C. glabrata accounted for more than one-half (53%) of the episodes, followed by *C. albicans* (35% of episodes) and *C. parapsilosis* (4% of episodes). The preponderance of non-*albicans Candida* species contrasts with other candiduria and candidemia studies, in which *C. albicans* was the most frequently isolated *Candida* species [11, 12], although the number of infections caused by non-*albicans* species appears to be increasing [12–14]. The predominance of *C. glabrata* in our study has important implications for therapy: the triazole class of drugs has reduced in vitro potency against *C. glabrata,* and caspofungin does not achieve therapeutic concentrations in the urine

Similar to other studies of candiduria, we found that more than one-half of the case patients were asymptomatic [2, 15]. The presence of fever was, however, strongly associated with the presence of *Candida* species in the urine. The diagnosis of fungal urinary tract infection is less well established than that of infection with a bacterial origin [16–18]. Approximately one-third of the cultures reported in our study had colony counts of $\geqslant$100,000 cfu/mL, but these cultures were not more commonly associated with signs and symptoms of disease, pyuria, upper respiratory tract disease, or candidemia.

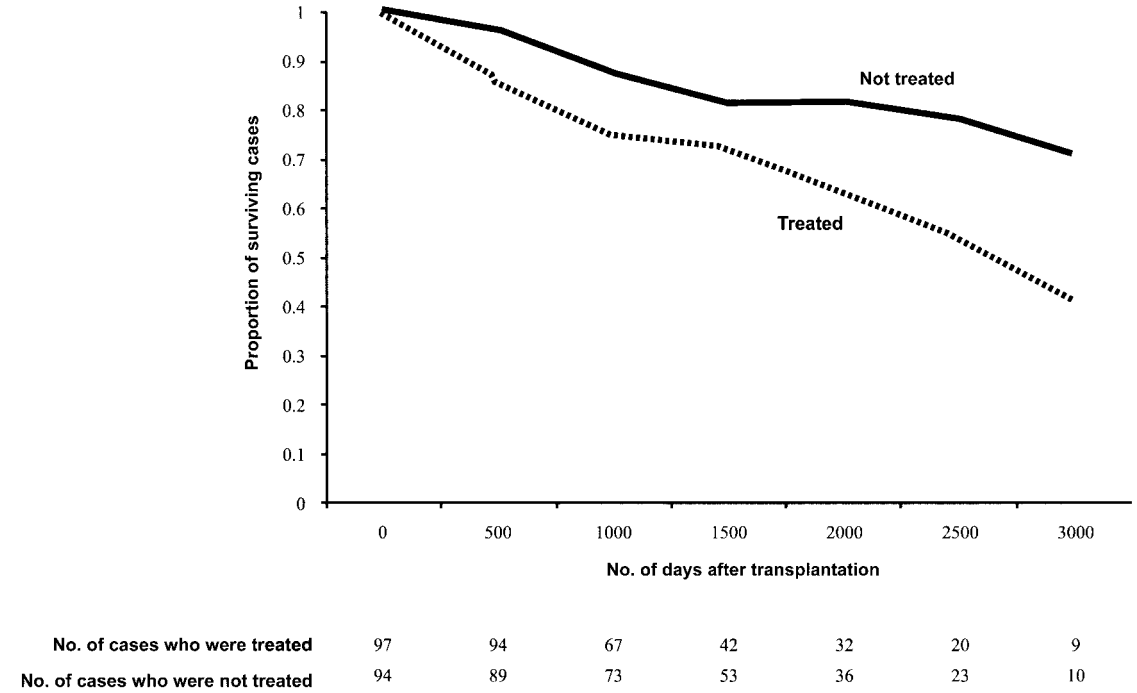

Figure 2. Survival rate after transplantation among case patients with candiduria after renal transplantation who did or did not receive treatment—University of Wisconsin (Madison), 1994–2001. The log-rank test revealed a statistically significant difference in the survival rate between the groups ($P = .007$).

In an analysis of >800 episodes of candiduria, Kauffman et al. [2] found that surgical procedures, diabetes mellitus, malignancy, and urologic abnormalities were common comorbid conditions associated with funguria. However, transplant recipients accounted for only 3% of the study population. We found that diabetes and urologic abnormalities, particularly neurogenic bladder, were important coexisting comorbidities. In our multivariable analysis, we found that female sex was associated with a risk for candiduria that was 12 times that for male sex. This finding is consistent with studies of bacterial UTIs, which found female sex to be a risk factor for bacterial UTIs, perhaps because the urethra is shorter and close to the vagina. We also found that invasive devices, including those distant from the genitourinary tract, greatly increased the risk of candiduria: the presence of an indwelling Foley catheter conferred a risk for UTIs that was 4 times that for transplant recipients without an indwelling Foley catheter. Invasive devices represent a potentially modifiable risk factor, and our results suggest that every effort should be made to limit the use of these devices in renal transplant recipients.

Previous studies have identified antimicrobial use to be a major risk factor for *Candida* infection, presumably because overgrowth of *Candida* species occurs in the absence of bacterial flora that compete for nutrients [2, 9, 19]. We found that antimicrobial use during the month before diagnosis of candiduria was associated with a risk of candiduria that was almost 4 times that for transplant recipients who had not received antimicrobials. However, we were not able to identify a particular class of antimicrobials that appeared to differentially increase the risk. In contrast, Harris et al. [19] reported that fluoroquinolone use was associated with an increased risk of *C. glabrata* funguria.

Table 5. Treatment regimens for case patients with candiduria after renal transplantation—University of Wisconsin (Madison), 1994–2001.

Therapy	*n/N* (%) of case patients
Antifungal regimen	
Fluconazole	59/97 (61)
Amphotericin B bladder irrigation	58/97 (60)
Amphotericin B IV	10/97 (10)
Amphotericin B lipid complex	6/97 (6)
Flucytosine	3/97 (3)
Caspofungin	2/97 (2)
Itraconazole	2/97 (2)
Amphotericin B colloidal dispersion	2/97 (2)
Removal of an indwelling bladder catheter	28/45 (62)[a]

NOTE. Data are no. of cases who received the specific treatment/total no. treated (%), unless otherwise indicated. The absolute number of patients is >97 because many received >1 kind of therapy.

[a] Data are no. of cases for whom the catheter was removed/total no. for whom data were available (%).

Subgroup analyses failed to identify species-specific risk factors. In contrast to results of a case-control study by Harris et al. [19] that involved hospitalized patients, we did not find fluconazole use to be a predictor of *C. glabrata* in our population.

The rate of candidemia we observed is higher than that reported in the study by Kauffman et al. [2], in which only 7 hospitalized patients with funguria (1.3%) had blood cultures positive for fungi. This discrepancy may be due to differences in the severity of underlying illnesses, the high degree of immunosuppression in our study population, the use of invasive devices, and the presence of urologic abnormalities (in 69 cases [36%]). In an earlier study evaluating the association between candidemia and its origin from the urinary tract, Ang et al. [20] found that 19 (73%) of the 26 episodes of candidemia were associated with urinary tract obstruction.

We found that candiduria was associated with a survival rate that was lower for cases, compared with controls. This is in keeping with the diminished survival rate associated with candiduria in studies of critically ill populations or persons without transplants [21] and likely reflects the greater severity of illness and comorbidities and the increased use of invasive devices in cases, compared with controls, with candiduria being a surrogate marker for these features rather than directly affecting the mortality rate. In an analysis of a large national database of 33,240 renal transplant recipients in the United States, Abbott et al. [22] reported that patients with a fungal infection had risk of mortality that was almost 3-fold higher than that for patients with no fungal infection (risk ratio, 2.88; 95% CI, 2.22–3.74). However, a candiduria-specific survival analysis was not performed.

We found that treatment of candiduria or the infecting agent did not impact the likelihood of urine clearance of candiduria (data not shown). This finding is similar to that of other studies in which treatment was not associated with a difference in the microbiologic outcome of candiduria. The greater mortality rate among treated patients likely reflects the greater severity of illness in that group, which may have influenced the decision to treat candiduria [23]. In a randomized, placebo-controlled trial of fluconazole treatment in 316 hospitalized patients with asymptomatic candiduria, Sobel et al. [24] found that, although fluconazole therapy initially was associated with higher eradication rates (79 [50%] of 159 in the fluconazole group vs. 46 [29%] of 157 in the placebo group; $P < .001$), the incidence of candiduria in both groups was similar after 2 weeks, and no patient in either group developed pyelonephritis or fungemia. Mortality was not reported as an outcome in this study.

In the renal transplantation population, many asymptomatic patients with candiduria are treated because of the perceived risk to the allograft. However, whether treatment of candiduria improves outcomes in renal transplant recipients is unclear. Recent guidelines from the Infectious Diseases Society of America [25] recommend treatment of candiduria in patients with renal allografts, preferably with fluconazole or intravenous amphotericin B; bladder irrigation with amphotericin B is of limited value. In our analysis, treatment of candiduria was not an independent predictor of the survival rate, nor did it result in a greater likelihood of clearing *Candida* from the urine. Treatment of asymptomatic candiduria in renal transplant recipients may not be warranted if there is no suspicion of disseminated or upper respiratory tract disease.

A number of possible explanations exist for our observations. First, it is possible that, given the increased frequency of *C. glabrata* in our population, resistance to fluconazole did not allow for effective therapy. The majority of patients in our cohort who received treatment received fluconazole in varying doses for differing durations, again reflecting the lack of consensus that exists in this area. The presence of non-*albicans* species of *Candida* was not associated with the inability to clear candiduria. Second, it is likely that the presence of candiduria reflects opportunistic colonization of the urinary tract in severely ill patients, whose mortality is predicated on comorbidities, organ failure, and severity of illness rather than on candiduria. In such a situation, treatment of candiduria would not be expected to improve the rate of survival.

The current study has a number of limitations, including the retrospective design, which may have limited the availability of data. However, the database was prospectively maintained and provided information about all but a few variables. We were not able to assess the impact of candiduria on allograft survival, because of limitations associated with data availability; however, this clearly is a relevant and important issue. Future prospective studies should evaluate graft as well as patient survival.

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References

1. United Network for Organ Sharing. Home page. Available at: http://www.unos.org. Accessed 18 October 2004.
2. Kauffman CA, Vazquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. The National Institute for Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis **2000**; 30:14–8.
3. Fisher JF, Newman CL, Sobel JD. Yeast in the urine: solutions for a budding problem. Clin Infect Dis **1995**; 20:183–9.
4. Morris PJ. Kidney transplantation principles and practice. 5th ed. Philadelphia: W. B. Saunders, **2001**.
5. Lemeshow S, Hosmer DWJ. A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol **1982**; 115:92–106.

6. Munoz P. Management of urinary tract infections and lymphocele in renal transplant recipients. Clin Infect Dis **2001**; 33(Suppl):S53–7.
7. Patel R. Infections in recipients of kidney transplants. Infect Dis Clin North Am **2001**; 15:901–52, xi.
8. Fraser VJ, Jones M, Dunkel J, Storfer S, Medoff G, Dunagan WC. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin Infect Dis **1992**; 15:414–21.
9. Storfer SP, Medoff G, Fraser VJ, Powderly WG, Dunagan WC. Candiduria: retrospective review in hospitalized patients. Infect Dis Clin Pract **1994**; 3:23–9.
10. Sobel JD, Kauffman CA, McKinsey D, et al. Candiduria: a randomized, double-blind study of treatment with fluconazole and placebo. Clin Infect Dis **2000**; 30:19–24.
11. Marchetti O, Bille J, Fluckiger U, et al. Epidemiology of candidemia in Swiss tertiary care hospitals: secular trends, 1991–2000. Clin Infect Dis **2004**; 38:311–20.
12. Fidel PL Jr, Vazquez JA, Sobel JD. *Candida glabrata:* review of epidemiology, pathogenesis, and clinical disease with comparison to *C. albicans*. Clin Microbiol Rev **1999**; 12:80–96.
13. Occhipinti DJ, Gubbins PO, Schreckenberger P. Frequency, pathogenicity and microbiologic outcome of non-*Candida albicans* candiduria. Eur J Clin Microbiol Infect Dis **1994**; 13:459–67.
14. Pappas PG, Rex JH, Lee J, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. Clin Infect Dis **2003**; 37:634–43.
15. Lundstrom T, Sobel J. Nosocomial candiduria: a review. Clin Infect Dis **2001**; 32:1602–7.
16. Rivett AG, Perry JA, Cohen J. Urinary candidiasis: a prospective study in hospital patients. Urol Res **1986**; 14:183–6.
17. Schonebeck J. Asymptomatic candiduria: prognosis, complications, and some other clinical considerations. Scand J Urol Nephrol **1972**; 6: 136–46.
18. Kozinn PJ, Taschdjian CL, Goldberg PK, Wise GJ, Toni EF, Seelig MS. Advances in the diagnosis of renal candidiasis. J Urol **1978**; 119:184–7.
19. Harris AD, Castro J, Sheppard DC, Carmeli Y, Samore MH. Risk factors for nosocomial candiduria due to *Candida glabrata* and *Candida albicans*. Clin Infect Dis **1999**; 29:926–8.
20. Ang BS, Telenti A, King B, Steckelberg JM, Wilson WR. Candidemia from a urinary tract source: microbiological aspects and clinical significance. Clin Infect Dis **1993**; 17:662–6.
21. Alvarez-Lerma F, Nolla-Salas J, Leon C, et al. Candiduria in critically ill patients admitted to intensive care medical units. Intensive Care Med **2003**; 29:1069–76.
22. Abbott KC, Hypolite I, Poropatich RK, et al. Hospitalizations for fungal infections after renal transplantation in the United States. Transpl Infect Dis **2001**; 3:203–11.
23. Occhipinti DJ, Gubbins PO, Schreckenberger P, Danziger LH. Frequency, pathogenicity and microbiologic outcome of non-*Candida albicans* candiduria. Eur J Clin Microbiol Infect Dis **1994**; 13:459–67.
24. Sobel JD, Kauffman CA, McKinsey D, et al. Candiduria: a randomized, double-blind study of treatment with fluconazole and placebo. The National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group. Clin Infect Dis **2000**; 30:19–24.
25. Pappas PG, Rex JH, Sobel JD, et al. Guidelines for treatment of candidiasis. Clin Infect Dis **2004**; 38:161–89.