RISK FACTORS FOR DEATH IN ACQUIRED IMMUNODEFICIENCY SYNDROME–ASSOCIATED DISSEMINATED HISTOPLASMOSIS

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Abstract. We performed a retrospective study of 164 human immunodeficiency virus (HIV)–infected patients with disseminated histoplasmosis to identify the risk factors for death. Death occurred in 32% of the cases. Univariate analysis identified the following risk factors: diarrhea (odds ratio [OR] = 3.9, P = 0.001), neurologic manifestations (OR = 5.8, P = 0.001), hemoglobin level < 8.0 g/dL (OR = 2.7, P = 0.004), urea level 2 times the normal upper limit (OR = 5.0, P < 0.001), creatinine level > 1.5 mg/dL (OR = 2.9, P = 0.005), aspartate aminotransferase (AST) level > 2.5 times the normal upper limit (OR = 3.1, P = 0.01), respiratory insufficiency (OR = 9.7, P < 0.001), sepsis (OR = 20.2, P < 0.001), and acute renal failure (OR = 2.5, P = 0.011). A hemoglobin level < 8.0 g/dL (OR = 3.8, P = 0.008), an AST level ≥ 2.5 times the normal limit (OR = 1.0, P = 0.007), acute renal failure (OR = 2.96, P = 0.015), and respiratory insufficiency (OR = 12.2, P = 0.01) were independent risk factors for death.

INTRODUCTION

Histoplasmosis is a common opportunistic infection in patients infected with human immunodeficiency virus (HIV) who reside in disease-endemic areas, such as Brazil. Disseminated histoplasmosis has been an acquired immunodeficiency syndrome (AIDS)–defining illness since 1987. It is reported to occur in approximately 5% of patients with AIDS who live in disease-endemic areas.

A study performed in southern Brazil using the histoplasmin skin test showed that 89% of reactors were young men between 17 and 19 years of age.

Comparison of AIDS–disseminated histoplasmosis patients from the United States and Brazil showed more frequent skin involvement (1–7% versus 66%) and death (5–13% versus 19%) in the Brazilian patients.

The infection is characterized by a wide spectrum of manifestations ranging from asymptomatic illness to severe disseminated histoplasmosis. Most patients have respiratory symptoms. Acute histoplasmosis is usually a self-limited disease, with fever, chills, nonproductive cough, headaches, and generalized malaise. In AIDS patients, the disease is associated with a nonspecific clinical presentation, usually unexplained fever and weight loss. Approximately 10–20% of these patients have septic shock at presentation, with fever, hypotension, renal and hepatic failure, respiratory distress syndrome, and coagulopathy. Laboratory findings such as a serum creatinine level > 2.1 mg/dL and an albumin level < 3.5 g/dL have been associated with an increased risk of severe manifestations such as septic shock, respiratory failure, and death. A prospective study among HIV–positive patients with disseminated histoplasmosis found that dyspnea, a platelet count < 100,000/mm³, and a lactate dehydrogenase (LDH) level > 2 times the normal upper limit were independent risk factors for death. Better knowledge of the factors associated with high mortality in patients with disseminated histoplasmosis would result in better treatment. The objective of this study was to investigate the risk factors potentially associated with death in patients with AIDS and disseminated histoplasmosis.

MATERIALS AND METHODS

We carried out a retrospective study of 164 HIV-positive patients with disseminated histoplasmosis to determine the risk factors associated with death. All reported cases met the 1987 AIDS case definition of the Centers for Disease Control and Prevention (Atlanta, GA). Physicians caring for these patients were contacted, and consent was obtained to review medical records. The patients were admitted between January 1995 and January 2004 to a public tertiary hospital in Fortaleza in northeastern Brazil. The study protocol was reviewed and approved by the Ethical Committee of the Universidade Federal do Ceará.

A diagnosis of histoplasmosis was confirmed by at least one of the following methods: identification of Histoplasma capsulatum in peripheral blood, bone marrow aspirate, blood and bone marrow culture; lysis-centrifugation system; and histopathologic examination of different tissues. An HIV infection was confirmed by indirect immunofluorescence and/or enzyme-linked immunosorbent assay. Patients with isolated pulmonary forms of histoplasmosis were not included in the study.

Case-patients were those who died before hospital discharge (non-survivors). Data on histoplasmosis included date of diagnosis, clinical manifestations, and laboratory test results at the time of admission and before antifungal treatment (for this analysis, data were obtained from seven days before admission through seven days after admission). Demographic factors were age, sex, sexual behavior, intravenous drug abuse, and previous blood transfusion. The following complications were also observed: respiratory insufficiency, hepatic dysfunction, sepsis and acute renal failure, and neurologic manifestations (including clinical signs and symptoms caused by nervous system injury or dysfunction). Respiratory insufficiency was defined as the need for mechanical ventilation. Hepatic dysfunction was defined as a serum total bilirubin...
level > 2 mg/dL or another clinical condition that indicated hepatic failure. Sepsis was defined according to the American College of Chest Physicians/Society of Critical Care Medicine. Acute renal failure was defined as a serum creatinine level > 1.5 mg/dL or an increase in the serum creatinine concentration by more than 50% or > 0.5 mg/dL above baseline.

Patients with histoplasmosis were treated with amphotericin B as induction therapy at a dose of 0.7–1 mg/kg/day (up to a cumulative dose of 1 gram), followed by a maintenance therapy with itraconazole, 600–800 mg/day.

**Statistical analysis.** Results were expressed mean ± SD or median (range) for quantitative variables. Univariate and multivariate analysis of clinical and laboratory data was conducted with SPSS version 10.0 (SPSS Inc., Chicago, IL) and Epi-Info version 6.04b (Centers for Disease Control and Prevention) software. Comparison of parameters was done with Student’s t-test and Fischer’s exact test. Analysis of associations between death and categorized risk factors was done with Fischer’s exact test and Pearson’s chi-square test. A logistic regression model was used for quantitative variables. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A multivariate logistic regression was performed to analyze the possible risk factors for death. The factors included in the multivariate model were those that showed a significance level < 20% in the univariate analysis (by Mann-Whitney test and chi-square test). P values < 0.05 were statistically significant.

**RESULTS**

A total of 164 patients had a confirmed diagnosis of infection with HIV and disseminated histoplasmosis. The sex ratio (men:women) was 4:1, and the mean ± SD age of the patients was 34.2 ± 8.19 years. Although differences in sex were not observed, sex was a decreased risk factor for death in heterosexual patients (P = 0.025). The demographic characteristics of the patients are shown in Table 1. The diagnosis of histoplasmosis was made through identification of *H. capsulatum* in bone marrow aspirate (81.1% of the cases), in peripheral blood smears by a lysis-centrifugation system (79.5%), culture of bone marrow aspirates (47.8%) and histopathologic examination of different tissues (57.9%).

All patients had disseminated manifestations; some also had pulmonary disease manifestations. The mean ± SD duration of illness before hospitalization was 1.94 ± 2.58 months in survivors and 2.21 ± 2.91 months in non-survivors, but this difference was not statistically significant. Diarrhea was observed at admission in 100 patients, of whom 43 died. Unusual manifestations included cerebral histoplasmosis, confirmed by autopsy, and pericarditis in one patient each. Of the 164 patients, 52 had respiratory insufficiency, of whom 34 (65.4%) died; 16 patients had sepsis, of whom 14 (87.5%) died; and 97 patients had acute renal failure, of whom 39 (42.2%) died during hospitalization.

The laboratory abnormalities in survivors and non-survivors before antifungal treatment are shown in Table 2. Analysis of CD4 cell counts before admission was not possible because the diagnosis of histoplasmosis occurred within one month of the diagnosis of HIV infection in many patients and because data were missing for patients, most of whom died.

Results of univariate logistic regression are shown in Table 2.
Clinical and laboratory factors associated with an increase in risk of death included diarrhea, neurologic disorders, a hemoglobin level < 8.0 g/dL, a serum urea concentration > 2 times the normal upper limit, a serum creatinine concentration > 1.5 mg/dL, an AST level > 2.5 times the normal upper limit, respiratory insufficiency, sepsis, and acute renal failure. Heterosexual behavior (man or women) was associated with a decreased risk of death by univariate analysis, but we could not provide any explanation for this finding.

Multivariate analysis showed associations between death and a hemoglobin level < 8.0 g/dL, an increase in AST levels, acute renal failure, and respiratory insufficiency. The association between low hemoglobin levels and death may be due to hemorrhagic disorders or bone marrow suppression. Several studies have shown the occurrence of hepatomegaly and/or high levels of AST and alanine aminotransferase in patients with histoplasmosis. Respiratory insufficiency is known to be a classic risk factor for death in patients with disseminated histoplasmosis, and this was confirmed in our study. Univariate analysis showed that serum creatinine levels > 1.5 mg/dL on hospital admission were associated with death. Some patients had signs of dehydration at admission, which could have contributed to the genesis of acute renal failure. High fever, extreme weight loss, thrombocytopenia, and coagulopathy were not associated with death, as previously reported. High levels of LDH have been associated with increased risk of death. In our study, LDH levels were higher which are the only other published studies on prognostic factors for AIDS-associated disseminated histoplasmosis. The prospective study by Couppié and others differed from those identified by Wheat and others and Couppié and others, which are the only other published studies on prognostic factors for AIDS-associated disseminated histoplasmosis. The prospective study by Couppié and others included 82 patients to determine the prognostic factors associated with death within one month after starting antifungal treatment, found associations by multivariate analysis between AIDS-associated disseminated histoplasmosis and dyspnea, thrombocytopenia, and an increased LDH levels. Wheat and others in a retrospective study of 155 patients treated with amphotericin B found that high levels of serum creatinine, low levels of serum albumin, and previous use of zidovudine were associated with septic shock, respiratory insufficiency, and death. In our study, the presence of acute renal failure was associated with an increased risk of death.

### DISCUSSION

Histoplasmosis is the first opportunistic infection observed in 22–85% of HIV-infected patients in disease-endemic areas. Disseminated histoplasmosis usually occurs when CD4 cell counts are < 100/mm³.

Some factors potentially associated with death that were identified by univariate and multivariate analysis in our study differed from those identified by Wheat and others and Couppié and others, which are the only other published studies on prognostic factors for AIDS-associated disseminated histoplasmosis. The prospective study by Couppié and others included 82 patients to determine the prognostic factors associated with death within one month after starting antifungal treatment, found associations by multivariate analysis between AIDS-associated disseminated histoplasmosis and dyspnea, thrombocytopenia, and an increased LDH levels. Wheat and others in a retrospective study of 155 patients treated with amphotericin B found that high levels of serum creatinine, low levels of serum albumin, and previous use of zidovudine were associated with septic shock, respiratory insufficiency, and death. In our study, the presence of acute renal failure was associated with an increased risk of death.

### TABLE 3

<table>
<thead>
<tr>
<th>Risk factors at admission</th>
<th>Survivors (n = 111)</th>
<th>Nonsurvivors (n = 53)</th>
<th>OR (95% CI)</th>
<th><em>p</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea, %</td>
<td>51</td>
<td>81</td>
<td>3.9 (1.8–8.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neurologic manifestation, %</td>
<td>7</td>
<td>32</td>
<td>5.8 (2.3–14.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hemoglobin &lt; 8.0 g/dL, %</td>
<td>32</td>
<td>58</td>
<td>2.7 (1.4–5.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Leukocyte count &lt; 4000 cells/mm³, %</td>
<td>61</td>
<td>39</td>
<td>0.4 (0.2–0.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Serum urea &gt; 2.5× upper normal limit, %</td>
<td>10</td>
<td>39</td>
<td>5.0 (2.2–11.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Serum creatinine &gt; 1.5 mg/dL, %</td>
<td>19</td>
<td>43</td>
<td>2.9 (1.4–6.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>AST &gt; 2.5× upper normal limit, %</td>
<td>44</td>
<td>60</td>
<td>3.1 (1.2–7.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>During hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory insufficiency, %</td>
<td>16</td>
<td>64</td>
<td>9.7 (4.5–21.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sepsis, %</td>
<td>18</td>
<td>26</td>
<td>2.0 (4.3–93.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Acute renal failure, %</td>
<td>52</td>
<td>73</td>
<td>2.5 (1.2–5.2)</td>
<td>0.011</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI = confidence interval; AST = aspartate aminotransferase.
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The usefulness of this study in identifying additional predictors of death was limited by the small sample size, the retrospective study design, and missing data. However, the main contribution of this study was identification of laboratory abnormalities associated with death, which resulted in early recognition of the cases that must be treated more aggressively.

In conclusion, the presence of low hemoglobin levels, increased serum AST levels, acute renal failure, and respiratory insufficiency were independent risk factors for death in AIDS patients with disseminated histoplasmosis. This was the first study to identify risk factors for death in Brazilian AIDS patients with disseminated histoplasmosis. Further prospective studies are necessary to establish additional risk factors.

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