Candiduria: A Randomized, Double-Blind Study of Treatment with Fluconazole and Placebo

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Management of candiduria is limited by the lack of information about its natural history and lack of data from controlled studies on the efficacy of treating it with antimycotic agents. We compared fungal eradication rates among 316 consecutive candiduric (asymptomatic or minimally symptomatic) hospitalized patients treated with fluconazole (200 mg) or placebo daily for 14 days. In an intent-to-treat analysis, candiduria cleared by day 14 in 79 (50%) of 159 receiving fluconazole and 46 (29%) of 157 receiving placebo ($P < .001$), with higher eradication rates among patients completing 14 days of therapy ($P < .0001$), including 33 (52%) of 64 catheterized and 42 (78%) of 54 noncatheterized patients. Pretreatment serum creatinine levels were inversely related to candiduria eradication. Fluconazole initially produced high eradication rates, but cultures at 2 weeks revealed similar candiduria rates among treated and untreated patients. Oral fluconazole was safe and effective for short-term eradication of candiduria, especially following catheter removal. Long-term eradication rates were disappointing and not associated with clinical benefit.

Candiduria, although rare in healthy people, is common in hospitalized patients [1–5]. In tertiary care facilities, as many as 10% of positive urine cultures yield a fungal pathogen [6, 7]. Nosocomial candidal urinary tract infections increased dramatically in the past 2 decades as the pool of at-risk patients increased, together with the cumulative pressure of contributing factors such as urinary instrumentation and prolonged use of broad-spectrum antibiotics [5, 8].

The overwhelming majority of fungal urinary tract infections are caused by *Candida albicans* and other *Candida* species, and they are usually acquired by the ascending route [1, 8]. A minority of patients with candiduria have systemic infections with renal involvement acquired by the hematogenous route. The presence of candiduria may signal diverse pathological states, including invasive renal parenchymal disease, fungal balls in obstructed ureters, superficial lower urinary tract infection, and lower urinary tract candidal colonization associated with urinary catheterization. Accordingly, a wide spectrum of clinical disease occurs, although the majority of patients present with asymptomatic candiduria.

Whereas symptomatic candidal urinary tract infection requires antifungal therapy, there is considerable controversy about whether and when to treat asymptomatic candiduria, primarily because the natural history of untreated candiduria and its morbidity have been poorly studied. Much of the confusion also results from a dearth of information regarding the efficacy of antimycotic agents in eradicating candiduria.

Controversy continues as to the effectiveness of systemic antifungal therapy as opposed to local irrigation of the lower urinary tract with amphotericin B [9–12]. In the past, systemic therapy with iv amphotericin B was often considered too extreme for asymptomatic or symptomatic fungal lower urinary tract infection; moreover, oral azole therapy with ketoconazole and itraconazole was frequently disappointing and ineffective [13]. The availability of oral fluconazole, which has a favorable side-effect profile and is excreted unchanged in high concentrations in the urine, afforded an opportunity to provide effective antifungal therapy to patients with candiduria [14].

We conducted the first prospective, multicenter placebo-controlled study evaluating the efficacy of fluconazole in eradicating candiduria in patients with asymptomatic or minimally symptomatic urinary tract infection.

Methods

Study population. This was a multicenter, randomized, double-blinded, placebo-controlled evaluation of the efficacy and safety of fluconazole (200 mg/d) for short-term eradication of candiduria.

Received 16 November 1998; revised 6 April 1999; electronically published 6 January 2000.

Financial support: Pfizer Pharmaceutical, Inc. and National Institutes of Health (contract no. NO1-A1-15082).

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Clinical Infectious Diseases 2000; 30:19–24

1058-4838/2000/3001-0006$03.00

The study was undertaken by the National Institute of Allergy and Infectious Diseases (NIAID) Mycoses Study Group.

Patients were eligible if 2 consecutive urine cultures that were performed at least 24 h apart were positive for yeast and if the patient had not received treatment with systemic or local antifungals within the previous 7 days. Candiduria was defined as the presence in both cultures of $\geq 10^3$ cfu/Ml. Urine for culture was obtained from noncatheterized patients by the clean-catch method.

Catheterized patients were eligible only if a follow-up culture was positive after removal or replacement of the catheter. Patients could either have the catheter removed and a second positive culture specimen obtained 24 h later, or else have the catheter changed and a second positive culture specimen taken 30 minutes later. Similarly, 2 positive urine cultures were required for patients undergoing intermittent catheterization.

Asymptomatic candiduria was defined as absence of both urinary symptoms and fever (temperature of 37.8°C [100°F]). Occasionally, afebrile patients (<5%) with mild lower urinary tract symptoms were also enrolled.

Eligible patients were stratified by catheterization status and randomized in a 1 : 1 fashion to receive either fluconazole or placebo for 2-weeks. In the analysis of therapeutic efficacy, patients were stratified according to presence or absence of a catheter, recent catheterization, or change of catheter.

Exclusion criteria included systemic antifungal treatment within the preceding 7 days, known urologic obstructive abnormalities, neutropenia, and history of intolerance of or allergy to azoles. Also excluded were patients who had clinical, radiological, histopathologic, serological, or microbiological evidence of fungal infection at an extraurinary site and those with an oral temperature >37.8°C (>100°F). Other exclusion criteria included a serum creatinine level >3.5 mg/dL, moderate or severe liver disease, and an anticipated life expectancy of <4 weeks. All patients or their legal guardians provided written informed consent according to local institutional review board guidelines.

Treatment regimens. Patients received a loading dose of four 100-mg capsules of fluconazole or 4 capsules of placebo, followed the next day by two 100-mg capsules of fluconazole or placebo, which they then received once a day for 13 days. Fluconazole doses were adjusted for renal insufficiency: for creatinine clearance of 21–50 mL/min, 100 mg daily; for creatinine clearance of 11–20 mL/min, 100 mg on alternate days.

Assessment of response. Once a week during antifungal therapy, patients were assessed clinically for efficacy and evidence of toxicity. On days 3, 7 and 14 urine was obtained for follow-up urinalysis and culture. Follow-up clinical evaluations were performed at 2 weeks post-therapy for assessment of response and relapse; these included hematologic studies, serum chemistries, and urine gram stains and cultures.

Endpoints were as follows. Improvement/satisfactory response was defined as resolution of baseline urine fungal culture positivity, i.e., mycologic eradication at completion of therapy. Lack of efficacy was defined as persistence or recurrence of urine fungal culture positivity or progressive clinical features compatible with fungal urinary tract infection or systemic fungal infection at end of therapy. All deaths were monitored and classified as either secondary or unrelated to fungal infection. Similar endpoints were evaluated at the posttherapy follow-up visit for mycologic cure or relapse.

Statistical methods. Fisher's exact test was used to compare the 2 treatment groups with respect to sex, presence of diabetes, catheterization, occurrence of *Candida albicans,* and mycologic eradication rates. χ^2 analyses and Student's *t*-test were used to compare the 2 groups with respect to race distribution and age, respectively. Logistic-regression analysis was performed to evaluate the effects of the following factors on microbiological efficacy for catheterized and noncatheterized patients: diabetes, *Candida* species, mixed species, and baseline serum creatinine levels.

Results

Study population. Three hundred and sixteen hospitalized patients with candiduria were evaluated in an intent-to-treat analysis (159 received fluconazole and 157 received placebo; table 1). No differences were observed in demographic characteristics of the 2 treatment groups with regard to age, sex, race, underlying comorbid conditions, prior use of antibiotics, and presence or absence of urinary catheter at the time of diagnosis of candiduria.

Among the catheterized subjects there were more women in both treatment groups, and more noncatheterized patients had underlying diabetes mellitus. For purposes of randomization, "catheterized" referred only to catheters in situ at the time the cultures were repeated (accounting for 56% of patients in both treatment groups); 19 patients undergoing intermittent catheterization were included in the noncatheterized group. It is noteworthy that only 14 patients in the fluconazole group and 13 patients receiving placebo had not been catheterized at all during the hospitalization. A further 12 patients in the fluconazole group and 16 patients in the placebo group had been catheter-free for at least 7 days before urine cultures were performed.

Table 1. Demographic characteristics at baseline of patients with candiduria who received fluconazole or placebo.

Characteristic	Fluconazole ($n=159$)	Placebo ($n=157$)
Age (y)	70.2 ± 1.2	70.2 ± 1.1
Male	65 (41)	55 (35)
Female	94 (59)	102 (65)
White	122 (77)	118 (75)
Black	33 (21)	38 (24)
Diabetes mellitus	77 (45)	70 (45)
Recent antibiotics	144 (91)	146 (93)
Catheterized	89 (56)	88 (56)
Age (y)	71.6 ± 1.6	72.0 ± 1.5
Male	27 (30)	27 (31)
Female	62 (70)	61 (69)
Diabetic	36 (40)	35 (40)
Noncatheterized[a]	70 (44)	69 (44)
Age (y)	68.3 ± 1.8	67.7 ± 1.4
Male	38 (54)	28 (41)
Female	32 (46)	41 (58)
Diabetic	41 (59)	35 (51)

NOTE. Data are no. (%) or mean ± SE. None of the comparisons achieved statistical significance.

[a] Includes 8 patients in fluconazole group and 11 patients in placebo group who underwent intermittent catheterization.

Microbiology. The 2 groups were well matched for urinary *Candida* species isolated prior to randomization and therapy: 50% of patients in the fluconazole group and 49% of patients in the placebo group were infected with *C. albicans* (table 2). The second most frequently isolated species was *Candida glabrata,* present in 28 patients (18%) receiving fluconazole and 37 patients (24%) receiving placebo. Seven percent of patients in the fluconazole group and 10% of patients in the placebo group had >1 fungal species identified in 1 or both of the urine specimens obtained at least 24 h apart.

Response to treatment. In the intent-to-treat analysis (n = 316), urine was available for culture on day 14 for 135 (85%) of 159 patients receiving fluconazole and 131 of (83%) 157 patients receiving placebo. In this analysis, missing specimens were considered culture-positive. By this method, cultures obtained on day 14 after initiation of therapy revealed mycologic eradication in 79 (50%) of the 159 patients receiving fluconazole and in 46 (29%) of the 157 receiving placebo ($P < .001$; table 3). Eradication rates were considerably higher in noncatheterized patients in both study groups. Fluconazole eradicated *Candida* organisms from 39% of catheterized patients, whereas mycologic eradication was achieved with fluconazole in 63% of patients who were noncatheterized (or intermittently catheterized; $P = .004$).

Of the 316 evaluable patients, 238 completed the full treatment regimen of 14 days of fluconazole or placebo; of these 238 patients, 235 had urine specimens obtained for culture. Urine samples from 3 patients receiving placebo were lost and hence considered culture-positive. A subgroup analysis of those 238 patients who completed the 14-day treatment protocol showed results similar to those obtained in the intent-to-treat analysis (table 3). Higher eradication rates were apparent in the fluconazole group than in the placebo group (75 [63%] of 118 patients vs. 42 [35%] of 120 patients; $P < .001$). Among patients who completed a 14-day course, fluconazole successfully eradicated candiduria in 78% of noncatheterized but only 52% of catheterized patients ($P = .0015$).

A separate subgroup analysis was performed to evaluate early clearance of candiduria (at day 7 of treatment) in those 117 of the 238 evaluable patients whose candiduria was found to be eradicated in testing on day 14. Among the noncatheterized patients, for 31 (74%) of 42 receiving fluconazole and 18 (69%) of 26 receiving placebo whose urine eventually cleared (by day 14), the candiduria had cleared by day 7 ($P = .78$). Among catheterized patients, for 18 (55%) of 33 receiving fluconazole and only 3 (19%) of 16 receiving placebo, candiduria had cleared by day 7 ($P = .03$).

Since at the time of study enrollment all catheterized patients had their catheters removed and (in the majority of cases) replaced with a new catheter, those persistently catheterized patients receiving placebo demonstrated the effect of catheter change per se on the natural history of candiduria in catheterized patients. In 20% of placebo-treated catheterized patients, candiduria resolved (table 3).

Table 2. Fungal species isolated from urine at baseline/pretreatment.

Fungal species	Fluconazole (n = 159)	Placebo (n = 157)
Candida albicans	79 (50)	77 (49)
Non-*albicans Candida*		
Candida glabrata	28 (18)	37 (24)
Candida tropicalis	18 (11)	15 (10)
Candida parapsilosis	5 (3)	0
Candida krusei	4 (3)	2 (1)
Candida lusitaniae	2 (1)	1 (<1)
Candida kefyr	1 (<1)	0
Other	4 (3)	1 (<1)
Saccharomyces cerevisiae	1 (<1)	0
Not specified (yeast)	4 (3)	8 (5)
Mixed	11 (7)	16 (10)

NOTE. Data are no. (%).

Similarly, since only 13 and 14 patients in each study group (8%) had not been catheterized at any time during the current hospitalization (before enrollment), the majority of noncatheterized placebo recipients demonstrate the effect of catheter removal alone on the outcome of candiduria. Thus in ~41% of catheterized subjects, candiduria resolved as the result of catheter removal only (table 3).

A stepwise logistic-regression model was used to evaluate the prognostic significance of comorbid factors, including fungal species, on microbiological efficacy at day 14 following initiation of therapy. Coexistent diabetes mellitus failed to influence response to therapy for both catheterized and noncatheterized patients. The presence of *Candida tropicalis* in pretherapy urine cultures was associated with a significantly higher treatment failure rate in both groups ($P = .018$), but not if patients whose cultures yielded *C. tropicalis* plus another fungal species were included. None of the other non-*albicans Candida* species, including *C. glabrata*, were associated with a suboptimal response to therapy ($P > .5$). Although mixed infections demonstrated a trend toward more difficult eradication, insufficient numbers precluded a definitive answer.

For noncatheterized patients, serum creatinine levels were inversely related to and significantly associated with microbiological efficacy at 14 days in the analysis of all patients ($P = .003$), patients completing at least 7 days of therapy ($P = .003$), and patients completing 14 days of treatment ($P = .003$). For catheterized patients, elevated serum creatinine levels were similarly associated with reduced microbiological efficacy in the analyses of all patient subgroups, but the association was not as highly significant ($P = .045$).

Follow-up studies. Culture results at 14 days after completion of therapy were available for 55% of enrolled patients (table 3). The majority of patients had already been discharged from the hospital, and follow-up was difficult. Missing data were equally represented (45% of patients) in both treatment groups. In the intent-to-treat analysis, among the patients whose urine was cleared at completion of therapy, 4 (9%) of 44 noncath-

Table 3. Rates of mycologic eradication of candiduria in the 2 recipient groups.

Analysis group	Fluconazole	Placebo	*P*
All enrolled patients (n = 316)[a]	79/159 (50)	46/157 (29)	<.001
Catheterized	35/89 (39)	18/88 (20)	.008
Uncatheterized	44/70 (63)	28/69 (41)	.01
Patients completing 14 days of therapy (n = 238)	75/118 (63)	42/120 (35)	<.0001
Catheterized	33/64 (52)	16/65 (25)	.002
Uncatheterized	42/54 (78)	26/55 (47)	.0015
Two-week follow-up[a] after therapy completed (n = 173)[b]	59/87 (68)	56/86 (65)	.7
Catheterized	27/44 (61)	22/39 (56)	.7
Uncatheterized	32/43 (74)	34/47 (72)	1.00

NOTE. Data are no. of recipients whose candiduria was eradicated/no. of recipients (%). Eradication was determined on the basis of urine culture status immediately after completion of therapeutic trial (day 14).

[a] Intent-to-treat analysis.

[b] Culture status 2 weeks after completion of therapeutic trial.

eterized patients who received fluconazole had relapsed at the 2-week follow-up, versus 1 (4%) of 28 noncatheterized patients who received placebo (P = .6). Among catheterized patients, 3 (9%) of 35 who received fluconazole relapsed, versus 5 (28%) of 18 who received placebo (P = .1).

The prevalence of candiduria after treatment was analyzed by 2 methods: by comparing only those patients in each group for whom culture data were available and by comparing all patients (in which case those whose urine culture results were missing were considered to be culture-positive). Both analyses showed that the percentage of urine cultures yielding fungi was not statistically different between the fluconazole-treated and placebo-treated groups 14 days after completion of treatment ($P > .5$). No patients in the study developed pyelonephritis or fungemia.

Adverse effects. There were few major adverse events recorded in either treatment group. Patients classified as experiencing any toxicities were equally represented in both treatment groups ($P > .5$). There were a total of 26 deaths (8.2%) recorded in the case-record forms: 12 in the fluconazole group and 14 in the placebo group (P = .69). None of these were related to fungal infection or treatment; however, 22 (85%) of 26 patients who died were catheterized at the time of enrollment. Elevated hepatic enzyme levels in 3 patients receiving fluconazole and 2 receiving placebo were reported, and 3 patients receiving fluconazole and 1 receiving placebo developed increases in serum creatinine levels. Nine fluconazole recipients and 7 placebo recipients developed bacteriuria.

Discussion

Although candiduria is common, its management is erratic. Physicians are inconsistent because they do not always understand the clinical significance of this finding, because they lack information about the natural history of asymptomatic candiduria, and are often unwilling to administer systemic amphotericin B [12, 15–17]. Although safer, systemically active azoles are now available, there is a paucity of data regarding their ability to eradicate candiduria. More important, however, is the need to document that patients benefit from eradication of asymptomatic candiduria.

As in most published studies of candiduria, our patients were hospitalized, elderly (mean age, 70.2 years), and predominantly female, and they had numerous comorbid medical conditions [1, 2, 18]. More than 50% were catheterized at the time they were enrolled in the study, and almost all of the remainder had undergone instrumentation or catheterization in the period preceding the study; approximately half of the patients were diabetic. Virtually every patient was receiving or had recently received broad-spectrum antibiotics. Death unrelated to fungal infection was common; 8.2% of the study population died over a 1-month period.

The present study was restricted to asymptomatic or minimally symptomatic patients with candiduria, since the management of symptomatic patients is less problematic. Fluconazole, given orally and in doses adjusted for renal insufficiency, eradicated candiduria in 63% of study patients who completed 14 days of therapy. Eradication occurred in only 52% of persistently catheterized patients but was considerably more frequent in noncatheterized and no-longer-catheterized patients (78%). Short-term eradication rates for these patients were therefore significantly better than for matched placebo-treated patients.

The placebo-treated group afforded an opportunity to study the natural history of untreated candiduria in hospitalized patients. Given the limitations of this post-hoc analysis, we estimate that candiduria resolved in ~20% of chronically catheterized patients because their catheter was changed only, and was eradicated in 41% of untreated patients when the catheter was removed. Our clearance rate among untreated patients is similar to that observed by Storfer et al. in a small retrospective study [19].

It is notable that in this large study population, complications of fungal urinary tract infection, including pyelonephritis, candidemia, systemic candidiasis, and fungus-related death, were not observed in either study group. These results provide evidence that asymptomatic or minimally symptomatic candiduria is in itself usually benign, even in debilitated patients with underlying diseases, including diabetes mellitus. Storfer et al. observed 11 episodes of candidemia in 105 patients with candiduria, although it is unclear whether in these symptomatic patients candidemia might have led to candiduria [19]. In a large review of candidemic subjects, Ang et al. concluded that candidemia was rarely the consequence of candiduria and then usually occurred only in the presence of upper urinary tract obstruction [20].

Several other authors have similarly concluded that asymptomatic candiduria is benign and often self-limiting if the predisposing factors are corrected. On the other hand, Nassoura

et al. emphasized that candiduria should never be ignored in septic patients, since it may be the only and is often the first indication of systemic or invasive candidiasis [21]. In their study of a small number of patients in a surgical intensive care unit, these authors emphasized the advantages of systemic antifungal therapy in this subpopulation of patients and reported failure of amphotericin B irrigation in candiduric patients [21].

Although we demonstrated high short-term rates of eradication of urinary *Candida* with fluconazole, the clinical benefits are less apparent in this predominantly elderly, debilitated, asymptomatic or minimally symptomatic population. Moreover, we were unable to document continued yeast eradication in the urinary tract 2 weeks after discontinuation of antifungal therapy. Although the data were incomplete, patients who had received either fluconazole or placebo had similar rates of candiduria 2 weeks after the end of therapy. Not surprisingly, candiduria was more common at the 2-week follow-up visit in those patients whose catheters remained in place.

Although this study was not designed to determine the optimal duration of therapy, eradication rates observed after 7 days of therapy indicate that, in the second week of therapy, candiduria cleared in at least one-quarter of noncatheterized patients and almost one-half of catheterized patients receiving fluconazole only. These results are not surprising, since most of these patients with complicated infections either still had or had recently had a catheter.

The results obtained with fluconazole in the present study are similar to those obtained in 3 other published studies that compared oral fluconazole with amphotericin B bladder irrigation for eradicating candiduria [22–24]. Fan-Havard et al. observed an 83% rate of eradication of candiduria with fluconazole in a small study of catheterized elderly men; results were similar with amphotericin B irrigation [23]. Similarly, Leu and Huang, in another small prospective study, achieved clearance of funguria in 77% of patients after administration of fluconazole for 7 days at a dosage of 100 mg/daily [24]. In that study, amphotericin B irrigation achieved more rapid clearance, but candiduria-eradication rates 7 days following therapy were similar to those obtained with fluconazole.

Finally, Jacobs et al. studied a large group of acutely hospitalized elderly patients but used a lower dose of fluconazole (100 mg/d) than we did for 7 days [22]. In contrast to the above small studies, Jacobs et al. observed not only more rapid fungal clearance with amphotericin B irrigation but, in a comparison 2 days after completion of therapy, higher eradication rates with amphotericin B (96%) than with fluconazole (73%). Follow-up at 1 month, however, showed virtually identical frequency of eradication. It is notable that in the study of Jacobs et al. the high mortality rate associated with candiduria was also emphasized: one-third of the enrolled patients died.

A unique observation in the present study was the high failure rate with funguria due to *C. tropicalis,* which in most series is the third most frequent *Candida* species (12%–28%) and is often found in mixed cultures. Although this organism is usually susceptible to fluconazole in vitro, local factors such as adherence to the catheter surface may contribute to the low clearance rate. In the present study, no difference in eradication rates with fluconazole were seen for *C. glabrata* versus *C. albicans* and other candidal infections. *C. glabrata* is frequently reported to demonstrate intrinsic resistance to fluconazole; hence, our findings were not anticipated, especially given the high frequency with which this species was found (20%) in candiduric patients [25]. The high rates of eradication of urinary *C. glabrata* may be the consequence of the high dosage and prolonged fluconazole therapy selected in this study.

An important finding in the present study was reduced fungal eradication from the urinary tract of patients with impaired renal function. A possible explanation is the reduced fluconazole concentrations in urine in association with reduced glomerular filtration. Traditionally, fluconazole doses are decreased in cases of renal failure to avoid the adverse sequelae of high serum levels of fluconazole; however, paradoxically, these measures may result in subtherapeutic urinary concentrations of fluconazole. This observation may be critical in selecting the fluconazole dosage for treating symptomatic fungal urinary infections with renal failure, obstruction, and fungus balls in the drainage system.

In conclusion, candiduria is common in an elderly, debilitated, hospitalized population with present or recent urinary catheters [1, 2, 5–7]. Candiduria may resolve spontaneously, depending on whether risk factors can be corrected. When catheters remain in situ, untreated candiduria resolves in 20% of patients. A variety of therapies, including amphotericin B irrigation and oral fluconazole, appear comparable in early clearance of candiduria, although long-term eradication in the presence of catheters and other risk factors appears unlikely regardless of therapy. However, amphotericin B irrigation is expensive and labor-intensive. When treatment of asymptomatic or minimally symptomatic candiduria is indicated, data obtained from this study suggest that oral fluconazole is safe and effective.

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