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

J Nates, T Allison

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 Candida 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.\(^11\)-\(^13\)\(^12\) 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). 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. 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. 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.

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

<table>
<thead>
<tr>
<th>Funguria</th>
<th>Definition</th>
<th>Treatment</th>
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</thead>
<tbody>
<tr>
<td>Patient is not critically ill</td>
<td>&gt;10^9 cfu fungi/ml + asymptomatic</td>
<td>Discontinue or change urinary catheter; control risk factors (control blood glucose, tailor antibiotic therapy, discontinue corticosteroids when possible)</td>
</tr>
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<th>Funguria</th>
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<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient is critically ill</td>
<td>Isolated organism, no evidence of sepsis or organ dysfunction</td>
<td>Antifungal therapy (amphotericin B 0.3 mg/kg IV Q1 in doses of 30 mg/kg/day for 4-7 days)</td>
</tr>
</tbody>
</table>

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<tr>
<th>Funguria</th>
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<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funguria and at high risk</td>
<td>Isolated organism, evidence of sepsis or organ dysfunction</td>
<td>Antifungal therapy (amphotericin B 0.5 mg/kg IV Q1 with amphotericin B bladder irrigation)</td>
</tr>
</tbody>
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<th>Funguria</th>
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</thead>
<tbody>
<tr>
<td>Funguria and at high risk</td>
<td>Isolated organism, evidence of sepsis or organ dysfunction</td>
<td>Antifungal therapy (fluconazole 200 mg PO IV daily X 7-14 days)</td>
</tr>
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**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. 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. 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. It is thought that in persistently febrile patients who only have funguria antifungal therapy may treat occult disseminated candidiasis.

Options for patients who require treatment include local and
Fisher and colleagues have suggested that a single end of treatment. However, these results were not sustained one week after the oral regimen of fluconazole. 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 eradication 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). 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. 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. It is important to consider the urinary yeast count regardless of the concentrations (5 mcg/ml, 100 mcg/ml, or 200 mcg/ml) administered during intermittent irrigations. 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.

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. 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. Because of the favorable ratio of therapeutic effectiveness to toxicity, we recommend maintaining conventional doses of fluconazole.

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 shown 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

<table>
<thead>
<tr>
<th>Medication Regimen</th>
<th>Route</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B 0.3 mg/kg</td>
<td>IV</td>
<td>$22.50</td>
</tr>
<tr>
<td>Amphotericin B 50 mg/100 ml X 2 days</td>
<td>Bladder Irrigation</td>
<td>$28.92</td>
</tr>
<tr>
<td>Combination therapy Amphotericin B</td>
<td>IV and Bladder Irrigation</td>
<td>$49.42</td>
</tr>
<tr>
<td>Fluconazole 200 mg X 1 then 100 mg qd X 4 days</td>
<td>PO, IV</td>
<td>$50.78</td>
</tr>
<tr>
<td>Fluconazole 200 mg X 7 days</td>
<td>PO, IV</td>
<td>$76.20</td>
</tr>
<tr>
<td>Fluconazole 200 mg X 14 days</td>
<td>PO, IV</td>
<td>$115.10</td>
</tr>
</tbody>
</table>

* Cost includes new Foley

# Based on 50mg vial

**References**


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