Cryptococcosis: We Should Do Better!

To the Editor—Ecevit and colleagues [1] should be congratulated, because their article on CNS cryptococcosis among nonimmunosuppressed patients raises an important issue—the optimal antifungal to be used for treatment.

In fact, in their article, Ecevit et al. [1] report that 2 patients initially received treatment with fluconazole at a dosage of 400 mg per day. As is shown in table 1, the use of fluconazole as initial therapy among non–HIV-infected patients affected by cryptococcosis is reported in 6%–46% of cases [2–7]. Our experience is somewhat more disturbing. In a 30-month prospective epidemiological survey [8] conducted in Italy from 1997 to 2000 and involving 154 patients (mainly HIV infected) with a diagnosis of cryptococcosis, 106 patients (68.8%) received monotherapy with either fluconazole (44 patients; 41.5%), amphotericin B deoxycholate (39 patients; 36.8%), liposomal amphotericin B (20 patients; 18.9%), itraconazole (2 patients; 1.9%), or fluconazole (1 patient; 0.9%). Of note, of the 44 patients treated with fluconazole, 22 patients (50%) received a daily dose ranging from 600 mg to 800 mg, but the remaining patients received lower dosages (ranging from 50 mg to 400 mg per day). It is well known that cryptococcal meningitis—especially among immunocompromised hosts—is associated with a high meningeal fungal burden, and it was recently reinforced that high CSF cryptococcal colony-forming units are associated with early death [9]. Thus, rapid fungicidal therapy is warranted. In addition to the seminal study of van der Horst et al. [10], which is the basis of the recommendations of the Infectious Diseases Society of America’s guidelines for the treatment of meningeal cryptococcosis, a recent open-label study conducted in Thailand also showed that amphotericin B plus flucytosine was the regimen that most rapidly achieved CSF sterilization, compared with amphotericin B alone (P = .006), amphotericin B plus fluconazole (P = .02), or triple therapy (amphotericin B, flucytosine, and fluconazole; P = .02) [7]. Of particular interest is the fact that, in a small randomized study conducted among patients with AIDS, the use of liposomal amphotericin B (at a dosage of 4 mg/kg per day), compared with conventional amphotericin B (at a dosage of 0.7 mg/kg per day), led to a higher rate of CSF sterilization at 2 weeks (10 of 15 patients vs. 1 of 9 patients; P = .01), although no differences in the clinical efficacy were demonstrated [11].

In conclusion, despite the fact that the actual treatment of cryptococcal meningitis is far from optimal, it should be reinforced, at least in this instance, that there is a need for combination antifungal ther-

Table 1. Antifungal treatment employed in different studies of immunocompetent and immunocompromised non–HIV-infected patients with cryptococcosis.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Health status (%)</th>
<th>Premortem diagnosis, no. (%)</th>
<th>Treatment (%)</th>
<th>Outcome (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[2]</td>
<td>63</td>
<td>Immunocompetent (70); underlying conditions + immunosuppressive treatment (30)</td>
<td>60 (95)</td>
<td>AmB (41.5); a AmB + flucyt (28.5)</td>
<td>Cure (57.1)</td>
</tr>
<tr>
<td>[3]</td>
<td>35</td>
<td>Immunocompetent b</td>
<td>35 (100)</td>
<td>AmB (8.6); AmB + flucyt (91.4)</td>
<td>Complete recovery (46); death (15)</td>
</tr>
<tr>
<td>[4]</td>
<td>94</td>
<td>Lymphoma (11.7); rheumatic disease (10.6); diabetes mellitus (8.5); cirrhosis (6.4); transplant recipients (6.4); cancer (6.4)</td>
<td>87 (92.5)</td>
<td>AmB + flucyt (69); AmB + flu (23); flu (5.7); AmB (2.3)</td>
<td>Cure (63)</td>
</tr>
<tr>
<td>[5]</td>
<td>31</td>
<td>Cancer (100)</td>
<td>29 (94)</td>
<td>Flu (46.4); AmB (14.3); AmB + flucyt + flu (10.7); AmB + flucyt + LAMB (10.7)</td>
<td>Cure (82)</td>
</tr>
<tr>
<td>[6]</td>
<td>28</td>
<td>Transplant recipients (100)</td>
<td>28 (100)</td>
<td>AmB + flucyt (89.3); AmB (10.7)</td>
<td>Death (50)</td>
</tr>
<tr>
<td>[7]</td>
<td>37</td>
<td>Immunosuppressive drug treatment (41); systemic lupus erythematosus (16); malignancies (16); diabetes mellitus (14); cirrhosis (5); other conditions (22)</td>
<td>34 (92)</td>
<td>AmB (53); AmB + flucyt (11.8); flu (8.8)</td>
<td>Death (27)</td>
</tr>
</tbody>
</table>

NOTE. AmB, amphotericin B deoxycholate; flu, fluconazole; flucyt, flucytosine; LAMB, liposomal amphotericin B.

a Refers to patients with a diagnosis of meningococcal meningitis.

b In all, 26 patients had Cryptococcus neoformans var. gattii.
therapy. Moreover, because fluconazole is essentially a fungistatic drug, it should not be used as the induction treatment for cryptococcal meningitis. If the use of amphotericin B is deemed unfeasible, the daily dose of fluconazole should not be <800 mg.

Acknowledgments

Potential conflicts of interest. S.A.: no conflicts.

Spinello Antinori
Department of Clinical Sciences, Section of Infectious and Tropical Diseases, L Sacco Hospital, University of Milan, Milan, Italy

References


Reply to Antinori

To the Editor—We thank Dr. Antinori [1] for highlighting the frequency with which cryptococcal meningitis among non–HIV-infected patients is treated with suboptimal antifungal regimes. We agree that amphotericin B in combination with flucytosine is the optimal initial regimen among this population. Although the duration of combination therapy has not been defined in the era of azole agents [2], the current recommendations of the Infectious Diseases Society of America call for a ≥2-week induction period [3]. Among patients who have a clinical and microbiological response to induction therapy, consolidation therapy for an additional 8–10 weeks with fluconazole can be considered. Data from randomized trials conducted before the HIV era support at least 4–6 weeks of therapy with amphotericin B and flucytosine [4, 5]. Initial therapy with a fluconazole-containing regimen, even among “low-risk” patients, is discouraged [3] on the basis of the poor outcome observed in a pilot study [6].

Furthermore, the observations of Dr. Antinori [1] and the findings of our study [7] are notable in the face of reports demonstrating that management of elevated intracranial pressure during cryptococcal meningitis often does not correspond to recommended practice [3, 8, 9]. Clearly, the infectious diseases community needs to do a better job of educating our colleagues about the recognition and treatment of this disease. At the same time, our experience suggests that more-timely diagnosis, appropriate antifungal therapy, and control of intracranial pressure will not ensure improved outcomes for all nonimmunosuppressed patients. As we reported, 2 (40%) of 5 patients treated with amphotericin B and flucytosine died; moreover, the conditions of 3 (33%) of 9 patients paradoxically worsened on receipt of antifungal therapy, despite initial clinical and laboratory improvement and the sterilization of CSF [7]. This worsening was accompanied by brain edema, cortical and laminar necrosis, new areas of leptomeningeal enhancement, cerebral infarcts, and the development of cystic lesions, suggesting that the host inflammatory response contributed to the pathogenesis of disease [7]. In this regard, our findings are consistent with the recently proposed damage-response framework of infectious diseases [10, 11].

The damage-response framework recognizes that both microbe and host contribute to the pathogenesis of disease [11]. As such, the host immune response should be considered along with the infecting organism during treatment. Before the era of HAART, the host response among HIV-infected patients was blunted, and therapy was directed at reducing infectious burdens and preventing relapse. During the HAART era, up to 30% of HIV-infected patients coinfected with Cryptococcus neoformans develop immune reconstitution inflammatory syndrome, particularly if HAART is initiated within 30 days after a diagnosis of cryptococcosis [12]. In severe cases of cryptococcal immune reconstitution inflammatory syndrome, patients might require anti-inflammatory therapy to dampen the deleterious effects of the reconstituted host immune response [12, 13]. Our data suggest that selected patients with no known immunosuppression might also benefit from corticosteroids or other anti-inflammatory measures, as has recently been demonstrated in tubercular meningitis [14]. For this reason, we suggest that the role of corticosteroids in the treatment of this population be assessed in future studies. As things currently stand, we join Dr. Antinori in saying: we have to do better!