Problems and Controversies in the Management of Hematogenous Candidiasis

Omrum Uzun and Elias J. Anaissie

Hematogenous candidiasis is associated with substantial mortality and morbidity. Amphotericin B has routinely been used to treat this infection. However, tolerance of therapy with amphotericin B is limited by the drug's toxicity. The results of recently completed prospective randomized clinical studies comparing amphotericin B with fluconazole for the treatment of hematogenous candididiasis suggest that fluconazole is as effective as amphotericin B and that fluconazole is better tolerated by patients. Nevertheless, several questions remain to be answered regarding the optimal choice of antifungal agent for both nonneutropenic and neutropenic patients, the dosing schedule and duration of therapy, the role of combination antifungal therapy, and the efficacy of the lipid formulations of polyenes. Controversial issues with respect to the role of central venous catheters in the pathogenesis of hematogenous candidiasis, as well as the roles of cytokines and white blood cell transfusions in the treatment of neutropenic patients with hematogenous candidiasis, also need to be addressed.

In general, the severity and extent of this condition tend to increase in accordance with the number and severity of predisposing factors. In a multivariate analysis of prognostic factors among 106 patients with candidemia, Fraser et al. [9] showed that mortality was associated with higher Acute Physiologic and Chronic Health Examination (APACHE) II scores (P = .0001), the presence of a rapidly fatal underlying disease (P = .009), and persistently positive blood cultures (P = .02).

We studied 479 cancer patients with hematogenous candidiasis to determine the prognostic factors for this patient population [10]. In a multivariate logistic analysis model, the presence of neutropenia, (P < .0001), disseminated candidiasis (P < .0001), and a high APACHE III score (P < .0001) were associated with an unfavorable outcome. Given these findings, patients with hematogenous candidiasis can be divided into two groups: those at high risk for morbidity and mortality resulting from this infection, and those at low risk (table 1). The presence of any one of these poor prognostic factors should be regarded as indicating high risk. A successful therapeutic strategy should therefore be based on a careful evaluation of the above-mentioned risk factors and on the susceptibility of the infecting Candida species to antifungal agents. In spite of recent advances in antifungal susceptibility testing, there is currently no standard method that can guide treatment in individual patients. The data on the correlation between the results of susceptibility testing and outcome are limited and controversial [11–13].

What Is the Agent of Choice for the Treatment of Hematogenous Candidiasis?

Nonneutropenic patients. For decades, amphotericin B has been the mainstay in the treatment of this infection [14–17]. However, tolerance of therapy with this drug has been limited by its acute and chronic toxicities [18]. Fluconazole, a well-tolerated triazole, has been shown to be effective against hematogenous candidiasis in experimental models [19]. A number of small series and retrospective studies [20–25], as well as a large prospective observational study [26], have shown response rates of 60%–100% when fluconazole is administered for treatment of serious candidal infections (table 2). There have been some concerns, however, regarding the use of fluconazole to treat hematogenous candidiasis because the drug is fungistatic and has limited activity against certain Candida species [30, 31].

The results of two recent prospective randomized multicenter trials comparing fluconazole with amphotericin B suggest that fluconazole is as effective as amphotericin B in the management of hematogenous candidiasis [28, 29]. Unfortunately, these studies included small numbers of infections caused by a
Table 1. Risk categories for patients with hematogenous candidiasis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underlying disease*</td>
<td>Rapidly fatal</td>
</tr>
<tr>
<td>Neutrophil count&lt;sup&gt;1&lt;/sup&gt;</td>
<td>≤1,000/mm&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Duration of candidemia*</td>
<td>&gt;48 h</td>
</tr>
<tr>
<td>Candidemia with organ infection&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Yes</td>
</tr>
<tr>
<td>APACHE III score*</td>
<td>High</td>
</tr>
</tbody>
</table>

NOTE. APACHE = Acute Physiologic and Chronic Health Examination.

* Factor found to be significant; data are from [9].

<sup>1</sup> Factor found to be significant; data are from [10].

<sup>2</sup> Infections including septic thrombophlebitis, endocarditis, and endophthalmitis.

Candida species other than C. albicans. Because of the serious morbidity and mortality among high-risk patients and the variable susceptibility of Candida species, other than C. albicans, to the two drugs (i.e., the low susceptibility or resistance of C. krusei [32, 33] and Torulopsis glabrata [34] to fluconazole and C. lusitaniae to amphotericin B [35]), it is important to adjust antifungal therapy according to the risk group in which the patient belongs and to the infecting Candida species.

One practical approach is to use the results of the germ-tube test to direct therapy. If the germ-tube test is positive, which is usually indicative of C. albicans infection, or if the patient is known to be colonized with C. albicans, we recommend that fluconazole therapy be started (figure 1). In addition, fluconazole would be the drug of choice if the infecting or colonizing organism, such as C. tropicalis, C. parapsilosis, or C. lusitaniae, is susceptible to it. Because Candida species other than C. albicans are typically less susceptible to fluconazole than is C. albicans and because higher doses of fluconazole appear to be more effective (table 2) [23], a dosage of 600–800 mg/d of intravenous fluconazole, given for 3 days, is probably the appropriate initial therapy for hematogenous candidiasis. This dosage could be decreased to 400 mg/d, given orally, depending on the rapidity of the response [28, 29]. On the other hand, if the patient is colonized with C. krusei or T. glabrata, if either of these species are present in the hospital flora, or if there is no information on the species causing infection, we recommend that therapy with amphotericin B (0.7 mg/[kg · d]) be started [29].

Neutropenic patients. Information on the outcome of hematogenous candidiasis in neutropenic patients treated with amphotericin B or fluconazole is limited. A combined preliminary analysis of findings from a randomized prospective multicenter trial of fluconazole vs. amphotericin B [29] and data from a matched-pair cohort study [25] (these studies included a total of 40 neutropenic patients with candidemia) suggests that fluconazole and amphotericin B have comparable activities (response rates, 63% and 52%, respectively) in neutropenic patients with candidemia (P > .1). However, it should

Table 2. Response to therapy with fluconazole or amphotericin B among patients with hematogenous candidiasis.

<table>
<thead>
<tr>
<th>Type of study, reference</th>
<th>Patient population</th>
<th>Fluconazole</th>
<th>Amphotericin B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total no. of patients</td>
<td>Percent with response</td>
<td>Total no. of patients</td>
</tr>
<tr>
<td>Small series and/or retrospective studies</td>
<td>[20]</td>
<td>General*</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>[21]</td>
<td>Surgical*</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>[22]</td>
<td>Surgical</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>[23]</td>
<td>General</td>
<td>30&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>[24]</td>
<td>Intensive care unit</td>
<td>30&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>[25]</td>
<td>General</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>[26]</td>
<td>Cancer</td>
<td>45</td>
</tr>
<tr>
<td>Prospective observational study</td>
<td>[26]</td>
<td>General</td>
<td>67</td>
</tr>
<tr>
<td>Prospective randomized trials</td>
<td>[27]</td>
<td>Surgical</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>[28]</td>
<td>General</td>
<td>103</td>
</tr>
<tr>
<td></td>
<td>[29]</td>
<td>General&lt;sup&gt;11&lt;/sup&gt;</td>
<td>75</td>
</tr>
</tbody>
</table>

NOTE. "General" includes medical, surgical, oncology, and ICU patients.

* Included patients with invasive organ infections.

<sup>1</sup> Dose, 5 mg/(kg · d).

<sup>1</sup> Dose, 10 mg/(kg · d).

<sup>8</sup> Amphotericin B plus flucytosine.

<sup>11</sup> Included patients with presumed candidiasis.
Identify patients at risk for the disease
- Immunosuppression, neutropenia
- Disruption of gastrointestinal tract integrity (abdominal surgery, diarrhea, mucositis, total parenteral nutrition)
- Fever unresponsive to broad-spectrum antibiotics
- Colonization by Candida at multiple body sites

Perform initial workup for the patient with all of the above-mentioned risk factors
- Obtain cultures of urine, wound, drain sites, throat, sputum, and stool
- Obtain two sets of blood cultures daily for 2 days (or longer if patient still febrile)
- Perform funduscopic examination to identify retinitis
- Exclude other conditions as cause of persistent fever on antibiotics

Blood cultures positive for Candida species, organ infection present, or patient colonized by Candida at more than two sites (one site sufficient if C. tropicalis)

- No
  - Continue surveillance cultures twice weekly
- Yes
  - Start antifungal treatment
  - Evaluate daily

Patients colonized with C. krusei or T. glabrata, hospital flora indicates high risk of infection with these species, or infection with an unknown organism and patient hemodynamically unstable:
- Amphotericin B (0.7 mg/[kg-d]) (plus fluconosine if hemodynamically unstable)

- Germ tube positive or patient colonized with C. albicans, C. tropicalis, C. parapsilosis, or C. lusitaneae:
- Fluconazole (600-800 mg/diy intravenously for 3 days, then 400 mg/diy orally)

Patient unstable or deteriorating, persistent (>72 hours) candidemia, retinitis or organ infection

- No
  - Treat for 7-10 days (at least 5 days without signs and symptoms of infection)
- Yes
  - Remove all venous catheters.
  - Exclude septic phlebitis and endocarditis.
  - Consider combination therapy (Amphotericin B plus fluconosine for T. glabrata or C. krusei) or (fluconazole plus fluconosine for C. albicans, C. tropicalis or C. parapsilosis)
  - Treat for 10-14 days after disappearance of all signs and symptoms of infection

Figure 1. Algorithm for the management of hematogenous candidiasis.

be emphasized that response to antifungal therapy in neutropenic patients is almost always associated with recovery from myelosuppression.

How Long Should Hematogenous Candidiasis be Treated?

Although therapy lasting 15–33 days has been reported in several clinical trials, the optimal duration of therapy for hematogenous candidiasis has not been well defined [20–22, 28]. Data from our controlled studies [25, 29] indicated that therapy of a short duration (median duration, 9 days) may be adequate in most cases. However, we recommend that patients at high risk for morbidity and mortality due to this infection be treated for 10–14 days after the disappearance of all signs and symptoms of infection. On the other hand, patients who are at low risk for morbidity and mortality can be treated safely for 7–10 days (a minimum of 5 days when the patient is afebrile and asymptomatic). This approach has important implications in terms of cost effectiveness and prevents unnecessary exposure of patients to potential adverse events and drug interactions.
Is There a Role for Combination Antifungal Chemotherapy?

Combining antifungal agents that have different modes of action is an attractive approach that may result in a potentially synergistic or additive effect, thereby broadening the spectrum of activity, decreasing the emergence of resistance, and perhaps, decreasing toxicity. Studies performed in vitro and in vivo have demonstrated synergy when flucytosine was added to a regimen containing amphotericin B [32, 33] or fluconazole [34]. Flucytosine has been found to be the most active agent against C. lusitaniae, an organism known to develop resistance to amphotericin B [35]; the MIC of flucytosine was <0.125 \( \mu g/mL \) for 90% of 27 strains tested in our laboratory [36]. This antifungal agent also has good activity against T. glabrata, an organism that may have innate or acquired resistance to fluconazole [37].

The attempt to combine amphotericin B with fluconazole in the treatment of fungal infections has been discouraged by in vitro studies that demonstrated antagonism between these antifungal agents [38, 39]. In a murine model of trichosporosis, the activity of the combination of amphotericin B plus fluconazole was shown to be superior to that of either agent alone [40]. Sugar et al. [41] recently reported that there was no antagonism between amphotericin B and fluconazole; furthermore, the effects were at least additive in murine models of acute hematogenous candidiasis.

On the basis of these findings, combination chemotherapy (amphotericin B plus flucytosine, if the causative pathogen is T. glabrata or C. krusei, or fluconazole plus flucytosine, for other Candida species) could perhaps be useful in high-risk patients (table 1). Amphotericin B plus fluconazole could be an option in certain high-risk patients, but it should be emphasized that the data from in vivo studies and the clinical experience with this combination are limited.

Should All Central Venous Catheters Be Removed in Patients with Hematogenous Candidiasis?

Whether removal of a central venous catheter is mandatory for patients with candidal infection of the bloodstream remains controversial. Theoretically, removal of the catheter would eliminate a potential site of persistent infection. The results of three retrospective studies have suggested that removal of central venous catheters plays an important role in decreasing the complications of candidiasis [42-44]. In a post hoc analysis, Rex et al. [45] showed that replacement of all vascular lines before therapy is begun or at the start of therapy shortened the duration of candidemia from 5.5 days to 4.2 days [45]. These authors recommended that all vascular catheters be removed from patients with candidemia. However, there is strong evidence in the literature that vascular catheters are not the primary source of hematogenous candidiasis; rather, the gastrointestinal tract is the source [46-50]. In addition, data from Memorial Sloan-Kettering Cancer Center (New York) [51] suggest that removal of catheters is not always necessary for a favorable outcome. Removal of central venous catheters from patients with candidemia did not improve the outcome in our prospective randomized study [29], in our matched-pair cohort study [25], or when data from both studies were combined in a meta-analysis (for a total of 143 episodes of candidemia; Anaissie et al., unpublished data). However, it should be kept in mind that none of the above-mentioned studies were specifically designed to address this particular question.

Given the high cost of removing central venous catheters (e.g., removal of a Hickmann catheter costs approximately $5,000), the discomfort to patients, and the difficulty in maintaining vital venous access in some settings, we believe that the decision to remove central venous catheters should be made on an individual basis and not performed routinely. The line should always be removed if there is suspicion of or clinical evidence for endovascular infection, such as septic thrombo phlebitis or endocarditis. Otherwise, the catheter may be kept in place if the patient is clinically stable. On the other hand, if the patient’s condition deteriorates or there is evidence of organ infection and persistent fungemia, serious consideration should be given to the removal of the central venous catheter. Because currently available data indicate that C. parapsilosis may be more frequently associated with catheter-related infections [52], it would seem prudent to remove catheters from all patients with candidemias caused by this species.

Is There a Role for the Lipid Formulations of Polyenes in the Treatment of Hematogenous Candidiasis?

The packaging of the polyenes—both amphotericin B and nystatin—into lipid vehicles offers new therapeutic options. There are three currently available lipid formulations of amphotericin B: amphotericin B lipid complex (ABLC; The Liposome Company, Princeton, NJ), amphotericin B colloidal suspension (ABCD; Liposome Technology, Menlo Park, CA), and liposomal amphotericin B (AmBisome; Vestar, San Dimas, CA), and one lipid formulation of nystatin (AR-121; Aronex, The Woodlands, Texas). These compounds are active in vitro [53], and in experimental models, they appear to have a superior therapeutic index to that of amphotericin B. However, substantially larger doses of these lipid formulations are needed to achieve the same overall response obtained with the parent compound [54].

The results from ongoing clinical trials suggest that these lipid formulations are less nephrotoxic than amphotericin B. The preliminary analysis of data from a recently completed prospective randomized multicenter trial comparing amphotericin B deoxycholate to ABLC in 231 patients with serious candidal infections shows that the overall response rates among the patients were the same (65% for patients treated with ABLC and 61% for those treated with amphotericin B) but that the incidence of nephrotoxicity was substantially lower with ABLC.
than with amphotericin B deoxycholate [54]. This finding has important implications in the treatment of patients with fluconazole-resistant candidiasis and who are at increased risk for nephrotoxicity (i.e., those undergoing transplantation of bone marrow or organs, for whom treatment with nephrotoxic agents such as cyclosporin A, FK506, vancomycin, high-doses acyclovir, foscarnet, aminoglycosides, and cisplatin is common).

Is There a Role for Colony-Stimulating Factors and WBC Transfusions in the Management of Hematogenous Candidiasis?

The addition of cytokines to antifungal therapy may have an impact in neutropenic patients with fungal infections for whom a favorable outcome depends on recovery from neutropenia. The effectiveness of these growth factors in treating hematogenous candidiasis has not been established. A phase 1 trial of recombinant human macrophage colony-stimulating factor in patients with invasive fungal infections has provided promising results [56], but this compound is no longer available. In another pilot study, the results obtained with granulocyte-macrophage colony-stimulating factor as adjuvant treatment in neutropenic patients with documented fungal infections were encouraging [57].

The therapeutic use of WBC transfusions is another option for immune reconstitution. In a canine model of neutropenia and hematogenous candidiasis, WBC transfusions were shown to reduce the tissue concentrations of Candida organisms [58]. The major problem associated with WBC transfusions has been the limited number of neutrophils that can be collected from healthy donors. Data from controlled studies indicate a correlation between the number of neutrophils transfused and the outcome of infection [59]. Pretreatment of leukapheresis donors with granulocyte colony-stimulating factor has been shown to result in greater increments in the number of neutrophils available for transfusion [60–62]. Early results obtained with transfusion of WBCs from donors stimulated with granulocyte colony-stimulating factor into profoundly neutropenic patients with fungal infections, including hematogenous candidiasis, have been promising [62]. However, at this point the clinical experience with WBC transfusions is too limited to be conclusive.

The main problem in establishing a therapeutic strategy for patients with hematogenous candidiasis is the scarcity of data from clinical trials, most of which have included a small sample size. Therefore, specific questions regarding the optimal antifungal agent, its dosage and duration of administration, the impact of immune reconstitution with cytokines and/or WBC transfusions, and the issue of vascular catheter management should be addressed in carefully planned, prospective, randomized (when applicable) trials with adequate sample sizes. The use of appropriate statistical methodology in such trials will be important for obtaining results that can provide sufficient, reliable information for the treatment of hematogenous candidiasis. In particular, the objective(s) should be defined before the studies have begun and not be subject to change once the studies are under way. The statistical power of the studies should be sufficient to detect any difference(s) between the treatment groups. In addition, the patient populations should be described in clear detail; a careful assessment of the baseline characteristics of the treatment groups, including the presence of poor prognostic factors, should be made. In the final stage of each study, an intent-to-treat analysis should be performed to prevent bias, and the reasons why patients do not complete the regimens should be clearly stated.

In conclusion, significant advances in the management of hematogenous candidiasis have been made. Namely, new antifungal agents with efficacy comparable to that of amphotericin B deoxycholate and with better safety profiles have been introduced to treat patients with this infection. However, several questions remain to be addressed; hopefully, prospective randomized trials with sufficient power to detect the impact of certain therapeutic strategies in carefully defined patient populations will be conducted in the near future.

References


