Antifungal Therapy and Management of Complications of Cryptococcosis due to Cryptococcus gattii

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(See the Editorial Commentary by Rolston on pages 552–4.)

Background. We describe antifungal therapy and management of complications due to Cryptococcus gattii infection in 86 Australian patients followed for at least 12 months.

Methods. Patient data from culture-confirmed cases (2000–2007) were recorded at diagnosis, 6 weeks, 6 months, and 12 months. Clinical, laboratory, and treatment variables associated with raised intracranial pressure (ICP) and immune reconstitution inflammatory syndrome (IRIS) were determined.

Results. Seven of 10 patients with lung infection received amphotericin B (AMB) induction therapy (6 with 5-flucytosine [5-FC] for a median of 2 weeks); median duration of therapy including azole eradication therapy was 41 weeks, with a complete/partial clinical response in 78%. For neurologic disease, 88% of patients received AMB, 78% with 5-FC, for a median of 6 weeks. The median total course was 18 months. Nine patients receiving fluconazole induction therapy were reinduced with AMB plus 5-FC for clinical failure. Raised ICP (31 patients) was associated with initial abnormal neurology, and neurologic sequelae and/or death at 12 months (both P = .02); cerebrospinal fluid drains/shunts were placed in 58% of patients and in 64% of 22 patients with hydrocephalus. IRIS developed 2–12 months after starting antifungals in 8 patients, who presented with new/enlarging brain lesions. Risk factors included female sex, brain involvement at presentation, and higher median CD4 counts (all P < .05); corticosteroids reduced cryptococcoma-associated edema.

Conclusions. Induction AMB plus 5-FC is indicated for C. gattii neurologic cryptococcosis (6 weeks) and when localized to lung (2 weeks). Shunting was often required to control raised ICP. IRIS presents with cerebral manifestations.

Keywords. Cryptococcus gattii; antifungal therapy; neurologic complications; IRIS.
The epidemiology, clinical presentation, mortality, and neurologic sequelae of cryptococcosis due to Cryptococcus gattii (CG) differ from those of its sibling species, Cryptococcus neoformans (CN) [1–3]. Management principles are based on randomized clinical trials of CN disease in human immunodeficiency virus (HIV)–infected patients [4], case reports of CG infection [5–7], and expert opinion.

In a contemporary Australian series of 86 patients with CG infection, mortality was increased in immunocompromised patients whereas initial cerebrospinal fluid (CSF) cryptococcal antigen (CRAG) titers of ≥256 predicted death and/or neurologic sequelae in central nervous system (CNS) disease [3]. Raised intracranial pressure (ICP), a predictor of mortality in CN meningoencephalitis [4], was frequent at presentation (66% where measured), and 9% of patients developed immune reconstitution inflammatory syndrome (IRIS) [3]. We now describe the management of cryptococcal infection and its complications in these patients, and compare this with the Infectious Diseases Society of America (IDSA) clinical practice guidelines for CG cryptococcosis [4].

METHODS

Study Design
The Australia and New Zealand Mycoses Interest Group conducted a nationwide study of CG infection in adults (January 2000–December 2007) with approval from human ethics review committees [3]. Clinical, laboratory, and radiologic data, disease complications (raised ICP, hydrocephalus, IRIS, neurologic sequelae), and patient outcomes were recorded. Treatment details included antifungal therapy (type, daily dose, duration); use of corticosteroids or immunomodulators, and surgery (excision, CSF shunt placement). Data were collected at diagnosis to 14 days after starting antifungal therapy and at 6 weeks, 6 months, and 12 months [3]; total duration of antifungal therapy was also recorded.

Definitions
Only culture-confirmed CG infections were included. Cryptococcal meningoencephalitis was defined by CG isolation from CSF. Brain involvement was diagnosed by a radiologist’s report of mass lesions (≥1 cm diameter) or other parenchymal abnormalities (eg, vasculitic lesions), without an alternative diagnosis. Abnormal neurology was defined as previously described [8]. An opening CSF pressure ≥25 cm water was considered elevated [4]. Induction therapy was the initial (intensive) antifungal regimen given for ≥3 consecutive days [9]. Consolidation/maintenance therapy, subsequently referred to as eradication therapy (see Discussion), was defined previously [4, 9]. Reinduction comprised intensified therapy following poor response to induction or eradication therapy, or worsening of symptoms [9]. IRIS was diagnosed when symptoms or radiologic features consistent with inflammation worsened or appeared following a clinical and/or microbiologic response to anticyptococcal therapy, and cultures were negative [3, 10, 11]. Clinical outcomes included all-cause mortality; progressive disease or failure (worsening clinical symptoms/signs); stable disease (no improvement in symptoms/signs); partial response (≤50% resolution of symptoms/signs); or complete response (resolution of clinical symptoms/signs) [3]. Relapse of infection beyond 12 months was recorded.

Data Analysis
Data were analyzed using SPSS software for Windows, version 20 (SPSS, Chicago, Illinois). Two-tailed tests with a significance level of 5% were used. The median and lower to upper quartile range (LQ–UQ) were used to summarize continuous variables. Two-sample t tests or Mann-Whitney tests were used to compare the distribution of continuous variables and χ² or Fisher exact tests were used to test for association between categorical variables. For analysis of the impact of raised ICP, only patients with CNS infection in whom CSF pressures were measured at diagnosis through to 14 days of therapy were included.

RESULTS

Seventy-three of 86 patients had CNS infection, 10 had lung without CNS involvement (normal CSF examination and brain imaging findings), and 2 had bloodstream infection only (Figure 1). One patient had biopsy-proven vertebral osteomyelitis and another had skin/subcutaneous disease (with meningitis).

Clinical responses at 12 months were complete in 33% of 85 patients, partial in 48%, and stable in 3.5%. Mortality was

![Figure 1. Bar chart showing body sites of infection in 88 patients with Cryptococcus gattii infection. Abbreviations: CNS, central nervous system; lung–CNS, lung infection in the absence of CNS infection; CNS-lung, CNS infection in the absence of lung infection; CNS + skin, both CNS and skin infection; blood + other, bloodstream infection plus at least 1 other site of infection; lung, lung infection only.]
13.6% in patients with CNS disease and 11% in those with isolated lung infection. There were no relapses; all patients with a partial response or stable disease at 12 months were subsequently cured.

Antifungal Therapy
All patients were treated; induction regimens are summarized in Table 1. Overall, 73 of 86 patients (85%) received amphotericin B (AMB), 74% in combination with 5-flucytosine (5-FC), and 15% received fluconazole monotherapy (Table 1).

One patient with isolated fungemia received AMB for 3 days and the other, fluconazole for 8.5 months. The patient with osteomyelitis received AMB plus 5-FC for 14 days followed by fluconazole for 6.5 months. All 3 patients had complete responses at 12 months.

Isolated Pulmonary Disease
Clinical data, treatment, and outcomes of 10 patients with isolated lung disease are shown in Table 2. Seven had moderate to severe lobar/generalized consolidation with or without mass lesions; 2 had single large (5–6 cm diameter) cryptococcomas. Seven patients received induction therapy with an AMB formulation (median, 2 weeks; mean, 3.9 weeks; range, 1–8 weeks), 6 in combination with 5-FC. Conventional AMB (AMB: 0.7–1.0 mg/kg/day) was initiated in all 7 cases but 2 were switched to liposomal AMB (L-AMB; 4 mg/kg/day) due to renal impairment after 2 and 16 days, respectively. Neither of 2 kidney transplant recipients (Table 2) treated with fluconazole monotherapy achieved a complete response at 12 months.

Azole eradication therapy was used in 9 patients, typically fluconazole 400–800 mg/day (Table 2). Total duration of therapy was 24–208 weeks (mean, 65.8; median, 41). No lesions were resected surgically.

CNS Disease
Of 73 patients, 25 (34%) achieved a complete clinical response, 33 (45%) achieved a partial response, and 10 (13.6%) who failed therapy died. AMB was initiated in 64 patients (88%), 57 (78%) in combination with 5-FC, for a median of 6 weeks (LQ–UQ, 3–8; Table 3). All patients received AMB initially, but 31 (48.4%) were switched to L-AMB after a median of 8 days due to renal impairment.

Nine patients (12%) received fluconazole induction therapy, 400–1600 mg daily; modal dose was 400 mg (Tables 3 and 4); 7 (78%) required reinduction with AMB plus 5-FC due to clinical failure after a median of 28 days, although 1 patient was later diagnosed with IRIS; the daily fluconazole dose in these 7 patients was 400 mg (n = 5), 1600 mg (n = 1), and 800 mg (n = 1). Five patients treated initially with AMB plus 5-FC received reinduction therapy (Table 3) for presumed treatment failure, later confirmed as IRIS in 4 cases. Fluconazole- and AMB-treated patients were equally likely to manifest 1 or more of CSF, brain, or lung infection (Table 4); 2 of the 9 (22.2%) fluconazole-treated patients were immunocompromised (vs 16 of 51 [31.3%] prescribed AMB plus 5-FC), and 3 of 5 had CSF CRAG titers of ≥256 vs 40 of 58 who received AMB (both P = .7).

Eradication therapy in patients surviving >6 weeks included fluconazole (n = 62), posaconazole (n = 1), and voriconazole (n = 1). Total antifungal courses lasted a median of 18 months (LQ–UQ, 14–22; range, 8–60 months). Similar 12-month outcomes were seen in 18 patients who received a total of 9–12 months of therapy: 6 had a complete, and 9, a partial response (response unknown in 3). All 10 deaths occurred in patients treated with AMB with/without 5-FC; 7 of them were immunocompromised. Proportionately more patients with CNS infection than with isolated lung disease were treated initially with AMB plus 5-FC (78% vs 60%), but these differences were not significant (P = .2).

Raised Intracranial Pressure
CSF pressures, measured in 48 patients, were elevated in 31 (66%), 23 at diagnosis, and an additional 8 at 14 days; 8 patients (26%) had ICPs >35 cm water. Median time from onset of symptoms to CG diagnosis was 26 days (LQ–UQ, 21–42 days) in patients with raised ICP and 29 days (LQ–UQ, 14–120 days), in those with normal ICP (P > .05); in all cases it was <48 hours from presentation to medical care. Mortality was 19%. Raised

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Table 1. Induction Antifungal Therapy Regimens in the First 14 Days of Treatment by Site of Infection

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Lung Without CNS (No.)</th>
<th>CNS Only (No.)</th>
<th>Bone Only (No.)</th>
<th>Blood Only (No.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMB plus 5-FC (n = 64)</td>
<td>6</td>
<td>57</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>AMB only (n = 7)</td>
<td>...</td>
<td>6</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>AMB plus fluconazoleb (n = 2)</td>
<td>1</td>
<td>1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Fluconazolec only (n = 12)</td>
<td>2</td>
<td>9</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Fluconazoled 4 d then voriconazole (n = 1)</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>73</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: 5-FC, 5-flucytosine; AMB, amphotericin B; CNS, central nervous system.

a Mutually exclusive categories.
b Fluconazole 400 mg daily in both cases.
c Fluconazole doses ranged from 200 to 1600 mg daily; mode, 400 mg daily (n = 8); 200 mg daily adjusted for creatinine clearance, n = 1; 800 mg daily, n = 2; 1600 mg daily, n = 1.
d Fluconazole 400 mg daily.

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ICP was associated with abnormal neurology at presentation and neurologic sequelae (4 patients had visual loss) and/or death at 12 months but not with concomitant/late hydrocephalus or serum CRAG titers of ≥256 (Table 5).

Elevated ICP was managed with daily/second daily lumbar punctures (LPs) in 13 patients, 6 of whom later received a CSF drain or shunt. Drains/shunts were inserted as primary ICP management in 11 patients (data unavailable for 7). Overall
lumbar or extraventricular drains were placed in 9 patients (median, 27 days; range, 4–36 days) for raised ICP and lumbar-peritoneal or ventriculo-peritoneal shunts in 13 (median, 42 days; range, 13–124 days), including 5 who had both procedures. Shunts were inserted in an additional 5 cases to treat concomitant hydrocephalus. The regimens and durations of induction and total antifungal therapy were similar in patients with/without raised ICP (Table 5). Eight patients received corticosteroids to treat raised ICP per se and 2, to reduce cryptococcoma-associated edema.

### Table 4. Patients Who Received Fluconazole Monotherapy in Central Nervous System Infection

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Immuno-compromise</th>
<th>Infection Site</th>
<th>Initial CSF CRAG ≥256</th>
<th>ICP Values (cm Water)</th>
<th>Duration Induction Therapy</th>
<th>Reinduction Therapy</th>
<th>Total Duration Therapy</th>
<th>12-mo Clinical Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>No</td>
<td>CSF</td>
<td>Yes</td>
<td>NA</td>
<td>4 wk</td>
<td>Yes (AMB, 5-FC)</td>
<td>17 mo</td>
<td>CR</td>
</tr>
<tr>
<td>16</td>
<td>No</td>
<td>CSF, lung</td>
<td>No</td>
<td>NA</td>
<td>8 wk</td>
<td>No</td>
<td>9 mo</td>
<td>PR</td>
</tr>
<tr>
<td>17*</td>
<td>Yes</td>
<td>Brain</td>
<td>NA</td>
<td>NA</td>
<td>4 wk</td>
<td>Yes (AMB, 5-FC)</td>
<td>&gt;14 mo</td>
<td>SD</td>
</tr>
<tr>
<td>18</td>
<td>No</td>
<td>CSF, brain</td>
<td>No</td>
<td>28</td>
<td>4 wk</td>
<td>Yes (AMB, 5-FC)</td>
<td>9 mo</td>
<td>PR</td>
</tr>
<tr>
<td>25</td>
<td>Yes</td>
<td>CSF, brain, lung</td>
<td>NA</td>
<td>NA</td>
<td>4 wk</td>
<td>Yes (AMB, 5-FC)</td>
<td>Not known</td>
<td>PR</td>
</tr>
<tr>
<td>28</td>
<td>No</td>
<td>Lung</td>
<td>NA</td>
<td>NA</td>
<td>16 wk</td>
<td>Yes (AMB, 5-FC)</td>
<td>24 mo</td>
<td>CR</td>
</tr>
<tr>
<td>34</td>
<td>No</td>
<td>Brain, lung</td>
<td>Yes</td>
<td>36</td>
<td>2 wk</td>
<td>Yes (AMB, 5-FC)</td>
<td>&gt;12 mo</td>
<td>PR</td>
</tr>
<tr>
<td>64</td>
<td>No</td>
<td>Brain, lung</td>
<td>No</td>
<td>4 wk</td>
<td>No</td>
<td>7 mo</td>
<td>PR</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>No</td>
<td>CSF, lung</td>
<td>Yes</td>
<td>NA</td>
<td>4 wk</td>
<td>Yes (AMB, 5-FC)</td>
<td>36 mo</td>
<td>PD</td>
</tr>
</tbody>
</table>

* Later developed immune reconstitution inflammatory syndrome–like syndrome.

### Table 5. Features of *Cryptococcus gattii* Infection in Patients With and Without Elevated Intracranial Pressure

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Raised ICP, No./Total No. (%)</th>
<th>Without Raised ICP, No./Total No. (%)</th>
<th>P Value (Fisher Exact or χ²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain disease</td>
<td>20/31 (65)</td>
<td>9/17 (53)</td>
<td>.63</td>
</tr>
<tr>
<td>Abnormal neurology, presentation</td>
<td>24/31 (77)</td>
<td>6/17 (35)</td>
<td>.02</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>10/31 (32)</td>
<td>6/17 (35%)</td>
<td>.91</td>
</tr>
<tr>
<td>Cryptococcoma, single or multiple</td>
<td>15/31 (48)</td>
<td>7/17 (41)</td>
<td>.86</td>
</tr>
<tr>
<td>Serum CRAG titer ≥512</td>
<td>17/28 (61)</td>
<td>10/15 (67)</td>
<td>.22</td>
</tr>
<tr>
<td>CSF CRAG titer ≥256</td>
<td>25/31 (77)</td>
<td>9/16 (63)</td>
<td>.09</td>
</tr>
<tr>
<td>Death at 12 mo</td>
<td>6/31 (19)</td>
<td>1/17 (6)</td>
<td>.39</td>
</tr>
<tr>
<td>Death/neurologic sequelae at 12 mo</td>
<td>16/31 (52)</td>
<td>2/17 (12)</td>
<td>.02</td>
</tr>
<tr>
<td>Duration induction antifungal therapy in weeks (median, LO–UQ)</td>
<td>6 (3–6)</td>
<td>6 (2–6)</td>
<td>.74</td>
</tr>
<tr>
<td>Total duration antifungal therapy in survivors (median, LO–UQ)</td>
<td>12 (6.5–17.5)</td>
<td>13.5 (9.2–20.5)</td>
<td>.51</td>
</tr>
</tbody>
</table>

Abbreviations: CRAG, cryptococcal antigen; CSF, cerebrospinal fluid; ICP, intracranial pressure; NA, not available; PD, progressive disease; PR, partial response; SD, stable disease.

Shunts were inserted in an additional 5 cases to treat concomitant hydrocephalus. The regimens and durations of induction and total antifungal therapy were similar in patients with/without raised ICP (Table 5). Eight patients received corticosteroids to treat raised ICP per se and 2, to reduce cryptococcoma-associated edema.

### Hydrocephalus

Obstructive hydrocephalus was identified by cerebral imaging in 22 (30%) patients with CNS cryptococcosis, 18 within 2 months, and 4 within 2–12 months after presentation. Brain cryptococcomas were present in 9 cases (5 had large single lesions and 3 had multiple lesions). Ten patients with early hydrocephalus also had raised ICP. Fourteen (64%) patients had CSF drains (n = 7) or shunts (n = 10) placed a median of 14 days (range, 3–504 days) after diagnosis with antifungal drugs being introduced at time of placement. Shunts remained in situ long-term and in most cases, indefinitely. Twenty patients received induction therapy with AMB with (n = 17) or without (n = 3) 5-FC. The remaining 2 failed fluconazole therapy and were reinduced with AMB and 5-FC. Thirteen patients were treated with corticosteroids, 5 for cryptococcoma-associated edema and 4 for concomitant raised ICP; in 4 the indication was uncertain. Three patients (13.6%) died.

### Other Surgery

Lung lobectomy was performed at presentation for suspected malignancy in 3 of 9 patients with CNS plus lung infection, and at 8 and 30 months in 2 patients to remove large lung lesions unresponsive to therapy. Resection of brain lesions (all cerebellar) was performed at diagnosis in 2 patients for suspected malignancy and at 12 months for therapeutic failure in a further 2; 1 of these was diagnosed with IRIS-like syndrome.
Immune Reconstitution Inflammatory Syndrome

Eight patients developed IRIS after 6 weeks to 12 months, while receiving azole eradication therapy; 2 were immunocompromised and 1 was pregnant (Table 6). New and/or enlarging brain lesions with surrounding edema were universally present and 4 patients developed new neurologic deficits, including blindness. One individual developed a concomitantly enlarging lung mass and new subcarinal lymphadenopathy. Risk factors for IRIS included female sex; brain involvement at presentation; concurrent brain, CSF, and lung disease; and higher median CD4 counts. CSF mononuclear leukocyte counts and protein and glucose concentrations at diagnosis of cryptococcosis were similar in patients with and without IRIS (Table 6).

Five patients were reinduced with AMB with/without 5-FC; 3 also received interferon gamma (IFN-γ) for presumed therapeutic failure, and in 5, corticosteroids were either commenced or doses were increased to reduce cerebral edema. Cerebral imaging abnormalities returned to pre-IRIS appearances within 4–6 months. No patient died but 4 had persistent neurologic sequelae at 12 months including the 3 who received IFN-γ.

DISCUSSION

This large study of therapy and long-term outcomes of CG cryptococcosis is unique and shows that despite antifungal and supportive therapy, CG-associated morbidity is substantial. To eradicate infection, longer antifungal treatment courses than those used in CN cryptococcosis [4] are required. Our data suggest that in both isolated lung and CNS cryptococcosis, induction therapy with AMB plus 5-FC leads to better outcomes than with fluconazole.

Lung Disease

Based primarily on case reports, IDSA guidelines recommend 4–6 weeks of induction therapy with AMB plus 5-FC for large/multiple CG cryptococcomas [4, 7, 12–14] although fluconazole has been effective in treatment of mild to moderate CG lung disease [13] and HIV-negative patients with CN lung infection [9, 15]. In our series, initial selection of AMB with or without 5-FC was likely driven by typical, radiologically extensive disease (80% patients), although not by specific radiologic abnormalities or host immunocompromise. Our data suggest that
2 weeks of induction therapy is sufficient in isolated lung disease. Fluconazole eradication therapy was continued, with a total treatment duration of 12 months, similar to that recommended for CN infection [4]. No patients relapsed, although 4 required >12 months’ therapy to achieve cure. Fluconazole induction therapy was given to 2 kidney transplant recipients to avoid AMB nephrotoxicity and consequent poor outcomes in such patients [16].

**CNS Disease**

The IDSA guidelines, informed by small series [2, 6, 7, 17], recommend induction, consolidation, and suppressive treatment for CNS disease due to CG [4]. A key finding of this study is that initial AMB plus 5-FC is essential in patients with CG: 80% of patients receiving AMB had a complete/partial clinical response at 12 months. Conversely, 78% of those receiving primary fluconazole failed therapy (although 1 had IRIS). Noting that the number of patients was small (n = 7), therapeutic failure was not correlated with fluconazole dose. Optimal duration of induction therapy for CG meningitis is uncertain; in our study, 6 weeks was used most commonly, consistent with recommendations for CN infection in immunocompetent hosts (4–6 weeks) [4, 18]. We have substituted the term “eradication therapy” for “consolidation/maintenance therapy” because fluconazole (typically 400 mg/day) was continued throughout the postinduction treatment period; “maintenance” therapy is not needed in the absence of ongoing immunosuppression and there were no late relapses (5–7 years) in this or a previous study [17]. A total of 6–12 months of therapy is recommended in CN patients [4], yet >70% of our patients received much longer courses (interquartile range, 14–22 months). Healthy hosts with CG infection have historically received longer courses of antifungals than immunosuppressed patients with CN disease [2]. The optimal duration of therapy is also uncertain. Details of antifungal therapy [6, 19, 20] are absent from previous reports, or therapy was not stratified by site of infection [7]. Although the 10 deaths occurred in AMB-treated patients, all were severely ill and 7 were immunocompromised; host immunocompromise is a risk factor for mortality [3]. We recommend a single treatment regimen in CNS infection due to CG, independent of host immune status.

Voriconazole or posaconazole were rarely used as induction or eradication therapy. In 2 patients, fluconazole caused alopecia and voriconazole was substituted with good outcomes. Fluconazole eradication therapy remains appropriate in Australia; notably, CG isolates with minimum inhibitory concentrations (MICs) of >8 μg/mL are rare (modal, range, and geometric mean MICs of 4, 0.75–8, and 2.98 μg/mL, respectively; Supplementary Table 1 and unpublished data). Surveillance of azole susceptibility is ongoing, given reports of some CG isolates with fluconazole MICs >8 μg/mL [14, 21, 22] and a reported association with genotypes not common in Australia, (eg, VGII and its subtypes) [21, 22], although the clinical significance of these elevated MICs is unknown.

Although AMB was the AMB formulation prescribed initially, 46.5% of patients were switched to L-AMB (4 mg/kg daily) due to AMB-induced nephrotoxicity. Lipid AMB formulations and AMB appear to be of equivalent efficacy in cryptococcal meningitis associated with HIV/AIDS and organ transplant [4]. Our data suggest that this is also true of CG cryptococcosis, although there are no comparative efficacy studies of AMB with lipid formulations in non-HIV, nontransplant populations.

Raised ICP was more common in patients presenting with abnormal neurologic features but, unlike in HIV/AIDS patients, not in those with CSF CRAG titers (≥256) [23]. CSF pressure control is a critical determinant of outcome [4]; in our study, raised ICP was associated with neurologic sequelae and/or death at 12 months, with 25% of such patients sustaining visual loss. Management of raised ICP in CG infection has not been investigated previously [6, 24, 25]. Raised ICP was controlled by daily/second daily LPs in only 45%, with the remainder requiring insertion of CSF drains/shunts, at a median of 4–6 weeks (range, 0.6–17 weeks). We cannot readily explain the apparent lag of 4–6 weeks prior to surgical correction of raised ICP, but recommend early neurosurgical review in all cases of raised ICP if frequent LPs fail to control CSF pressure after 1–2 weeks. Corticosteroids were used in 8 patients. However, this approach is reportedly of no benefit in HIV/AIDS patients and may increase mortality [4].

Hydrocephalus was frequent (30%) and can occur late. Shunt insertion was usually required and should be considered early. Shunts may be placed during active infection as long as effective antifungal therapy has been introduced [4] (this study). Resection of extensive pulmonary or cerebellar cryptococcomas was undertaken after 8–30 months in 4 patients with progressive disease; after resection, one was diagnosed with a cerebellar IRIS-like syndrome. The impact of early resection on duration of antifungal therapy is unknown.

That 9.4% of patients (5.9% immunocompetent) developed IRIS is noteworthy. IRIS has occasionally been described in CG infection including in association with pregnancy [26–28]; 1 of our patients presented postpartum. Risk factors included female sex, initial presentation with brain, or brain, meningeal, and lung involvement, and a higher median CD4 count; enlarging/new brain lesions were the predominant presenting feature. Interestingly, initial CSF leukocyte counts, protein and glucose, and high cryptococcal loads (positive India ink stain and CSF CRAG titers of ≥256) were similar in patients with and without IRIS, contrasting with IRIS in HIV-associated cryptococcal meningitis, where low initial CSF leukocyte counts and protein levels were risk factors [27]. In HIV/AIDS and organ transplant patients, IRIS correlates with recovery of immune function and...
reduction of immune suppression, respectively [4, 29]. It is proposed that in healthy hosts, cryptococcal capsular polysaccharide induces a Th2 anti-inflammatory cytokine response, which is then replaced by proinflammatory Th1 responses following response to antifungal therapy; in some cases the latter are sufficiently robust to cause IRIS [30].

Based on reported cases and the present study, IRIS develops 4 weeks to as long as 12 months after initiating antifungal drugs. Its recognition is important as it can be misdiagnosed as clinical failure; indeed, 5 of our 8 patients received unnecessary reinduction AMB and 5-FC. Furthermore, 3 also received IFN-γ, the use of which carries a theoretical risk of exacerbating IRIS due to its proinflammatory effect. Prognosis is good. Corticosteroids were used successfully to control symptoms and cryptococcoma-associated edema.

In summary, key points highlighted by this CG study are as follows: induction therapy with AMB plus 5-FC is indicated in patients with CNS disease; 6 weeks is standard. In lung disease, 2 weeks of induction AMB plus 5-FC is likely sufficient. Eradication therapy with fluconazole is appropriate to complete total therapy of 18 months in CNS disease and 12 months in lung infection, longer than that recommended for CN infection. Routine identification of Cryptococcus isolates should distinguish between CG and CN. Antifungal susceptibility is recommended in patients not responding to therapy, for tracking MICs and for correlating them with clinical outcomes. Surgical relief of CSF pressure is often needed in patients with persistently raised pressures.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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