Bladder irrigation with amphotericin B and fungal urinary tract infection—systematic review with meta-analysis

Felipe Francisco Tuon a,b,*, Valdir Sabbaga Amato c, Sergio Ricardo Penteado Filho b

a Department of Infectious and Parasitic Diseases, Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo, Avenida Dr. Enéas de Carvalho Aguiar 255, 4 andar. Sala 4028 — ICHC, Cerqueira Cesar, CEP 05403-010, São Paulo, Brazil
b Clinic of Infectious and Parasitic Diseases, Hospital Universitário Evangélico de Curitiba, Curitiba, PR, Brazil
c Infectious and Parasitic Diseases Clinic, Hospital das Clínicas, School of Medicine, University of São Paulo, SP, Brazil

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KEYWORDS
Candida; Urinary tract infection; Bladder; Amphotericin B; Funguria; Candiduria

Summary
Background: Candiduria is a hospital-associated infection and a daily problem in the intensive care unit. The treatment of asymptomatic candiduria is not well established and the use of amphotericin B bladder irrigation (ABBI) is controversial. The aim of this systematic review was to determine the best place for this therapy in practice.

Methods: The databases searched in this study included MEDLINE, EMBASE, Web of Science, and LILACS (January 1960—June 2007). We included manuscripts with data on the treatment of candiduria using ABBI. The studies were classified as comparative, dose-finding, or non-comparative.

Results: From 213 studies, nine articles (377 patients) met our inclusion criteria. ABBI showed a higher clearance of the candiduria 24 hours after the end of therapy than fluconazole (odds ratio (OR) 0.57, 95% confidence interval (CI) 0.32—1.00). Fungal culture 5 days after the end of both therapies showed a similar response (OR 1.51, 95% CI 0.81—2.80). The evaluation of ABBI using an intermittent or continuous system of delivery showed an early candiduria clearance (24 hours after therapy) of 80% and 82%, respectively (OR 0.87, 95% CI 0.52—1.36). Candiduria clearance at >5 days after the therapy showed a superior response using continuous bladder irrigation with amphotericin B (OR 0.52, 95% CI 0.29—0.94). The use of continuous ABBI for more than 5 days showed a better result (88% vs. 78%) than ABBI for less than 5 days, but without significance (OR 0.55, 95% CI 0.34—1.04).

* Corresponding author. Tel.: +55 11 30696530; fax: +55 11 30697508.
E-mail address: ffbt@pop.com.br (F.F. Tuon).
Introduction

Candiduria is a hospital-associated infection with increasing frequency, although most of these cases have been considered as contamination. Furthermore, patients with diabetes mellitus or a urinary catheter outside the hospital also have a high prevalence of candiduria. In a previous study, 5% of the urine cultures from a large metropolitan teaching-hospital were positive for fungi. Also, it was reported that almost 25% of hospitalized nursing-home patients with indwelling urinary catheters had urine cultures positive for yeast cells. After contamination, the second cause of candiduria is colonization. These two fungal problems are recognized after repetition of the urine culture plus association with common risk factors, such as antibiotic use and presence of an indwelling urinary catheter.

Clinicians have experienced difficulties managing candiduria in the intensive care unit. Several guidelines have been published, but controversies about its management continue. Candiduria can be related to Candida pyelonephritis, candidemia, Candida cystitis, or may be asymptomatic. The differential diagnosis of these conditions is difficult. Candida cystitis is very rare because the bladder wall is extremely resistant. Candida pyelonephritis is also rare and always associated with systemic signs and urinary tract obstruction. Currently, there is no method of differentiating upper tract from lower tract candidiasis, and pathognomonic signs of upper infections such as Candida casts and fungal balls on ultrasound are extremely rare. The main reason why clinicians treat patients with asymptomatic candiduria is the risk of associated candidemia. Candiduria can be associated with fungemia in more than 10% of cases, and PCR of blood samples from patients with candiduria increases the diagnosis rate of candidemia. However, no difference in genetic background between blood and urine strains of Candida species has been found.

The treatment of asymptomatic candiduria (without fever) is not well established because the natural history of this entity is unknown. It has been shown that continuous amphotericin B bladder irrigation eradicates the lower tract Candida infection or colonization, and is a potentially useful test for locating the site of infection (upper or lower). The treatment of candiduria with amphotericin B bladder irrigation (ABBI) is controversial. Recent studies have shown the efficacy of azoles in the treatment of asymptomatic candiduria, and ABBI treatment has, for the most part, been abandoned. Some clinical trials have compared the two methods of treatment, however, doubts remain.

Amphotericin was discovered more than 50 years ago and its use in bladder irrigation was described in 1960. Since then, several manuscripts on its use have been published, but information on the dose, duration, and method of ABBI is lacking. In this systematic review, we performed an extensive search of articles on this subject; most of them are reviews and expert opinions. We listed all the in vivo studies to show the evidence in the literature on the use of amphotericin by this route, and sought to determine the best place for this therapy in practice.

Materials and methods

Search strategy

A systematic search of the medical literature was performed as previously described. The databases searched included MEDLINE, EMBASE, Web of Science, and LILACS (January 1960—June 2007), as well as the Cochrane Library database up to 2007. The search terms used were “amphotericin”, “irrigation”, and “catheter”. Other search terms used were: “candiduria”, “funguria”, “candidiasis”, and “bladder”. Bibliographies from the studies were also reviewed.

Study selection

The articles were selected with no language restriction. We included manuscripts with data on the treatment of candiduria using ABBI. The diagnosis of candiduria was based on quantitative or qualitative culture, with Candida spp in at least two samples. The studies were classified as comparative (ABBI vs. another drug), dose-finding (comparisons of different dosing regimens of ABBI), or non-comparative (single-arm studies). For the comparative and dose-finding studies we assessed the adequacy of methods for further calculation and, if possible, included these in a meta-analysis. Single-arm studies were allocated sequentially and response to treatment was evaluated (see data extraction).

Data extraction

Cases included patients with diagnostic criteria for asymptomatic candiduria defined microbiologically, as previously described. All studies needed to provide (1) data necessary for the computation of the clearance and treatment failure of the candiduria; (2) information to establish internal and external validity: randomized, blinded, prospective, controlled (placebo vs. other drug), number and age of patients, patient origin and follow-up, culture methodology; (3) indication of fungal therapy; (4) the dose, duration, and method (intermittent vs. continuous) of ABBI; (5) the dose and duration of the other antifungal therapy (controlled trial).

Statistical analysis

The validation of this systematic review was based on guidelines to guarantee quality, as well as good article selection and data extraction. The parameters evaluated were: fluconazole vs. ABBI, continuous vs. intermittent ABBI, and continuous ABBI for less than 5 days vs. ABBI for more than 5 days. Candiduria clearance was compared by percentage of
response using urine culture at 24—72 hours (early) and after 5 days (late); Chi-square odds ratios (OR) and 95% confidence intervals (CI) were calculated using SPSS 11.5 and significance was set at a \( p \) value of <0.05.

**Results**

**Description of studies included**

The search strategy yielded a total of 213 studies, of which 182 were excluded after initial screening. From the 31 remaining articles, nine (377 patients) met the inclusion criteria. The number of controlled and randomized studies was sufficient to perform a meta-analysis (Figure 1).

**Study validity and data quality**

Of the nine studies selected, \(^{2,18—23}\) all were prospective with hospitalized adult patients. Five studies were randomized and controlled. Data on the method of diagnosis and species found are described in Table 1. Three studies compared ABBI with intravenous fluconazole. All studies allowed a comparison of indirectly continuous vs. intermittent ABBI. Studies that evaluated continuous ABBI allowed the comparison of more than 5 days of therapy against less than 5 days.

**Results of the variables**

In comparison with intravenous fluconazole, ABBI showed a higher clearance of the candiduria 24 hours after the end of therapy (OR 0.57, 95% CI 0.32—1.00). Fungal culture 5 days after the end of both therapies showed a similar response (OR 1.51, 95% CI 0.81—2.80) (Figure 2; Table 2).

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**Table 1**

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>N</th>
<th>Weight of each study (^{a})</th>
<th>Age</th>
<th>Prospective or retrospective</th>
<th>Controlled</th>
<th>Placebo</th>
<th>&gt;10 patients</th>
<th>Fungal culture with treatment</th>
<th>Species identification</th>
<th>Follow-up</th>
<th>Follow-up method</th>
<th>Species methodology</th>
<th>Study validity and data quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nesbit, 1999, USA</td>
<td>26</td>
<td>7%</td>
<td>Adults</td>
<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>C. albicans</td>
<td>Hospital</td>
<td>Qualitative discharge</td>
<td>Qualitative culture &amp; identification</td>
<td>Yes (hospital discharge)</td>
</tr>
<tr>
<td>Trinh, 1995, USA</td>
<td>20</td>
<td>5%</td>
<td>Adults</td>
<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>C. albicans</td>
<td>Hospital</td>
<td>Qualitative discharge</td>
<td>Qualitative culture &amp; identification</td>
<td>Yes (hospital discharge)</td>
</tr>
<tr>
<td>Wise, 1982, USA</td>
<td>40</td>
<td>11%</td>
<td>Adults</td>
<td>Prospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>C. albicans</td>
<td>Hospital</td>
<td>Hospital discharge</td>
<td>Qualitative culture &amp; identification</td>
<td>No (hospital discharge)</td>
</tr>
<tr>
<td>Wise, 1973, USA</td>
<td>10</td>
<td>3%</td>
<td>Adults</td>
<td>Prospective</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>C. albicans</td>
<td>30 days</td>
<td>Qualitative discharge</td>
<td>Qualitative culture &amp; identification</td>
<td>No (hospital discharge)</td>
</tr>
<tr>
<td>Jacobs, 1996, USA</td>
<td>39</td>
<td>10%</td>
<td>Adults</td>
<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Candida spp</td>
<td>7 days</td>
<td>Qualitative discharge</td>
<td>Qualitative culture &amp; identification</td>
<td>No (hospital discharge)</td>
</tr>
<tr>
<td>Leu, 1995, China</td>
<td>38</td>
<td>10%</td>
<td>Adults</td>
<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Candida spp</td>
<td>16 days</td>
<td>Qualitative discharge</td>
<td>Qualitative culture &amp; identification</td>
<td>No (hospital discharge)</td>
</tr>
<tr>
<td>Fan, 1995, USA</td>
<td>35</td>
<td>9%</td>
<td>Adults</td>
<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Candida spp</td>
<td>30 days</td>
<td>Qualitative discharge</td>
<td>Qualitative culture &amp; identification</td>
<td>No (hospital discharge)</td>
</tr>
<tr>
<td>Hsu, 1990, China</td>
<td>65</td>
<td>17%</td>
<td>Adults</td>
<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Candida spp</td>
<td>7 days</td>
<td>Qualitative discharge</td>
<td>Qualitative culture &amp; identification</td>
<td>No (hospital discharge)</td>
</tr>
<tr>
<td>Fong, 1995, Canada</td>
<td>54</td>
<td>14%</td>
<td>Adults</td>
<td>Prospective</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Candida spp</td>
<td>16 days</td>
<td>Qualitative discharge</td>
<td>Qualitative culture &amp; identification</td>
<td>No (hospital discharge)</td>
</tr>
<tr>
<td>Total</td>
<td>377</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) The weight is the total number of patients per study divided by the total number of patients in all studies.
The evaluation of ABBI using an intermittent or continuous system of delivery showed an early candiduria clearance (24 hours after therapy) of 80% for intermittent and 82% for continuous (OR 0.87, 95% CI 0.52—1.36). The candiduria clearance at 7 days after the therapy showed a superior response using continuous bladder irrigation with amphotericin B (79%) vs. intermittent irrigation (60%) (OR 0.52, 95% CI 0.29—0.94) (Table 3).

The use of continuous bladder irrigation with amphotericin B for more than 5 days showed a better result than ABBI for less than 5 days (88% versus 78%), but without significance (OR 0.55, 95% CI 0.34—1.04) (Table 4).

Discussion

This meta-analysis compared the different methods used to treat asymptomatic candiduria, showing a better clearance of the Candida in the first days using amphotericin B irrigation than fluconazole, but with no difference between these approaches after one week. Considering this fact, clinicians may use either therapy. If ABBI is the preferred method, a continuous delivery over 5 days is the ideal. Sobel et al. compared fungal eradication using fluconazole or placebo daily for 14 days, in 316 patients with asymptomatic candiduria. Fluconazole cleared candiduria by day 14 in 50%; this was only 29% in the placebo group. Unfortunately, cultures at 2 weeks revealed similar candiduria rates among treated and untreated patients using a bladder catheter. This study showed that treatment may result in a short-term clearance of the colonization, but that catheter removal is the main treatment required to avoid new colonization and further infection.

The heterogeneity of data from our study does not allow us to confirm the results. It was not possible to draw any definitive conclusions from the comparison of fluconazole and intermittent or continuous ABBI and the duration of ABBI. This meta-analysis has several biases. The selection of the studies was done well, but data extraction was difficult. Papers used different inclusion criteria for patients, the method of culture was often poorly described, and we could not separate studies using quantitative from qualitative methods. Although all studies were prospective, patient underlying diseases were not described. We believe that this was the greatest problem in this meta-analysis. The duration of follow-up of the patients was short; a 30-day follow-up should be performed, including the rate of mortality, to determine the real benefits of therapy against candiduria.

ABBI requires the use of a new three-way catheter and drug disposal by an uncommon route. Fong et al. determined the minimal concentration of amphotericin B necessary to kill Candida in urine samples from hospitalized patients. Nevertheless, this study determined in vitro measures and several articles from this systematic review showed positive urine for Candida 24 hours after therapy.

The evaluation of ABBI using an intermittent or continuous system of delivery showed an early candiduria clearance (24 hours after therapy) of 80% for intermittent and 82% for continuous (OR 0.87, 95% CI 0.52—1.36). The candiduria clearance at 7 days after the therapy showed a superior response using continuous bladder irrigation with amphotericin B (79%) vs. intermittent irrigation (60%) (OR 0.52, 95% CI 0.29—0.94) (Table 3).

Table 2  Studies comparing fluconazole and amphotericin B bladder irrigation in the treatment of asymptomatic candiduria.

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>N</th>
<th>Indication</th>
<th>Drug</th>
<th>Dose</th>
<th>Duration (mean)</th>
<th>Clearance of candiduria (24 hours) %</th>
<th>Clearance of candiduria (&gt;5 days) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobs, 1996, USA</td>
<td>39 Persistent candiduria</td>
<td>AmphBcont</td>
<td>50 mg/l</td>
<td>5 days</td>
<td>33</td>
<td>85%</td>
<td>13/17</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>Fluconazole</td>
<td>100 mg</td>
<td>4 days</td>
<td>20</td>
<td>69%</td>
<td>15/19</td>
</tr>
<tr>
<td>Leu, 1995, China</td>
<td>30 Persistent candiduria</td>
<td>AmphBint</td>
<td>50 mg/l</td>
<td>3×</td>
<td>26</td>
<td>87%</td>
<td>13/19</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>AmphBint</td>
<td>200 mg/l</td>
<td>3×</td>
<td>25</td>
<td>83%</td>
<td>15/22</td>
</tr>
<tr>
<td></td>
<td>29</td>
<td>Fluconazole</td>
<td>100 mg</td>
<td>4 days</td>
<td>17</td>
<td>59%</td>
<td>17/22</td>
</tr>
<tr>
<td>Fan-Havard, 1995, USA</td>
<td>17 Persistent candiduria</td>
<td>AmphBcont</td>
<td>50 mg/l</td>
<td>1 day</td>
<td>14</td>
<td>82%</td>
<td>9/12</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>AmphBcont</td>
<td>50 mg/l</td>
<td>7 days</td>
<td>17</td>
<td>94%</td>
<td>11/14</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>Fluconazole</td>
<td>100 mg</td>
<td>7 days</td>
<td>15</td>
<td>83%</td>
<td>10/13</td>
</tr>
</tbody>
</table>

AmphBcont, continuous bladder irrigation with amphotericin B; AmphBint, intermittent bladder irrigation with amphotericin B.
A major problem of ABBI is the scarcity of publications using the same method to compare with other therapies. We showed that continuous irrigation is better than intermittent. Therefore, we investigated the duration of continuous irrigation. The use of ABBI for a median of 2 days was less effective than its use for a median of 5.5 days.

Several opinions have been published recommending abandoning the use of ABBI. Drew et al. considered that ABBI is rarely needed in present day clinical practice, and that other therapeutic modalities should be used. Nevertheless, amphotericin is easy to administer, does not have drug interactions, and is useful in anuric patients with purulent cystitis caused by Candida and other yeasts.

Untreated candiduria may lead to further complications, such as fungus ball formation, systemic dissemination, or renal candidiasis, due to the spread of infection by the ascending route, mainly in oliguric patients. Nevertheless, these events are very rare. Whether or not any candiduria requires treatment is controversial. Candiduria will spontaneously remit without therapy, although this may take several months. One study, however, indicated that mortality increased significantly in patients with candiduria who did not receive antifungal treatment. Although the strength of the underlying literature is not sufficient to allow the drawing of definitive conclusions, we believe that ABBI can be used in patients with asymptomatic candiduria showing risk of dissemination (pyuria, oliguria,

<table>
<thead>
<tr>
<th>Author, year, country</th>
<th>N</th>
<th>Indication</th>
<th>Dose</th>
<th>Duration (mean)</th>
<th>Clearance of candiduria %</th>
<th>Clearance of candiduria (&gt;5 days) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous bladder irrigation with amphotericin B (&lt;5 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nesbit, 1999, USA</td>
<td>13</td>
<td>Candiduria</td>
<td>10 mg/l</td>
<td>3 days</td>
<td>8</td>
<td>62%</td>
</tr>
<tr>
<td>Trinh, 1995, USA</td>
<td>10</td>
<td>Candiduria</td>
<td>50 mg/l</td>
<td>6 days</td>
<td>37</td>
<td>93%</td>
</tr>
<tr>
<td>Hsu, 1990, China</td>
<td>65</td>
<td>Candiduria</td>
<td>50 mg/l</td>
<td>2 days</td>
<td>8</td>
<td>80%</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
<td></td>
<td></td>
<td></td>
<td>82</td>
<td>78%</td>
</tr>
<tr>
<td>Continuous bladder irrigation with amphotericin B (&gt;5 days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trinh, 1995, USA</td>
<td>18</td>
<td>Persistent candiduria</td>
<td>50 mg/l</td>
<td>7 days</td>
<td>17</td>
<td>94%</td>
</tr>
<tr>
<td>Wise, 1973, USA</td>
<td>40</td>
<td>Persistent candiduria</td>
<td>50 mg/l</td>
<td>5 days</td>
<td>7</td>
<td>70%</td>
</tr>
<tr>
<td>Jacobs, 1996, USA</td>
<td>39</td>
<td>Funguria</td>
<td>50 mg/l</td>
<td>5 days</td>
<td>33</td>
<td>85%</td>
</tr>
<tr>
<td>Total</td>
<td>107</td>
<td></td>
<td></td>
<td></td>
<td>94</td>
<td>88%</td>
</tr>
</tbody>
</table>
urinary tract obstruction, patients using cystostomy). ABBI appears to be as effective as fluconazole, and the best method involves continuous irrigation for more than 5 days. Local irrigation does not offer systemic antifungal therapy and should only be used for asymptomatic candiduria.

A practicing urologist, Gilbert Wise, said: “until such time as an effective treatment is available, amphotericin B irrigation should remain in the armamentarium of the clinician”.

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**References**