A Protocol For The Use Of Antifungals In An ICU: Funguria And Fungal Urinary Infection

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Abstract

Fungal infections are one of the most serious problems in hospitals today. Among them, funguria and urinary infections account for 40% of all the nosocomial infections and over one million new infections in the United States each year. The increase incidence of funguria is associated with risk factors including urinary catheters, treatment with broad-spectrum antibiotics, age, gender, diabetes mellitus, and chronic renal failure. Currently the majority of fungal urinary tract infections involve Candia albicans, however, non-albicans Candida and non-Candida yeasts are increasing as the etiological cause. A protocol for the treatment of funguria and urinary infections based on current medical evidence and cost effective therapy for use in the ICU is discussed.

INTRODUCTION

Since the clinical introduction of penicillin, infections with rare or resistant organisms have become more frequent until today when they are considered the norm in infectious diseases.[1,2,3,4] One complication observed in modern medicine is an increase rate of fungal infections, and most notably funguria.[5,6] Urinary tract infections (UTI) are now among the most frequent nosocomial infections, and catheter associated urinary infections (CAUTI) account for up to 40% of all nosocomial infections in the United States.[7] The incidence of all CAUTI caused by fungi in two recent studies has been reported to be 24.8% and 26.5%, respectively. [8-9] Additionally, Candida is now reported to be the most frequently isolated organism from the urine of patients in surgical intensive care units.[10] The rise in fungal infections is such that, candiduria essentially unknown before 1940 has become a nosocomial problem. 5

The increase incidence of funguria is associated with the use of urinary catheters, treatment with broad-spectrum antibiotics, corticosteroids, immunosuppressive agents, and antineoplastics. Other risk factors include advanced age, female gender, diabetes mellitus, chronic renal failure and hemodialysis.[11,12,13] The majority of fungal UTI involve Candida species. The most frequent organism is Candida albicans followed by Candida glabrata, Candida tropicalis, and Candida krusei.[12-13] However, non-albicans Candida and non-Candida yeasts are increasing as the etiological cause of fungal UTI. [14-15]

Despite an increase in the frequency of funguria, there is not a consensus in the literature as to the diagnosis and management of fungal UTI. There is still much discussion as to colonization versus infection along with the need and efficacy of treatment. Practice guidelines for the treatment of candidiasis by the Infectious Diseases Society of America (IDSA) as recent as April 2000 fail to clearly define funguria and fungal UTI.[10] Additionally, the IDSA does not adequately address recent prospective randomized studies comparing amphotericin B bladder irrigation versus intravenous amphotericin B therapy or oral fluconazole therapy. Several therapeutic options have been discussed but no regimen appears superior. Presented below is a protocol for the management of funguria and fungal UTI in an intensive care unit. Treatment of ascending pyelonephritis and renal candidiasis is beyond the scope of this review and is discussed elsewhere.[13]

DEFINITION OF FUNGURIA AND URINARY TRACT INFECTION

The findings of fungus in the urine may represent contamination, colonization of the catheter, or infection.[16] As of now, there is no reliable method for differentiating colonization from infection.[13,17] It is not known whether quantitative urinalysis, presence of pyuria, or symptoms correlate with fungal infection. However, Tambyah and Maki found recently that there is a significant difference in

the urine white blood cell count between patients with and without bacterial CAUTI (p=0.009).[18]

An asymptomatic bacteriuria is defined by the Centers for Disease Control (CDC) according to one of the following criteria:

According to the CDC a symptomatic UTI must meet at least one of the following criteria:

Other sources will traditionally define a UTI from a microbiological perspective when pathogenic microorganisms are detected in a properly collected urine sample at a concentration of 105 organisms per milliliter. However, these same sources will acknowledge that a smaller number of bacteria (102 – 104 organisms per milliliter) in some cases signify true urinary infection, especially in symptomatic patients.[20,21] Some authors go even further, defining a CAUTI as less than 103 organisms per milliliter urine without signs or symptoms, which is in disagreement with the above CDC definitions. Tambyah and Maki observed that 90% of patients diagnosed with a CAUTI (< 103 organisms per milliliter) were asymptomatic and that only 52% of the so-called infections were diagnosed by physicians.[18] Additionally, it has been shown that isolation of less than 105 organisms per milliliter or colony forming units of yeast per milliliter progressed to concentrations above 105 organisms per milliliter 96% of the time within three days of the initial culture in catheterized patients.[7]

For the purpose of this protocol we have extrapolated the CDC definitions used for bacteriuria and bacterial UTI to funguria and fungal UTI. It is not known if the threshold for bacterial urinary infections is the same for fungal infections. A funguria is defined as > 102 cfu fungi/ml in a properly collected urine sample and the patient is asymptomatic. A fungal UTI is defined as >102 cfu fungi/ml in two properly collected non-voided urine samples or 105 cfu fungi/ml in a properly collected voided urine sample, and the patient presents with clinical signs and symptoms.

Figure 1

Table 1: Protocol for the treatment of funguria/urinary tract infection

	Definition	Treatment
Funguria Patient is not critically ill	> 10^2 cfu fungi/ml + asymptomatic	Discontinue or change urinary catheter Control risk factors (control blood glucose, tailor antibiotic therapy, discontinue corticosteroids when possible)
Patient is critically ill		Above interventions plus pharmacological options: Primary agent: Amphotericin B 0.3 mg/kg IV X 1 (cheapest and simplest) Alternative agent: Fluconazole 200mg PO/IV daily X 7-14 days (more expensive, less invasive) Second alternative agent: Amphotericin B bladder irrigation (Dose = 50 mg/1000 ml at 42 ml/hr) X 2 days (greater patient discomfort and risk of dissemination or secondary infection)
Patient is critically ill and at high risk		Above interventions plus pharmacological options: Combination therapy: Amphotericin B 0.3mg/kg IV X 1 with Amphotericin B bladder irrigation (Dose = 50 mg/1000 ml at 42 ml/hr) X 2 days Alternative agent: Fluconazole 200mg PO/IV daily X 7-14 days
Urinary Infection	>10^2 cfu fungi/ml in nonvoided samples + clinical signs and symptoms	Above interventions plus pharmacological options: Rule out urinary tract obstruction by ultra sound Primary agent: Amphotericin B 0.3 mg/kg IV X 1 Alternative agent: Combination therapy: Amphotericin B 0.3mg/kg IV X 1 with Amphotericin B bladder irrigation as above X 2 days Second alternative agent: Fluconazole 200mg PO/IV daily X 7-14 days

Note: This protocol was developed following the CDC definitions, current evidence-based literature, patient comfort issues, risk/benefits, and economical factors.

DISCUSSION OF PROTOCOL

The management of asymptomatic catheter-associated funguria is unclear. Many authors have concluded that asymptomatic or minimally symptomatic funguria is benign and should generally not be treated except for modification of risk factors and changing the urinary catheter.[6,10,12,13] Funguria may clear without treatment over a time course of greater than a month.[11] Changing the urinary catheter will result in elimination of the funguria in less than 20% of the patients, while, discontinuation of the catheter alone may result in eradication of funguria in almost 40% of the patients.[22] However, in some patients funguria may be the source of dissemination or a marker of acute hematogenous dissemination. Reported mortality rates of 46 –75% in patients with candidemia have led to recommendations that all patients with candidemia receive antifungal therapy.[23] Patient populations, in which treatment of funguria should be considered, include neutropenic patients, critically-ill patients in the intensive care units, low-birth weight infants, and transplant recipients.[10,24] It is thought that in persistently febrile patients who only have funguria antifungal therapy may treat occult disseminated candidiasis.[10]

Options for patients who require treatment include local and

systemic drug regimens. Based on anecdotal experiences, amphotericin B bladder irrigation has generally been the standard of treatment for funguria. However, the efficacy of amphotericin B via continuous irrigation has been debated secondary to concerns that it may only reach organisms near the bladder trigone.[5] In a randomized trial Fan-Havard and colleagues evaluated the efficacy and safety of amphotericin B bladder irrigation (50 mg/L) over 24 hours and over 7 days as compared to an oral regimen of fluconazole.[25] Eradication rates for funguria at 24 hours and 5-9 days after therapy were 82.4% and 75%, respectively with the 1-day amphotericin B irrigation; 94.4% and 78.6%, respectively with the 7-day amphotericin B irrigation; and 83.3% and 76.9%, respectively with fluconazole. There were no differences in the post-therapy eradiation rates between the regimens at 24 hours (p = 0.597) and at 5-9 days (p = 0.66). Amphotericin B bladder irrigations and fluconazole appeared to be equally efficacious in the treatment of funguria. Adverse effects included bladder fullness in a patient receiving a bladder irrigation and hypoglycemia in a patient receiving fluconazole and glyburide concomitantly. However, in a randomized trial conducted by Jacobs and colleagues an increase in all-cause mortality (at one month) was observed in patients treated with amphotericin B bladder irrigation as compared to patients treated with oral fluconazole (41% versus 22%, p < 0.05), despite higher initial eradication rates with amphotericin B (96% versus 73%, p<0.05).[26]

Additionally, the optimal concentration has not been determined. Information suggesting that concentrations of 50 mcg/ml of amphotericin B are very toxic to mammalian cells has led Sanford to previously recommended concentrations of 5-10 mcg/ml for local irrigation with amphotericin B.[5] However in the 31st edition of Guide to Antimicrobial Therapy- 2001, it is recommended to use a bladder irrigation with a concentration of 50 mcg/ml.[27] Leu and colleagues in a prospective, randomized, controlled study showed that local irrigation with amphotericin B has prompt effects on clearance of funguria and the urinary yeast count regardless of the concentrations (5 mcg/ml, 100 mcg/ml, or 200 mcg/ml) administered during intermittent irrigations.[11] Amphotericin B bladder irrigation appeared to more rapidly clear the funguria as compared to a single intravenous dose of amphotericin B and an oral 5-day regimen of fluconazole. However, these results were not sustained one week after the end of treatment.

Fisher and colleagues have suggested that a single

intravenous dose of amphotericin B (0.3 mg/kg) administered over four hours may be effective therapy.[28] It is suggest that the combination of local and systemic therapies may be useful in certain groups such as critically ill patients and patients with ascending pyelonephritis.[11,13]

Oral fluconazole has been shown to be safe, effective, and as equally efficacious as amphotericin B bladder irrigation for short-term eradication of funguria, especially following catheter removal. [22,25] Sobel and colleagues showed higher eradication rates in patients who were treated with a full 14 day- course of fluconazole 200mg po daily as compared to placebo (p < 0.0001). Fluconazole initially produced high eradication rates, but cultures at two weeks revealed similar funguria rates among treated and untreated patients. Finally, pretreatment serum creatinine levels were inversely related to funguria eradication. A possible explanation is the reduced fluconazole concentrations in the urine in association with reduced glomerular filtration. By reducing the doses in renal dysfunction subtherapeutic urinary concentrations may result.[22] Because of the favorable ratio of therapeutic effectiveness to toxicity, we recommend maintaining conventional doses of fluconazole.

Even though these regimens have high rates of eradication initially, relapse in the presence of catheters and other risk factors is likely regardless of the therapy chosen. This leads one to believe that the treatment of funguria is extremely difficult. Another point of consideration is the development of resistance. Centers that have shown an increase in fluconazole use have also shown an increase in Candida species that are tolerant or resistant to fluconazole and a change in fungal flora.[29,30] Furthermore, these medication regimens cost between $22.00 and $980.00 depending on the therapeutic regimen (table 2).

As of now, there are still unanswered questions as who to treat, when to treat, and for how long. In addition to the fact that therapy of asymptomatic funguria in the non-neutropenic catheterized patient has never been shown to be of value no one regimen has been show to be superior in efficacy. Additionally, we are subjecting patients to possible adverse reactions from these medications. These factors make it hard to justify the cost of some of the therapeutic regimens at this time patients with asymptomatic funguria. However, because there are many unanswered questions one must consider treating critically-ill patients with systemic antifungals for concern of disseminated candidemia that can not be discovered. Due to the proliferation of different definitions of urinary tract infection, we recommend

adherence to the CDC definitions of urinary tract infections.

Figure 2

Table 2: Cost of selected therapeutic regimens for the treatment of funguria

Medication Regimen	Route	Cost*
Amphotericin B 0.3mg/kg	IV	$22.50#
Amphotericin B 50mg/1000ml X 2 days	Bladder Irrigation	$26.92#
Combination therapy: Amphotericin B	IV and Bladder Irrigation	$49.42*#
Fluconazole 200mg X 1 then 100mg qd X 4 days	PO IV	$50.78 $221.08
Fluconazole 200mg X 7 days	PO IV	$84.58 $498.63
Fluconazole 200mg x 14 days	PO IV	$151.08 $979.18

* Cost includes new foley

Based on 50mg vial

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