Bladder Irrigation with Amphotericin B for Treatment of Fungal Urinary Tract Infections

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Fungal urinary tract infection has become a frequent clinical entity. Despite limited evaluation of its efficacy, bladder irrigation with amphotericin B has become the usual means of therapy for such infections. The outcome of treatment with amphotericin B bladder irrigation for an average of 5 days for 95 hospitalized patients with funguria (mean age, 75 years) during a 14-month period is presented. All patients who received treatment were identified from pharmacy records; those for whom urine culture results were obtained after treatment were studied. Fever and/or pyuria was identified in the majority of cases. Funguria was eradicated in 80% (confidence interval, 72%–88%). Concomitant diabetes mellitus or the previous use of indwelling bladder catheters did not alter response to treatment. The mortality rate following treatment of funguria was 39%, compared to 30.5% for a similar population during the same period. Amphotericin B bladder irrigation may not prove to be ideal therapy despite the fact that it initially eradicated funguria in the majority of subjects in this study.

Fungal urinary tract infection has become a frequent clinical entity as a result of the increased use of broad-spectrum antibiotics, corticosteroids, immunosuppressive agents, and bladder catheters in the acute care setting [1–4]. The definition of fungal infection versus colonization of the urinary tract and the indications and timing for initiation of treatment remain unclear [2–6]. By virtue of widespread usage, bladder irrigation with amphotericin B has become standard treatment, although it has not undergone controlled trials [5–14]. The development of new oral antifungal agents [15–17] necessitates reassessment of this therapy. This retrospective study was undertaken to assess the outcome of treatment of funguria with amphotericin B bladder irrigation, in preparation for a prospective controlled clinical trial comparing the efficacy of amphotericin B bladder irrigation with that of an oral antifungal agent.

Methods

All adult patients hospitalized at our facility who underwent continuous bladder irrigation with amphotericin B for a minimum of 2 days during the period of 1 July 1989 to 1 September 1990 for treatment of funguria, as defined below, and for whom results of a urine culture were obtained at the conclusion of therapy were considered for inclusion in this study. During that period, oral antifungal agents were not in use at our institution for treatment of funguria, and all patients were treated with a standard protocol for administration of amphotericin B bladder irrigation (25 mg of amphotericin B in 500 mL of 5% dextrose in water, infused continuously at 42 mL/h). The duration of therapy was defined by the prescribing physician.

The definition of a fungal urinary tract infection and indications for therapy remain subjects of debate in the literature. The correlation between fungal concentration in culture and clinical infection is also unclear. For this reason, all patients whose urine yielded >10,000 cfu of fungi per mL and/or who had funguria that was detected by microscopic examination of the urine were considered for inclusion in our study if they met the preliminary criteria mentioned previously.

Potential subjects were identified from the pharmacy record of drug orders for amphotericin B bladder irrigation and were considered for inclusion only once, for the first course of treatment received. The pharmacy department identified 262 drug orders for amphotericin B bladder irrigation during the 14-month period; 19 orders were canceled before the initiation of treatment, 14 were duplicate orders, and 55 were from 43 medical records that were unavailable for review. Fifty-five orders were for patients whose medical records did not document results of a urine culture following therapy, usually because of hospital discharge or death. There were 24 orders for subsequent courses of therapy for 16 of the 95 subjects included in this review. This report describes the clinical data, treatment, and outcome for 95 patients who met all the above criteria for inclusion.

The medical records of all subjects were abstracted with use of a data collection form. Demographic data included age, sex, type of residence before admission, length of hospital stay, discharge status, and postdischarge residence. Medi-

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cal notes and orders were reviewed to determine whether an indwelling bladder catheter was present, the criteria for diagnosis of a fungal urinary tract infection, and the reason for initiating therapy with amphotericin B bladder irrigation. Signs and symptoms of infection, comorbid medical conditions, medications used prior to and during amphotericin B bladder irrigation, and adverse effects of therapy were noted.

Microbiological data collected included results of urinalyses and urine cultures performed prior to and at the conclusion of treatment. All urine cultures were plated (1:1,000 inoculum), and the number of cfu/mL was reported for those demonstrating growth of 10,000 cfu/mL to 100,000 cfu/mL. Fungal growth that was not within this range was reported as <10,000 cfu/mL or >100,000 cfu/mL. The blood leukocyte count and hemoglobin concentration at the time of diagnosis of the fungal urinary tract infection were recorded.

The outcome of treatment of funguria with continuous amphotericin B bladder irrigation was evaluated by the presence or absence of fungal growth in a urine culture performed following completion of therapy (generally between 24 and 48 hours after discontinuation of the irrigation). The subjects were placed in two groups: those whose funguria was eradicated and those with persistent funguria. The number of cfu/mL and species of fungi were noted for the subjects with persistent funguria. The influence of certain factors that are thought to be associated with a poor response to therapy, such as diabetes or the presence of an indwelling bladder catheter, was analyzed. Because of the limitations of a retrospective review of hospitalized patients, no consistent follow-up data could be obtained for evaluating the rate of relapse for those subjects whose funguria was eradicated.

Statistical methodology. Descriptive statistics are provided as means and standard deviations or as medians and ranges, as appropriate. Relative frequency distributions are provided for categorical variables. The percentage of subjects who had no fungal growth in urine cultures performed at the conclusion of therapy is presented in relation to the study population as a whole as well as to subgroups devised according to sex, indwelling catheter status, and the concomitant presence of diabetes. No adequate control group was available; for those patients who were identified as having funguria during the same period (through microbiology laboratory records) but who were not treated, subsequent urinalyses or urine cultures were not consistently performed for various reasons (i.e., physicians' indifference to this entity, hospital discharge, or death). As a result, the rate of eradication for the subset of subjects with indwelling catheters prior to infection is compared to that for a similar historical group from the literature [13]. Wise et al. [13] reported eradication of funguria in 37 (92.5%) of 40 hospitalized patients with indwelling bladder catheters who underwent bladder irrigation with a 5 mg/dL suspension of amphotericin B for an average period of 6 days (range, 4–14 days). This group consisted of 29 women and 11 men with a mean age of 72 years [13].

Table 1. Characteristics of the patient population (n = 95).

Characteristic	No. (%) of patients*
Sex	
Female	71 (74.7)
Male	24 (25.3)
Age (mean ± SD)	74.7 ± 12.9
Women	73.9 ± 12.8
Men	77.0 ± 13.3
Ethnicity	
White, non-Hispanic	67 (70.5)
Black, non-Hispanic	17 (17.9)
Hispanic	9 (9.5)
Other	2 (2.1)
Residence before admission	
Private residence	48 (50.6)
Nursing home	47 (49.4)
Discharge status	
Went home	18 (18.9)
Went to nursing home	40 (42.1)
Died	37 (38.9)
Risk factors for infection	
Prior use of broad-spectrum antibiotic	87 (91.6)
Indwelling bladder catheter	70 (73.7)
Diabetes mellitus	39 (41.1)
Corticosteroid use	5 (5.3)
Hematologic malignancy	2 (2.1)
AIDS	2 (2.1)
Diagnosis at admission	
Infectious disease other than funguria	41 (43.2)
Gastrointestinal disease	12 (12.6)
Neurologic disease	7 (7.4)
Vascular disease	7 (7.4)
Pulmonary disease	6 (6.3)
Malignancy	5 (5.3)
Other	17 (17.8)

* Except as indicated.

Results

Our study population (table 1) consisted of 71 women and 24 men with a mean age of 75 years. Forty-nine percent were nursing home residents before admission; 43% were admitted for treatment of an infectious disease other than funguria. Ninety-two percent of subjects had been treated with broad-spectrum antibiotics prior to the development of funguria. Indwelling bladder catheters were in use in 74% of the subjects before funguria was identified. At the time of identification of funguria, mean laboratory values for the entire population were as follows: leukocyte count, 13.2 ± 6.4 × $10^3/mm^3$; hemoglobin, 9.7 ± 1.9 g/dL; and hematocrit, 28.5 ± 5.2%.

The diagnosis of a fungal urinary tract infection was based predominantly on persistence of fungi in urine cultures, although results of urinalysis and clinical data were used as confirmatory findings (table 2). Treatment was initiated on the basis of results of a single urine culture for 37 subjects and of two or more cultures of consecutive samples obtained

Table 2. Clinical and microbiological findings at the time of diagnosis of fungal urinary tract infection.

Finding	No. (%) of patients per indicated group		
	Total population (n = 95)	No indwelling bladder catheter (n = 25)	Indwelling bladder catheter (n = 70)
Temperature (°C)			
Unspecified (afebrile)	10 (10.6)	2 (8)	8 (11)
37.2–38.3	35 (36.8)	6 (24)	29 (41)
>38.3	46 (48.4)	15 (60)	31 (44)
No data	4 (4.2)	2 (8)	2 (3)
Urinalysis			
Pyuria	61 (64)	19 (76)	42 (60)
and temperature >38.3°C	26 (27)	11 (44)	15 (21)
Hematuria	18 (18.9)	4 (16)	14 (20)
Bacteriuria	29 (30.6)	5 (20)	24 (34)
Mycology			
Candida albicans	44 (46.3)		
Non-*albicans Candida* species	20 (21.1)		
Yeast (species not identified)	31 (32.6)		

on different days for 43 subjects (in addition to results of urinalyses). Urine culture results were as follows: >100,000 cfu/mL for 79% of subjects, 50,000–100,000 cfu/mL for 7.5%, 10,000–50,000 cfu/mL for 10%, and <10,000 cfu/mL for 3% (three subjects, all of whom were noncatheterized and had pyuria and funguria demonstrated by two urinalyses). Fifteen patients, six of whom had indwelling bladder catheters, were treated on the basis of documentation of funguria by a urinalysis. Of these 15, 11 had pyuria without bacteriuria, and eight had a fever (temperature, >38.3°C).

Candida albicans was the organism identified most frequently in urine cultures; the urine of 74% of subjects yielded >100,000 cfu/mL. Urinalyses (table 2) revealed pyuria (>5 leukocytes per high-power field) in 64% of patients, microscopic hematuria (>5 red blood cells per high-power field) in 19%, and bacteriuria in 31%, although urine cultures revealed 10^5 cfu of bacteria per mL (in addition to yeast) in only four subjects and $<10^4$ cfu/mL in two. The percentage of patients exhibiting pyuria, hematuria, and bacteriuria among those who had indwelling bladder catheters at the time of diagnosis was similar to that among those who did not.

The identification of funguria was the indication for initiation of amphotericin B bladder irrigation for the majority of the subjects. The urinalyses and urine cultures by which funguria was identified, however, were ordered because of clinical indications (often fever) rather than for screening purposes. Forty-eight percent of patients had a fever at the time treatment was initiated. Although concurrent disease (including other infections) was present in these subjects, treatment with amphotericin B bladder irrigations was initiated due to a clinical impression that the fever could not be attributed to these other processes. Only 27% of subjects had both fever and pyuria, although this association was more frequent in the noncatheterized patients. The medical records rarely noted symptoms of infection that have been described in the literature, such as suprapubic pain, urgency to urinate, frequent urination, or dysuria. This fact may have been due to the high proportion of subjects experiencing delirium and/or dementia, which may have impaired their ability to report symptoms. The majority (74%) had indwelling bladder catheters, which may diminish such symptoms.

Although a 5-day course of therapy is most frequently prescribed at our institution, the duration of treatment varied (median, 5 days; range, 2–11 days). Documentation of the rationale for the length of treatment was scant. No notations regarding adverse effects attributed to the bladder irrigations with amphotericin B were found in the medical records.

Urine cultures were usually performed 24–48 hours after completion of the irrigation. For 80% of subjects (table 3), funguria was eradicated (95% confidence interval [CI], 72%–88%). Subjects with diabetes mellitus had a rate of response similar to that of nondiabetics. The subset of patients with indwelling bladder catheters (n = 70) had a rate of eradication of 82.9% (CI, 74.0%–91.7%). The rate of eradication for noncatheterized patients (n = 25), which was 72.0% (CI, 54.4%–89.0%), was comparable to that for catheterized patients. The presence of fever and pyuria did not correlate with response to treatment with amphotericin B bladder irrigation. Of the 76 patients whose funguria was eradicated, 47% had a fever and 63% had pyuria at diagnosis; 53% of the 19 subjects with persistent funguria following treatment had fever, and 68% had pyuria.

Before admission, one-half of the subjects resided in nursing homes because of frailty, dementia, and/or disability. At the time of diagnosis of the fungal urinary tract infection, subjects had been hospitalized for 35.4 ± 62.0 days, and at

Table 3. Rate of eradication of fungal urinary tract infection with amphotericin B bladder irrigation as analyzed according to risk factors and duration of treatment.

Variable	Proportion (%) of patients*
Risk factor	
Any type	76/95 (80)
Sex	
Female	59/71 (83.1)
Male	17/24 (70.8)
Prior antibiotic therapy	68/87 (78.2)
Indwelling bladder catheter	58/70 (82.9)
No indwelling bladder catheter	18/25 (72.0)
Diabetes mellitus	32/39 (82.0)
Duration of treatment (days):	
2	4/5 (80.0)
3	15/16 (93.8)
4	9/10 (90.0)
5	38/50 (76.0)
Indwelling bladder catheter	30/37 (81.1)
No indwelling bladder catheter	8/13 (61.5)
6	5/8 (62.5)
7	2/3 (66.7)
8	1/1 (100)
9	1/1 (100)
11	1/1 (100)

* No. (%) of eradications per no. of patients with indicated variable.

discharge they had been hospitalized for 73.0 ± 120.3 days. These figures reflect the frailty and severity of illness of the subjects of this study. Inpatient treatment of this infection extended the length of stay by 4.7 ± 1.4 days (range, 2–11 days). Sixty-nine percent of those who survived were discharged to nursing homes. The mortality rate among the study population (following treatment but during the hospital stay) was 39%. In comparison, the mortality rate for patients aged ≥70 years who were hospitalized at our institution during the study period for >51 days but were not study subjects was 30.5% (81 of 266 discharges were due to death).

Discussion

Amphotericin B is a polyene antibiotic derived from the fermentation process of *Streptomyces nodosus*, a soil actinomycete. Its activity derives from its binding to the sterol component of the cell wall and altering membrane permeability. It has demonstrated activity against infections due to a wide variety of fungi. Amphotericin B was first reported in 1960 to have efficacy as a bladder irrigant for the treatment of fungal urinary tract infections [7]. Two studies [11, 13] with 10 and 40 subjects, respectively, have examined the efficacy of this treatment for hospitalized patients. The subjects in both studies had persistent candiduria and indwelling bladder catheters and were treated for an average of 6 days. Infection was eradicated in 70% and 92.5% of subjects. Neither study included a control group because a higher mortality had been previously noted among patients with candiduria who were not given antifungal therapy [12]. No similar evaluation of patients with funguria who did not have indwelling bladder catheters has been done.

The majority of subjects in our study were elderly white females, characteristics reflecting the demographics of the geriatric population at our institution and nationally. It is in this population that the incidence of fungal urinary tract infections is increasing most rapidly. The predominant risk factors associated with the development of such infection that were observed in our study were similar to those previously described: age, female gender, diabetes mellitus, presence of indwelling bladder catheters, and recent treatment with broad-spectrum antibiotics.

The diagnosis of urinary tract infection, rather than colonization, is important to examine. A recent review [6] of the treatment of funguria stated that "no criteria exist to differentiate between fungal colonization and infection." Other investigators [18, 19] have described a technique of washing out the bladder with amphotericin B, which may prove useful in this regard. Until controlled trials are undertaken, however, the characteristics distinguishing colonization from infection will remain unclear. For the aged, acutely ill population in our study, the finding of candidal growth (>10,000 cfu/mL) but no significant bacterial growth in urine cultures, often in association with fever (for which there was no other clear etiology) and/or pyuria, led to the diagnosis of infection and the decision to initiate treatment. The purpose of this study was to determine the outcome of treatment, as it is our opinion that this population reflects a subset of individuals with funguria for whom samples should be recultured to determine persistence and for whom treatment should be strongly considered.

The rate of eradication of funguria (80%) in this study of elderly hospitalized subjects treated with amphotericin B bladder irrigation, the majority of whom did have indwelling bladder catheters, differs from that cited in previous reports [11, 13]. For the subset of patients with indwelling bladder catheters (n = 70), the rate of eradication was 82.9% (CI, 74.0%–91.7%), which differs significantly from the 92.5% reported by Wise et al. [13]. No inference can be drawn from a comparison of the rate of eradication of infection to duration of therapy, because for some patients therapy was terminated early because of discharge, removal of the bladder catheter, or the perception that the infection was not severe. The lack of benefit for patients whose treatment was extended beyond 5 days may be due to the severity of the acute or underlying conditions that precipitated the prescription of a longer course of therapy.

This study did not demonstrate a statistically significant difference between rates of efficacy for catheterized and noncatheterized subjects. Indwelling bladder catheters are thought to be a risk factor for the development of infection

because colonization of the catheter occurs. It has been suggested that patients with such catheters have infections that are less invasive and that may resolve simply by replacement of the catheter. The frequent finding of pyuria and fever in our subjects with indwelling bladder catheters as well as in those without would suggest that both groups of subjects did have cystitis rather than simply colonization. This circumstance may explain why rates of response to treatment for patients with bladder catheters in use prior to the development of infection were similar to rates for those who did not. It should be noted that 31% of all subjects (34% of catheterized and 20% of noncatheterized subjects) had bacteriuria, as proven by microscopy, but cultures for only four subjects (two of whom had indwelling catheters) yielded significant bacterial growth. The observation of bacteriuria in an aged, predominantly female population, particularly in association with the use of indwelling catheters, is not uncommon.

Subjects who developed fungal sepsis (blood cultures demonstrated growth of fungi) following the initiation of local treatment for a fungal urinary tract infection were given systemic therapy and not included in this report. It is of great concern, however, that the mortality among our population during their hospitalization (subsequent to the course of amphotericin B bladder irrigation reviewed in our study) was 39%, as compared with the 30.5% rate for a group of nonsubjects (matched by age and length of stay) who were hospitalized at our institution during the same period of time. It is possible that some patients with funguria harbor the fungus in the upper urinary tract and that it later leads to fungal sepsis and their eventual demise; however, this has not been documented. The high proportion of subjects with either pyuria or fever would seem to support the suggestion that the high mortality observed may have been due to renal or systemic infection; however, pyuria or fever was found with equal frequency in those whose funguria cleared with therapy and in those with persistent funguria. Conversely, the development of funguria may be a signal of waning immunologic competence correlating with other causes of mortality in such a predominantly frail geriatric population.

Any retrospective chart review is limited by the information contained in the medical record, which may not reflect clinical impressions or any sense of urgency about treatment. The extent to which the patients were evaluated prior to and at the conclusion of therapy may have varied. All of the subjects included in this study were treated with continuous amphotericin B bladder irrigation at the discretion of their own physician and may have had infections of varying severity, which would not be made evident by a simple review of their clinical records and data concerning culture results, temperatures, and laboratory findings.

This study aimed to identify the outcome of patients' treatment with amphotericin B as it is currently prescribed rather than to determine the optimal method and timing for initiation of therapy. Sanford [19], in a recent discussion of this entity, suggests that treatment of funguria has moved from anecdote to dogma without careful evaluation. He provides a qualified recommendation for the use of amphotericin bladder irrigation for the treatment of funguria and discusses at length suggestions concerning dosage and administration that should be considered until further trials are completed. This form of treatment did, however, extend the length of hospitalization by an average of 5 days in our study. Although the majority of patients were discharged to nursing homes, most of these facilities are not equipped to administer amphotericin B bladder irrigation. A comparison of the cost and efficacy of amphotericin B bladder irrigation and those of the newer oral antifungal agents for treatment of fungal urinary tract infections is needed. A controlled clinical trial in which we compare amphotericin B bladder irrigation with oral fluconazole for treatment of funguria is in progress.

In summary, for 80% of a group of frail, elderly patients in an acute care setting, funguria was eradicated following amphotericin B bladder irrigation that was performed continuously for an average of 5 days. The rate of eradication of funguria was similar between patients with indwelling bladder catheters and noncatheterized patients, as well as between diabetics and nondiabetics. Although fever and pyuria were common, they were not predictive of response to treatment with amphotericin B bladder irrigation.

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ARCANUM

The arcanum is a new feature that will occasionally appear in *Clinical Infectious Diseases*. A short "brain teaser" that may be accompanied by a photograph or photographs will appear toward the front of the issue. The answers to the arcanum will appear toward the back of the issue. Submissions may be sent to the editorial office of *Clinical Infectious Diseases* or to Dr. Philip Mackowiak, Medical Services (111), VA Medical Center, 10 North Green Street, Room 5D143, Baltimore, Maryland 21201.

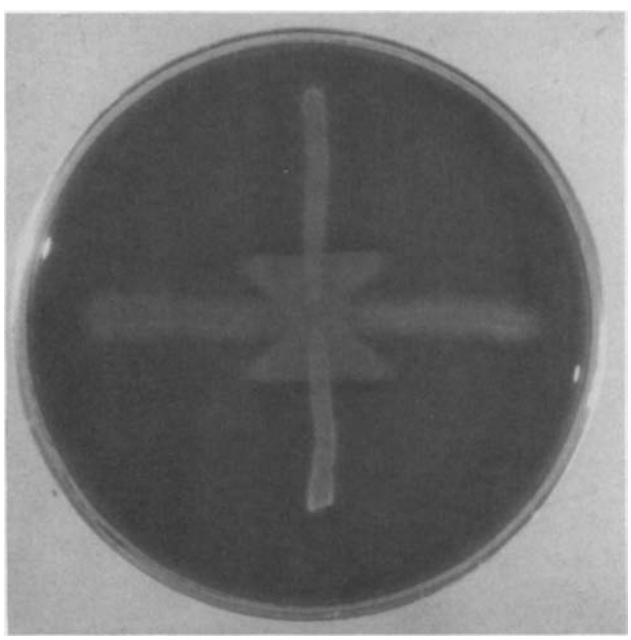

Figure 1. For almost fifty years, clinical microbiology laboratories have used the CAMP test to presumptively identify group B streptococci. What is the origin of the test's name? (See page 446 for answers to arcanum and commentary).