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Clinical Practice Guidelines for the Management of Cryptococcal Disease: 2010 Update by the Infectious Diseases Society of America

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Cryptococcosis is a global invasive mycosis associated with significant morbidity and mortality. These guidelines for its management have been built on the previous Infectious Diseases Society of America guidelines from 2000 and include new sections. There is a discussion of the management of cryptococcal meningoencephalitis in 3 risk groups: (1) human immunodeficiency virus (HIV)–infected individuals, (2) organ transplant recipients, and (3) non–HIV-infected and nontransplant hosts. There are specific recommendations for other unique risk populations, such as children, pregnant women, persons in resource-limited environments, and those with *Cryptococcus gattii* infection. Recommendations for management also include other sites of infection, including strategies for pulmonary cryptococcosis. Emphasis has been placed on potential complications in management of cryptococcal infection, including increased intracranial pressure, immune reconstitution inflammatory syndrome (IRIS), drug resistance, and cryptococcomas. Three key management principles have been articulated: (1) induction therapy for meningoencephalitis using fungicidal regimens, such as a polyene and flucytosine, followed by suppressive regimens using fluconazole; (2) importance of early recognition and treatment of increased intracranial pressure and/or IRIS; and (3) the use of lipid formulations of amphotericin B regimens in patients with renal impairment. Cryptococcosis remains a challenging management issue, with little new drug development or recent definitive studies. However, if the diagnosis is made early, if clinicians adhere to the basic principles of these guidelines, and if the underlying disease is controlled, then cryptococcosis can be managed successfully in the vast majority of patients.

EXECUTIVE SUMMARY

In 2000, the Infectious Diseases Society of America (IDSA) first published "Practice Guidelines for the Management of Cryptococcal Disease" [1]. In this updated version of the guidelines, a group of medical mycology experts have approached cryptococcal management using the framework of key clinical questions. The goal is to merge recent and established evidence-based clinical data along with shared expert clinical opinions and insights to assist clinicians in the management of infection with this worldwide, highly recognizable invasive fungal pathogen. The foundation for the successful management of cryptococcal disease was

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

carefully detailed in the previous IDSA guidelines published in 2000. In fact, by following specific parts of these guidelines for management of cryptococcal meningoencephalitis, an improvement in outcome has been validated in retrospective studies [2, 3]. However, over the past decade a series of new clinical issues and host risk groups have arisen, and it is timely that these guidelines be revised to assist practicing clinicians in management of cryptococcosis.

Cryptococcus neoformans and *Cryptococcus gattii* have now been divided into separate species, although most clinical laboratories will not routinely identify cryptococcus to the species level [4]. *C. gattii* has recently been responsible for an ongoing outbreak of cryptococcosis in apparently immunocompetent humans and animals on Vancouver Island and surrounding areas within Canada and the northwest United States, and the management of *C. gattii* infection in immunocompetent hosts needs to be specifically addressed [5]. Similarly, the human immunodeficiency virus (HIV) pandemic continues, and cryptococcosis is a major opportunistic pathogen worldwide, but its management strongly depends on the medical resources available to clinicians in specific regions. In the era of highly active antiretroviral therapy (HAART), the management of cryptococcosis has become a blend of established antifungal regimens together with aggressive treatment of the underlying disease.

Although the widespread use of HAART has lowered the incidence of cryptococcosis in medically developed countries [6–9], the incidence and mortality of this infection are still extremely high in areas where uncontrolled HIV disease persists and limited access to HAART and/or health care occurs [10]. It is estimated that the global burden of HIV-associated cryptococcosis approximates 1 million cases annually worldwide [11]. In medically developed countries, the modest burden of patients with cryptococcal disease persists, largely consisting of patients with newly diagnosed HIV infection; a growing and heterogeneous group of patients receiving high-dose corticosteroids, monoclonal antibodies such as alemtuzumab and infliximab, and/or other immunosuppressive agents [12, 13]; and otherwise "normal" patients. It is sobering that, despite access to advanced medical care and the availability of HAART, the 3-month mortality rate during management of acute cryptococcal meningoencephalitis approximates 20% [14, 15]. Furthermore, without specific antifungal treatment for cryptococcal meningoencephalitis in certain HIV-infected populations, mortality rates of 100% have been reported within 2 weeks after clinical presentation to health care facilities [16]. It is apparent that insightful management of cryptococcal disease is critical to a successful outcome for those with disease caused by this organism.

Antifungal drug regimens for management of cryptococcosis are some of the best-characterized for invasive fungal diseases [17]. However, there remain poorly studied issues and confounders, many of which revolve around the host. For example, correcting and controlling host immunodeficiency and immune reconstitution, respectively, can become a complex clinical scenario during management of cryptococcal meningoencephalitis. Furthermore, specific complications, such as immune reconstitution inflammatory syndrome (IRIS), increased intracranial pressure, and cryptococcomas, may require special strategies for their successful management in cryptococcosis. Since the last IDSA guidelines in 2000, only the extended-spectrum azoles (posaconazole and voriconazole) and the echinocandins (anidulafungin, caspofungin, and micafungin) have become available as new antifungal drugs. The former have been studied clinically in salvage situations [18, 19], and the latter have no in vivo activity versus *Cryptococcus* species. Also, additional experience with lipid polyene formulations and drug combination studies have added to our direct anticryptococcal drug treatment insights [20, 21]. Pathobiologically, although recent studies from the cryptococcosis outbreak in Vancouver support the observation that a recombinant strain in nature became more virulent than its parent [22], there are few other clinical data to suggest that cryptococcal strains have become more virulent or drug resistant over the past decade. In fact, control of host immunity, the site of infection, antifungal drug toxicity, and underlying disease are still the most critical factors for successful management of cryptococcosis, and these will be emphasized in these new management guidelines.

TREATMENT STRATEGIES FOR PATIENTS WITH CRYPTOCOCCAL MENINGOENCEPHALITIS

The strength of the recommendations and the quality of evidence are described in Table 1.

HIV-Infected Individuals

Primary therapy: induction and consolidation

1. Amphotericin B (AmB) deoxycholate (AmBd; 0.7–1.0 mg/kg per day intravenously [IV]) plus flucytosine (100 mg/kg per day orally in 4 divided doses; IV formulations may be used in severe cases and in those without oral intake where the preparation is available) for at least 2 weeks, followed by fluconazole (400 mg [6 mg/kg] per day orally) for a minimum of 8 weeks (A-I). Lipid formulations of AmB (LFAmB), including liposomal AmB (3–4 mg/kg per day IV) and AmB lipid complex (ABLC; 5 mg/kg per day IV) for at least 2 weeks, could be substituted for AmBd among patients with or predisposed to renal dysfunction (B-II).

Primary therapy: alternative regimens for induction and consolidation (listed in order of highest recommendation top to bottom)

2. AmBd (0.7–1.0 mg/kg per day IV), liposomal AmB (3–4

Table 1. Strength of Recommendation and Quality of Evidence

Assessment	Type of evidence
Strength of recommendation	
Grade A	Good evidence to support a recommendation for or against use
Grade B	Moderate evidence to support a recommendation for or against use
Grade C	Poor evidence to support a recommendation
Quality of evidence	
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from the Canadian Task Force on the Periodic Health Examination Health Canada [23]. Reproduced with the permission of the Minister of Public Health Works and Government Services Canada, 2009.

mg/kg per day IV), or ABLC (5 mg/kg per day IV) for 4–6 weeks (A-II). Liposomal AmB has been given safely at 6 mg/kg per day IV in cryptococcal meningoencephalitis and could be considered in the event of treatment failure or high–fungal burden disease.

3. AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg per day orally) for 2 weeks, followed by fluconazole (800 mg per day orally) for a minimum of 8 weeks (B-I).

4. Fluconazole (≥800 mg per day orally; 1200 mg per day is favored) plus flucytosine (100 mg/kg per day orally) for 6 weeks (B-II).

5. Fluconazole (800–2000 mg per day orally) for 10–12 weeks; a dosage of ≥1200 mg per day is encouraged if fluconazole alone is used (B-II).

6. Itraconazole (200 mg twice per day orally) for 10–12 weeks (C-II), although use of this agent is discouraged.

Maintenance (suppressive) and prophylactic therapy

7. Fluconazole (200 mg per day orally) (A-I).

8. Itraconazole (200 mg twice per day orally; drug-level monitoring strongly advised) (C-I).

9. AmBd (1 mg/kg per week IV); this is less effective than azoles and is associated with IV catheter–related infections; use for azole-intolerant individuals (C-I).

10. Initiate HAART 2–10 weeks after commencement of initial antifungal treatment (B-III).

11. Consider discontinuing suppressive therapy during HAART in patients with a CD4 cell count >100 cells/μL and an undetectable or very low HIV RNA level sustained for ≥3 months (minimum of 12 months of antifungal therapy) (B-II); consider reinstitution of maintenance therapy if the CD4 cell count decreases to <100 cells/μL (B-III).

12. For asymptomatic antigenemia, perform lumbar puncture and blood culture; if results are positive, treat as symptomatic meningoencephalitis and/or disseminated disease. Without evidence of meningoencephalitis, treat with fluconazole (400 mg per day orally) until immune reconstitution (see above for maintenance therapy) (B-III).

13. Primary antifungal prophylaxis for cryptococcosis is not routinely recommended in HIV-infected patients in the United States and Europe, but areas with limited HAART availability, high levels of antiretroviral drug resistance, and a high burden of disease might consider it or a preemptive strategy with serum cryptococcal antigen testing for asymptomatic antigenemia (see above) (B-I).

Organ Transplant Recipients

14. For central nervous system (CNS) disease, liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day in 4 divided doses) for at least 2 weeks for the induction regimen, followed by fluconazole (400–800 mg [6–12 mg/kg] per day orally) for 8 weeks and by fluconazole (200–400 mg per day orally) for 6–12 months (B-II). If induction therapy does not include flucytosine, consider LFAmB for at least 4–6 weeks of induction therapy, and liposomal AmB (6 mg/kg per day) might be considered in high–fungal burden disease or relapse (B-III).

15. For mild-to-moderate non-CNS disease, fluconazole (400 mg [6 mg/kg] per day) for 6–12 months (B-III).

16. For moderately severe–to-severe non-CNS or disseminated disease (ie, >1 noncontiguous site) without CNS involvement, treat the same as CNS disease (B-III).

17. In the absence of any clinical evidence of extrapulmonary or disseminated cryptococcosis, severe pulmonary disease is treated the same as CNS disease (B-III). For mild-to-moderate

symptoms without diffuse pulmonary infiltrates, use fluconazole (400 mg [6 mg/kg] per day) for 6–12 months (B-III).

18. Fluconazole maintenance therapy should be continued for at least 6–12 months (B-III).

19. Immunosuppressive management should include sequential or step-wise reduction of immunosuppressants, with consideration of lowering the corticosteroid dose first (B-III).

20. Because of the risk of nephrotoxicity, AmBd should be used with caution in transplant recipients and is not recommended as first-line therapy in this patient population (C-III). If used, the tolerated dosage is uncertain, but 0.7 mg/kg per day is suggested with frequent renal function monitoring. In fact, this population will frequently have reduced renal function, and all antifungal dosages will need to be carefully monitored.

Non–HIV-Infected, Nontransplant Hosts

21. AmBd (0.7–1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 4 weeks for induction therapy. The 4-week induction therapy is reserved for persons with meningoencephalitis without neurological complications and cerebrospinal fluid (CSF) yeast culture results that are negative after 2 weeks of treatment. For AmBd toxicity issues, LFAmB may be substituted in the second 2 weeks. In patients with neurological complications, consider extending induction therapy for a total of 6 weeks, and LFAmB may be given for the last 4 weeks of the prolonged induction period. Then, start consolidation with fluconazole (400 mg per day) for 8 weeks (B-II).

22. If patient is AmBd intolerant, substitute liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV) (B-III).

23. If flucytosine is not given or treatment is interrupted, consider lengthening AmBd or LFAmB induction therapy for at least 2 weeks (B-III).

24. In patients at low risk for therapeutic failure (ie, they have an early diagnosis by history, no uncontrolled underlying disease or immunocompromised state, and excellent clinical response to initial 2-week antifungal combination course), consider induction therapy with combination of AmBd plus flucytosine for only 2 weeks, followed by consolidation with fluconazole (800 mg [12 mg/kg] per day orally) for 8 weeks (B-III).

25. After induction and consolidation therapy, use maintenance therapy with fluconazole (200 mg [3 mg/kg] per day orally) for 6–12 months (B-III).

Management of Complications in Patients with Cryptococcosis

Persistence

26. Check that adequate measures have been taken to improve immune status (eg, decrease immunosuppressants and introduce HAART) and optimize management of increased intracranial pressure (B-III).

27. Reinstitute induction phase of primary therapy for longer course (4–10 weeks) (B-III).

28. Consider increasing the dose if the initial dosage of induction therapy was $\leq$0.7 mg/kg IV of AmBd per day or $\leq$3 mg/kg of LFAmB per day (B-III), up to 1 mg/kg IV of AmBd per day or 6 mg/kg of liposomal AmB per day (B-III); in general, combination therapy is recommended (B-III).

29. If the patient is polyene intolerant, consider fluconazole ($\geq$800 mg per day orally) plus flucytosine (100 mg/kg per day orally in 4 divided doses) (B-III).

30. If patient is flucytosine intolerant, consider AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg [12 mg/kg] per day orally) (B-III).

31. Use of intrathecal or intraventricular AmBd is generally discouraged and is rarely necessary (C-III).

32. Ideally, persistent and relapse isolates should be checked for changes in the minimum inhibitory concentration (MIC) from the original isolate; a $\geq$3-dilution difference suggests development of direct drug resistance. Otherwise, an MIC of the persistent or relapse isolate $\geq$16 μg/mL for fluconazole or $\geq$32 μg/mL for flucytosine may be considered resistant, and alternative agents should be considered (B-III).

33. In azole-exposed patients, increasing the dose of the azole alone is unlikely to be successful and is not recommended (C-III).

34. Adjunctive immunological therapy with recombinant interferon (IFN)-γ at a dosage of 100 μg/m^2 for adults who weigh $\geq$50 kg (for those who weigh <50 kg, consider 50 μg/m^2) 3 times per week for 10 weeks can be considered for refractory infection, with the concomitant use of a specific antifungal drug (B-III).

Relapse

35. Restart induction phase therapy (see "Persistence," above) (B-III).

36. Determine susceptibility of the relapse isolate (see "Persistence," above) (B-III).

37. After induction therapy and in vitro susceptibility testing, consider salvage consolidation therapy with either fluconazole (800–1200 mg per day orally), voriconazole (200–400 mg twice per day orally), or posaconazole (200 mg orally 4 times per day or 400 mg twice per day orally) for 10–12 weeks (B-III); if there are compliance issues and a susceptible isolate, prior suppressive doses of fluconazole may be reinstituted (B-III).

Elevated CSF pressure

38. Identify CSF pressure at baseline. A prompt baseline

lumbar puncture is strongly encouraged, but in the presence of focal neurologic signs or impaired mentation, it should be delayed pending the results of a computed tomography (CT) or magnetic resonance imaging (MRI) scan (B-II).

39. If the CSF pressure is ⩾25 cm of CSF and there are symptoms of increased intracranial pressure during induction therapy, relieve by CSF drainage (by lumbar puncture, reduce the opening pressure by 50% if it is extremely high or to a normal pressure of ⩽20 cm of CSF) (B-II).

40. If there is persistent pressure elevation ⩾25 cm of CSF and symptoms, repeat lumbar puncture daily until the CSF pressure and symptoms have been stabilized for >2 days and consider temporary percutaneous lumbar drains or ventriculostomy for persons who require repeated daily lumbar punctures (B-III).

41. Permanent ventriculoperitoneal (VP) shunts should be placed only if the patient is receiving or has received appropriate antifungal therapy and if more conservative measures to control increased intracranial pressure have failed. If the patient is receiving an appropriate antifungal regimen, VP shunts can be placed during active infection and without complete sterilization of CNS, if clinically necessary (B-III).

Other medications for intracranial pressure

42. Mannitol has no proven benefit and is not routinely recommended (A-III).

43. Acetazolamide and corticosteroids (unless part of IRIS treatment) should be avoided to control increased intracranial pressure (A-II).

Recurrence of signs and symptoms

44. For recurrence of signs and symptoms, reinstitute drainage procedures (B-II).

45. For patients with recurrence, measurement of opening pressure with lumbar puncture after a 2-week course of treatment may be useful in evaluation of persistent or new CNS symptoms (B-III).

Long-term elevated intracranial pressure

46. If the CSF pressure remains elevated and if symptoms persist for an extended period of time in spite of frequent lumbar drainage, consider insertion of a VP shunt (A-II).

IRIS

47. No need to alter direct antifungal therapy (B-III).

48. No definitive specific treatment recommendation for minor IRIS manifestations is necessary, because they will resolve spontaneously in days to weeks (B-III).

49. For major complications, such as CNS inflammation with increased intracranial pressure, consider corticosteroids (0.5–1.0 mg/kg per day of prednisone equivalent) and possibly dexamethasone at higher doses for severe CNS signs and symptoms. Length and dose of the corticosteroid taper are empirically chosen and require careful following of the patient, but a 2–6-week course is a reasonable starting point. The course should be given with a concomitant antifungal regimen (B-III).

50. Nonsteroidal anti-inflammatory drugs and thalidomide have been used but with too little experience to make a recommendation (C-III).

Cerebral cyptococcomas

51. Induction therapy with AmBd (0.7–1 mg/kg per day IV), liposomal AmB (3–4 mg/kg per day IV), or ABLC (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 6 weeks (B-III).

52. Consolidation and maintenance therapy with fluconazole (400–800 mg per day orally) for 6–18 months (B-III).

53. Adjunctive therapies include the following:

A. Corticosteroids for mass effect and surrounding edema (B-III).

B. Surgery: for large (⩾3-cm lesion), accessible lesions with mass effect, consider open or stereotactic-guided debulkment and/or removal; also, enlarging lesions not explained by IRIS should be submitted for further tissue diagnosis (B-II).

Treatment Strategies for Patients with Nonmeningeal Cryptococcosis

Pulmonary (immunosuppressed)

54. In immunosuppressed patients with pulmonary cryptococcosis, meningitis should be ruled out by lumbar puncture; the presence of CNS disease alters the dose and duration of induction therapy and the need for intracranial pressure monitoring (B-II).

55. Pneumonia associated with CNS or documented dissemination and/or severe pneumonia (acute respiratory distress syndrome [ARDS]) is treated like CNS disease (B-III).

56. Corticosteroid treatment may be considered if ARDS is present in the context of IRIS (B-III).

57. For mild-to-moderate symptoms, absence of diffuse pulmonary infiltrates, absence of severe immunosuppression, and negative results of a diagnostic evaluation for dissemination, use fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months (B-III).

58. In HIV-infected patients who are receiving HAART with a CD4 cell count >100 cells/μL and a cryptococcal antigen titer that is ⩽1:512 and/or not increasing, consider stopping maintenance fluconazole after 1 year of treatment (B-II).

59. Surgery should be considered for either diagnosis or persistent radiographic abnormalities and symptoms not responding to antifungal therapy (B-III).

Pulmonary (nonimmunosuppressed)

60. For mild-to-moderate symptoms, administer fluconazole (400 mg per day orally) for 6–12 months; persistently positive serum cryptococcal antigen titers are not criteria for continuance of therapy (B-II).

61. For severe disease, treat similarly to CNS disease (B-III).

62. Itraconazole (200 mg twice per day orally), voriconazole (200 mg twice per day orally), and posaconazole (400 mg twice per day orally) are acceptable alternatives if fluconazole is unavailable or contraindicated (B-II).

63. Surgery should be considered for either diagnosis or persistent radiographic abnormalities and symptoms not responding to antifungal therapy (B-III).

64. In nonimmunocompromised patients with pulmonary cryptococcosis, consider a lumbar puncture to rule out asymptomatic CNS involvement. However, for normal hosts with asymptomatic pulmonary nodule or infiltrate, no CNS symptoms, and negative or very low serum cryptococcal antigen, a lumbar puncture can be avoided (B-II).

65. ARDS in the context of an inflammatory syndrome response may require corticosteroid treatment (B-III).

Nonmeningeal, nonpulmonary cryptococcosis

66. For cryptococcemia or dissemination (involvement of at least 2 noncontiguous sites or evidence of high fungal burden based on cryptococcal antigen titer $\geqslant$1:512), treat as CNS disease (B-III).

67. If CNS disease is ruled out, fungemia is not present, infection occurs at single site, and there are no immunosuppressive risk factors, consider fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months (B-III).

Treatment in Special Clinical Situations (Pregnant Women, Children, Persons in a Resource-Limited Environment, and *C. gattii*–Infected Persons)

Pregnant women with cryptococcosis

68. For disseminated and CNS disease, use AmBd or LFAmB, with or without flucytosine (B-II). Flucytosine is a category C drug for pregnancy, and therefore, its use must be considered in relationship to benefit versus risk.

69. Start fluconazole (pregnancy category C) after delivery; avoid fluconazole exposure during the first trimester; and during the last 2 trimesters, judge the use of fluconazole with the need for continuous antifungal drug exposure during pregnancy (B-III).

70. For limited and stable pulmonary cryptococcosis, perform close follow-up and administer fluconazole after delivery (B-III).

71. Watch for IRIS in the postpartum period (B-III).

Children with cryptococcosis

72. Induction and consolidation therapy for CNS and disseminated disease is AmBd (1 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for 2 weeks (for the non–HIV-infected, non-transplant population, follow the treatment length schedule for adults), followed by fluconazole (10–12 mg/kg per day orally) for 8 weeks; for AmB-intolerant patients, either liposomal AmB (5 mg/kg per day) or ABLC (5 mg/kg per day) (A-II).

73. Maintenance therapy is fluconazole (6 mg/kg per day orally) (A-II).

74. Discontinuation of maintenance therapy in children receiving HAART is poorly studied and must be individualized (C-III).

75. For cryptococcal pneumonia, use fluconazole (6–12 mg/kg per day orally) for 6–12 months (B-II).

Cryptococcosis in a resource-limited health care environment

76. For CNS and/or disseminated disease where flucytosine is not available, induction therapy is AmBd (1 mg/kg per day IV) for 2 weeks or AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg per day orally) for 2 weeks, followed by consolidation therapy with fluconazole (800 mg per day orally) for 8 weeks (A-I).

77. Maintenance therapy is fluconazole (200–400 mg per day orally) until immune reconstitution (A-I).

78. With CNS and/or disseminated disease where polyene is not available, induction therapy is fluconazole ($\geqslant$800 mg per day orally; 1200 mg per day is favored) for at least 10 weeks or until CSF culture results are negative, followed by maintenance therapy with fluconazole (200–400 mg per day orally) (B-II).

79. With CNS and/or disseminated disease when polyene is not available but flucytosine is available, induction therapy is fluconazole ($\geqslant$800 mg per day orally; 1200 mg per day is favored) plus flucytosine (100 mg/kg per day orally) for 2–10 weeks, followed by maintenance therapy with fluconazole (200–400 mg per day orally) (B-II).

80. With use of primary fluconazole therapy for induction, both primary or secondary drug resistance of the isolate may be an issue, and MIC testing is advised (B-III).

81. For azole-resistant strains, administer AmBd (1 mg/kg per day IV) until CSF, blood, and/or other sites are sterile (B-III).

***C. gattii* infection**

82. For CNS and disseminated disease due to *C. gattii,* induction, consolidation, and suppressive treatment are the same as for *C. neoformans* (A-II).

83. More diagnostic focus by radiology and follow-up examinations are needed for cryptococcomas/hydrocephalus due

to *C. gattii* than that due to *C. neoformans,* but the management principles are the same (B-II).

84. Pulmonary cryptococcosis (same as *C. neoformans*): single, small cryptococcoma suggests fluconazole (400 mg per day orally); for very large and multiple cryptococcomas, consider a combination of AmBd and flucytosine therapy for 4–6 weeks, followed by fluconazole for 6–18 months, depending on whether surgery was performed (B-III).

85. Consider surgery if there is compression of vital structures, failure to reduce size of cryptococcoma after 4 weeks of therapy, or failure to thrive (B-III).

86. Recombinant IFN-γ use remains uncertain (C-III).

INTRODUCTION

These recommendations represent an excellent starting point for the development of a management strategy for cryptococcal disease and are organized under 4 major headings: "Treatment of Meningoencephalitis," "Complications during Treatment," "Treatment of Nonmeningeal Cryptococcosis," and "Cryptococcosis in Special Clinical Situations." In "Treatment of Cryptococcal Meningoencephalitis," the recommendations are divided into 3 specific risk groups: (1) HIV-infected individuals, (2) transplant recipients, and (3) non–HIV-infected and nontransplant hosts. For the section on complications and their management in cryptococcosis, 4 areas were examined: (1) persistence and relapse, (2) elevated intracranial pressure, (3) IRIS, and (4) mass lesions (cryptococcomas). For further recommendations regarding non-CNS infections, sites were separated into pulmonary (immunosuppressed vs nonimmunosuppressed host) and extrapulmonary sites. Finally, for management of cryptococcosis in 4 special clinical situations, recommendations were made for (1) pregnant women, (2) children, (3) resource-limited environments, and (4) *C. gattii* infections.

PRACTICE GUIDELINES

"Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances" [24]. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation [24].

UPDATE METHODOLOGY

Panel composition. The IDSA Standards and Practice Guidelines Committee (SPGC) convened experts in the management of patients with cryptococcal disease.

Literature review and analysis. For the 2010 update, the Expert Panel completed the review and analysis of data published since 1999. Computerized literature searches of the PubMed database were performed. The searches of the English-language literature from 1999 through 2009 used the terms, "cryptococcal," "cryptococcosis," "*Cryptococcus,*" "meningeal," "pulmonary," "pregnancy," "children," "cerebrospinal fluid," "intracranial," "cerebral," "immunosuppressed," "HIV," "transplant," and "Immune Reconstitution Inflammatory Syndrome" and focused on human studies. Data published up to December 2009 were considered during final preparation of the manuscript. Relevant studies included randomized clinical trials, open-label clinical trials, retrospective case series, cohort studies, case reports, reports of in vitro studies, and animal model experiments. Abstracts from international meetings were also included. Because of the limited nature of the data in many areas, the Expert Panel made a decision to also retain high-quality reviews or background papers. Expert Panel members were assigned sections of the guideline and reviewed the relevant literature.

Limitations in the literature. Review of the literature revealed a paucity of clinical trials evaluating the newer agents for treatment of cryptococcal disease. Most data came from cohort studies; case series; small, nonrandomized clinical trials; or case reports.

Process overview. In evaluating the evidence regarding the management of cryptococcal disease, the Expert Panel followed a process used in the development of other IDSA guidelines. This included a systematic weighting of the quality of the evidence and the grade of recommendation (Table 1) [23].

Consensus development based on evidence. The Expert Panel met on 3 occasions via teleconference and once in person to complete the work of the guideline. The purpose of the teleconferences was to discuss the questions to be addressed, make writing assignments, and discuss recommendations. All members of the Expert Panel participated in the preparation and review of the draft guideline. Feedback from external peer reviews was obtained. The guidelines were reviewed and approved by the SPGC and the Board of Directors prior to dissemination.

Guidelines and conflicts of interest. All members of the Expert Panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided the IDSA's conflict of interest disclosure statement and were asked to identify ties to companies developing products that might be affected by promulgation of the guideline. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Expert Panel made decisions on a case-by-case basis as to whether an individual's role should be limited as a result of a

conflict. Potential conflicts are listed in the Acknowledgements section.

Revision dates. At annual intervals, the Expert Panel Chair, the SPGC liaison advisor, and the Chair of the SPGC will determine the need for revisions to the guideline on the basis of an examination of current literature. If necessary, the entire Expert Panel will be reconvened to discuss potential changes, and when appropriate, the Expert Panel will recommend revision of the guideline to the SPGC and the IDSA Board for review and approval.

GUIDELINE RECOMMENDATIONS FOR THE MANAGEMENT OF CRYPTOCOCCAL DISEASE

The guideline recommendations for cryptococcal meningoencephalitis management are summarized in Tables 2–5.

I. WHAT ARE THE MOST APPROPRIATE TREATMENT STRATEGIES IN THE PATIENT WITH CRYPTOCOCCAL MENINGOENCEPHALITIS?

HIV-Infected Individuals

The treatment of cryptococcal meningoencephalitis in patients with HIV coinfection has received substantial attention over the past 2 decades. Its principles are based on a high burden of yeasts at the site of infection and a severely depressed immune system (ie, profound CD4 lymphocytopenia). With the recent advances of HAART, immune enhancement during treatment of cryptococcosis can occur. These therapeutic advances may be followed by both positive consequences (goal of complete yeast elimination from host and limited therapy) and negative consequences (IRIS). Furthermore, the treatment of meningoencephalitis in HIV-infected individuals formalized the concept of induction, consolidation (clearance), and maintenance (suppression) phases in management of invasive mycoses in a severely immunosuppressed host.

Primary therapy: induction and consolidation

1. AmBd (0.7–1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses; IV formulations may be used in severe cases and in those without oral intake where the preparation is available) for at least 2 weeks, followed by fluconazole (400 mg [6 mg/kg] per day orally) for a minimum of 8 weeks (A-I). LFAmB, including liposomal AmB (3–4 mg/kg per day IV) and ABLC (5 mg/kg per day IV) for at least 2 weeks, could be substituted for AmBd among patients with or predisposed to renal dysfunction (B-II).

Table 2. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Human Immunodeficiency Virus–Infected Individuals

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)[a]	2 weeks	A-I
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)[a]	2 weeks	B-II
AmBd (0.7–1.0 mg/kg per day) or liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients)	4–6 weeks	B-II
Alternatives for induction therapy[b]		
AmBd plus fluconazole	…	B-I
Fluconazole plus flucytosine	…	B-II
Fluconazole	…	B-II
Itraconazole	…	C-II
Consolidation therapy: fluconazole (400 mg per day)	8 weeks	A-I
Maintenance therapy: fluconazole (200 mg per day)[a]	⩾1 year[c]	A-I
Alternatives for maintenance therapy[b]		
Itraconazole (400 mg per day)[d]	⩾1 year[c]	C-I
AmBd (1 mg/kg per week)[d]	⩾1 year[c]	C-I

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate; HAART, highly active antiretroviral therapy.

[a] Begin HAART 2–10 weeks after the start of initial antifungal treatment.

[b] In unique clinical situations in which primary recommendations are not available, consideration of alternative regimens may be made—but not encouraged—as substitutes. See text for dosages.

[c] With successful introduction of HAART, a CD4 cell count ⩾100 cells/μL, and low or nondetectable viral load for ⩾3 months with minimum of 1 year of antifungal therapy.

[d] Inferior to the primary recommendation.

Table 3. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Transplant Recipients

Regimen	Duration	Evidence
Induction therapy:[a] liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) plus flucytosine (100 mg/kg per day)	2 weeks	B-III
Alternatives for induction therapy		
Liposomal AmB (6 mg/kg per day) or ABLC (5 mg/kg per day)	4–6 weeks	B-III
AmBd (0.7 mg/kg per day)[b]	4–6 weeks	B-III
Consolidation therapy: fluconazole (400–800 mg per day)	8 weeks	B-III
Maintenance therapy: fluconazole (200–400 mg per day)	6 months to 1 year	B-III

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate.

[a] Immunosuppressive management may require sequential or step-wise reductions.

[b] Many transplant recipients have been successfully treated with AmBd; however, issues of renal dysfunction with calcineurin inhibitors are important and the effective dose is imprecise.

Primary therapy: alternative regimens for induction and consolidation (listed in order of highest recommendation top to bottom)

2. AmBd (0.7–1.0 mg/kg per day IV), liposomal AmB (3–4 mg/kg per day IV), or ABLC (5 mg/kg per day IV) for 4–6 weeks (A-II). Liposomal AmB has been given safely at 6 mg/kg per day IV in cryptococcal meningoencephalitis and could be considered in the event of treatment failure or high–fungal burden disease.

3. AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg per day orally) for 2 weeks, followed by fluconazole (800 mg per day orally) for a minimum of 8 weeks (B-I).

4. Fluconazole (≥800 mg per day orally; 1200 mg per day is favored) plus flucytosine (100 mg/kg per day orally) for 6 weeks (B-II).

5. Fluconazole (800–2000 mg per day orally) for 10–12 weeks; a dosage of ≥1200 mg per day is encouraged if fluconazole alone is used (B-II).

6. Itraconazole (200 mg twice per day orally) for 10–12 weeks (C-II), although use of this agent is discouraged.

Evidence summary. Cryptococcal disease in HIV-infected patients always warrants therapy. Current recommendations for drug(s) of choice are essentially the same as in the previous IDSA Guidelines. Ideally, antifungal therapy should rapidly and consistently sterilize the CNS and other infected sites, and the principle of rapid fungicidal activity should be the primary focus of any induction strategy [25]. A CSF culture at 2 weeks that is sterile after the start of therapy should provide an appreciation of a successful fungicidal induction regimen and has been linked to favorable outcome [27]. For example, a large clinical trial compared AmBd (0.4–0.5 mg/kg per day) with fluconazole (200 mg per day) for the treatment of AIDS-associated cryptococcal meningoencephalitis [26], demonstrated disappointing clinical outcomes (success rates of 40% of 63 AmBd recipients and 34% of 131 fluconazole recipients), and emphasized the need for a more effective primary therapy for AIDS-associated cryptococcal meningoencephalitis. This study also demonstrated higher early mortality and reduced ability to rapidly convert CSF culture results to negative with fluconazole alone.

In a subsequent trial for the treatment of AIDS-associated cryptococcal meningoencephalitis, a higher dosage of AmBd (0.7 mg/kg per day) was used, along with a lower dosage of flucytosine (100 mg/kg per day) [27] than earlier antifungal combination studies involving HIV-uninfected patients [28, 29]. After 2 weeks of therapy, CSF culture results were negative 9% more often in patients receiving AmBd plus flucytosine than in patients treated with AmBd alone ($P = .06$). The impact of the combination on mycological outcome was further demonstrated in the multivariate analysis. Three hundred six patients were then eligible for the consolidation phase of this study: 151 patients received fluconazole, and 155 received itraconazole. After 8 weeks of consolidation therapy, CSF culture results were negative in 72% of the patients receiving fluconazole and in 60% of the patients receiving itraconazole. This treatment trial defined our preferred regimen of AmBd and flucytosine followed by fluconazole, as noted in the previous IDSA guidelines, and likely reflects differences in the pharmacokinetics, bioavailability, and drug interactions between the 2 azoles.

Additional supportive evidence for the efficacy of AmBd plus flucytosine for induction therapy is provided by a uniquely designed randomized trial that evaluated 4 different antifungal therapies. Sixty-four patients with AIDS in Thailand with a first episode of cryptococcal meningoencephalitis were randomized to receive primary therapy with AmBd (0.7 mg/kg per day), AmBd (0.7 mg/kg per day) plus flucytosine (100 mg/kg per day), AmBd (0.7 mg/kg per day) plus fluconazole (400 mg per day), or a triple-drug regimen consisting of AmBd, flucytosine, and fluconazole at the dosages above [21]. The primary end

Table 4. Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in Non–Human Immunodeficiency Virus–Infected and Nontransplant Patients

Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)	⩾4 weeks[a,b]	B-II
AmBd (0.7–1.0 mg/kg per day)[c]	⩾6 weeks[a,b]	B-II
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day) combined with flucytosine, if possible[d]	⩾4 weeks[a,b]	B-III
AmBd (0.7 mg/kg per day) plus flucytosine (100 mg/kg per day)[e]	2 weeks	B-II
Consolidation therapy: fluconazole (400–800 mg per day)[f]	8 weeks	B-III
Maintenance therapy: fluconazole (200 mg per day)[b]	6–12 months	B-III

NOTE. ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmBd, amphotericin B deoxycholate.

[a] Four weeks are reserved for patients with meningitis who have no neurological complications, who have no significant underlying diseases or immunosuppression, and for whom the cerebrospinal fluid culture performed at the end of 2 weeks of treatment does not yield viable yeasts; during the second 2 weeks, lipid formulations of AmB may be substituted for AmBd.

[b] Fluconazole is given at 200 mg per day to prevent relapse after induction therapy, and consolidation therapy is recommended.

[c] For flucytosine-intolerant patients.

[d] For AmBd-intolerant patients.

[e] For patients who have a low risk of therapeutic failure. Low risk is defined as an early diagnosis by history, no uncontrolled underlying condition or severe immunocompromised state, and an excellent clinical response to initial 2-week antifungal combination course.

[f] A higher dosage of fluconazole (800 mg per day) is recommended if the 2-week induction regimen was used and if there is normal renal function.

point of this study was the rate of reduction in CSF cryptococcal colony-forming units (CFUs) from serial quantitative CSF cultures obtained on days 3, 7, and 14 of treatment. AmBd plus flucytosine was the most rapidly fungicidal regimen. Clearance of cryptococci from the CSF was exponential and significantly faster with AmBd and flucytosine than with AmBd alone, AmBd plus fluconazole, and triple-drug therapy. Logistic regression modeling in this study showed that both cerebral dysfunction and high counts of *C. neoformans* per milliliter of CSF at baseline were independently associated with early death. Finally, results from a recent cohort study with 208 HIV-positive and HIV-negative patients with meningoencephalitis clearly emphasized the success of therapy with AmBd plus flucytosine for 14 days over any other induction regimen in persons with high–fungal burden disease and abnormal neurological features, showing a 26% failure rate in the combination group versus a 56% failure rate for other treatments ($P < .001$). Less than 14 days of flucytosine treatment was also independently associated with treatment failure at 3 months in 168 cases of cryptococcosis [3]. The use of different dosages of AmBd (0.7 vs 1.0 mg/kg per day) plus flucytosine has recently been compared, and the higher dosage was more fungicidal and had manageable toxicity, although no difference in 2- and 10-week mortality was observed [30].

This primary induction/consolidation therapeutic regimen for cryptococcal meningoencephalitis may need to be adjusted for individual patients. For example, continuation of combination induction therapy beyond 2 weeks may be considered if (1) a patient remains comatose; (2) the patient is clinically deteriorating; (3) the patient has not improved, with persisting elevated, symptomatic intracranial pressure; and/or (4) the results of CSF culture obtained after 2 weeks of induction therapy is anticipated to remain positive. These patients may require additional weeks (eg, 1–6 weeks) of the induction phase of treatment. If the CSF culture after 2 weeks of treatment is reported to be positive after discontinuation of the induction regimen, reinstitution of at least another 2-week combination induction course might be considered, depending on the clinical assessment of the patient. In cases in which fluconazole cannot be given as consolidation therapy because of patient intolerance or drug toxicity, itraconazole is an acceptable, albeit less effective, azole alternative and requires careful serum drug level monitoring. LFAmB may be substituted for AmBd, especially if there is concern regarding nephrotoxicity [31–34]. There are still scant reports of LFAmB in combination with flucytosine for treatment of cryptococcal meningoencephalitis, but clinical experience strongly suggests that combination therapy with LFAmB is effective. The optimal dosage of LFAmB remains uncertain. In a comparative study of 100 patients treated with liposomal AmB versus AmBd, the 2-week mycological success of liposomal AmB dosages between 3 mg/kg per day (64%) and 6 mg/kg per day (54%) was similar. The clinical response was 75% (3 mg/kg per day) and 66% (6 mg/kg per day) and showed no difference; at 10 weeks, there was no significant difference in outcome with the 2 dosages [34]. In smaller studies, liposomal AmB at 4 mg/kg per day was more fungicidal than AmBd at 0.7 mg/kg per day [7, 20].

Other primary treatment regimens for AIDS-associated cryptococcal meningoencephalitis have been used but are considered to be suboptimal alternatives to the induction/consolidation regimen described above. Combination therapy with fluconazole and flucytosine has been shown to be moderately effective as primary therapy [35, 36], and use of flucytosine improves induction therapy with fluconazole at dosages of 800–

Table 5. Antifungal Treatment Recommendations for Nonmeningeal Cryptococcosis

Patient group	Initial antifungal regimen	Duration	Evidence
Immunosuppressed patients and immunocompetent patients with mild-to-moderate pulmonary cryptococcosis	Fluconazole (400 mg per day)	6–12 months	B-III
Immunosuppressed patients[a] and immunocompetent patients with severe pulmonary cryptococcosis	Same as CNS disease	12 months	B-III
Patients with nonmeningeal, nonpulmonary cryptococcosis			
Patients with cryptococcemia	Same as CNS disease	12 months	B-III
Patients for whom CNS disease has been ruled out with no fungemia, with a single site of infection, and with no immunosuppressive risk factors	Fluconazole 400 mg per day	6–12 months	B-III

NOTE. CNS, central nervous system.

[a] Should directly rule out CNS disease with lumbar puncture.

2000 mg per day [37]. In a very recent study of 143 randomized patients, the combination use of AmBd (0.7 mg/kg per day) plus fluconazole (800 mg per day) demonstrated satisfactory outcomes, compared with AmBd alone, and may be a reasonable approach to therapy in settings where flucytosine is not available or contraindicated [38]. In this phase II study, the 14-day end point of success in the AmBd alone, AmBd plus fluconazole (400 mg [6 mg/kg] per day), and AmBd plus fluconazole (800 mg [12 mg/kg] per day) treatment arms was 41%, 27%, and 54%, respectively. If this combination is used, the higher fluconazole dosage is recommended. Primary therapy with either fluconazole or itraconazole alone administered for 10–12 weeks has also been evaluated in several trials, with variable responses [26, 39–43]. Results of large-scale experiences with fluconazole in Africa have been very disappointing, and fluconazole monotherapy is not recommended as primary therapy if polyene therapy is available, not contraindicated, and can be monitored. If fluconazole is used alone, then higher daily doses should be administered. Notably, low success rates at 800 mg per day have been substantially improved with dosages of 1200–2000 mg per day [37]. When using higher daily doses of fluconazole, divided doses are recommended to minimize gastrointestinal toxicity, and it should be emphasized that the possible fluconazole toxicity with these very high doses will need to be carefully monitored. Experiences with itraconazole, a triazole, which produces minimal concentrations of active drug in the CSF, as primary therapy for AIDS-associated cryptococcal meningoencephalitis have been very limited and demonstrated only moderate success [42, 43]. Generally, the panel recommends itraconazole only if other regimens have failed or are not available. If used, the suspension preparation should be preferred over the capsule formulation because of absorption issues, and drug levels must be monitored to ensure bioavailability.

Routine in vitro susceptibility testing of *C. neoformans* isolates during initiation of therapy is not recommended for 2 principal reasons: (1) primary resistance to first-line antifungal drugs is not currently a significant clinical problem, and (2) in vitro susceptibility testing (including methods and breakpoints) for *Cryptococcus* species against azoles and AmB is not well validated. For example, primary in vitro resistance to flucytosine is low for *C. neoformans* [44], and flucytosine resistance does not abrogate synergy or produce antagonism of the combination with specific in vivo methods [45, 46]. Furthermore, in vitro susceptibility testing has not yet been shown to predict early treatment outcome [47]. However, there are reports of reduced efficacy when fluconazole MICs are $\geqslant$16 μg/mL [48, 49]. Secondary resistance to fluconazole is an emerging problem in some areas of the world—especially Africa, where prophylactic fluconazole is prescribed widely and where the drug is often used alone as primary therapy for cryptococcosis. In a small, unvalidated retrospective analysis of 27 patients with HIV-associated cryptococcal meningoencephalitis who received fluconazole as initial therapy, 32 episodes of relapse were documented [50]. Seventy-six percent of the culture-positive relapse episodes were associated with isolates that had reduced susceptibility to fluconazole (MIC, $\geqslant$64 μg/mL), raising concerns about the efficacy of fluconazole alone as initial therapy for this disease, particularly in those with prior azole exposure. Generally, in vitro susceptibility testing should be reserved for patients for whom primary therapy has failed, for those who experience relapse after apparently successful primary therapy, and for those who develop cryptococcosis and had recent exposure to an antifungal drug (eg, a patient receiving long-term prophylactic fluconazole therapy for oral/esophageal candidiasis). Ideally, original *C. neoformans* and *C. gattii* isolates should be stored so that relapse isolates can be compared with previous isolate(s) for in vitro drug susceptibility. When possible, relapse isolate(s) from an area where resistance has been documented should undergo in vitro susceptibility testing.

Flucytosine treatment recipients should be carefully monitored for serious toxicities, such as cytopenia, with frequent complete blood cell counts. Serum flucytosine levels should be measured after 3–5 days of therapy, with a target 2-h postdose

level of 30–80 μg/mL; flucytosine levels >100 μg/mL should be avoided. In areas where flucytosine serum level measurements are unavailable or untimely, careful attention to hematologic parameters (white blood cell and platelet counts) and dose adjustments of flucytosine according to creatinine clearance are critical (eg, 50% of standard dose for creatinine clearance of 20–40 mL/min, 25% of standard dose for creatinine clearance of 10–20 mL/min); see specific adjustment schedules for severe renal dysfunction and dialysis [51].

Maintenance (suppressive) and prophylactic therapy. Maintenance therapy should be initiated after completion of primary therapy with an induction and consolidation regimen. Ideally, this is begun when CSF yeast culture results are negative and continued until there is evidence of persistent immune reconstitution with successful HAART.

Maintenance (suppressive) and prophylactic therapy

7. Fluconazole (200 mg per day orally) (A-I).
8. Itraconazole (200 mg twice per day orally; drug-level monitoring strongly advised) (C-I).
9. AmBd (1 mg/kg per week IV); this is less effective than azoles and is associated with IV catheter–related infections; use for azole-intolerant individuals (C-I).
10. Initiate HAART 2–10 weeks after commencement of initial antifungal treatment (B-III).
11. Consider discontinuing suppressive therapy during HAART in patients with a CD4 cell count >100 cells/μL and an undetectable or very low HIV RNA level sustained for ⩾3 months (minimum of 12 months of antifungal therapy) (B-II); consider reinstitution of maintenance therapy if the CD4 cell count decreases to <100 cells/μL (B-III).
12. For asymptomatic antigenemia, perform lumbar puncture and blood culture; if results are positive, treat as symptomatic meningoencephalitis and/or disseminated disease. Without evidence of meningoencephalitis, treat with fluconazole (400 mg per day orally) until immune reconstitution (see above for maintenance therapy) (B-III).
13. Primary antifungal prophylaxis for cryptococcosis is not routinely recommended in HIV-infected patients in the United States and Europe, but areas with limited HAART availability, high levels of antiretroviral drug resistance, and a high burden of disease might consider it or a preemptive strategy with serum cryptococcal antigen testing for asymptomatic antigenemia (see above) (B-I).

Evidence summary. Early in the history of the AIDS pandemic, primary therapy for cryptococcal meningoencephalitis was associated with high relapse rates in patients who did not receive long-term maintenance therapy. In 1991, in a placebo-controlled double-blind trial, Bozzette et al [52] demonstrated the effectiveness of fluconazole (no relapses) compared with placebo (15% relapses) as maintenance therapy for patients with cryptococcal meningoencephalitis who had received successful primary therapy with AmBd, with or without flucytosine.

Recommendations for initial maintenance therapy have not changed since they were initially published. Three options exist for antifungal maintenance therapy of AIDS-associated cryptococcal meningoencephalitis: (1) oral fluconazole (200 mg per day), (2) oral itraconazole (200 mg twice per day orally), or (3) AmBd (1 mg/kg per week IV). Two large, prospective, randomized, comparative trials showed that fluconazole is the most effective maintenance therapy [53]. The first trial demonstrated the superiority of fluconazole (200 mg per day) over AmBd (1.0 mg/kg per week) [53]. Relapses of symptomatic cryptococcal disease were observed in 18% and 2% of AmBd and fluconazole recipients, respectively ($P < .001$). In addition, patients receiving AmBd had more frequent adverse events and associated bacterial infections, including bacteremia. A second trial compared fluconazole (200 mg per day) with itraconazole (200 mg per day) for 12 months as maintenance therapy for cryptococcal disease. This trial, which proved fluconazole to be superior, was terminated prematurely after interim analysis revealed that 23% of itraconazole-treated patients had a relapse, compared with only 4% of the fluconazole-treated patients. In addition, this trial demonstrated that the risk of relapse was increased if the patient had not received flucytosine during the initial 2 weeks of primary therapy for cryptococcal meningoencephalitis [54]. Results of these 2 trials established fluconazole as the drug of choice for maintenance therapy of AIDS-associated cryptococcal disease. These studies provide clinical experience with AmBd and itraconazole as alternative, albeit less effective, choices for maintenance therapy. Their toxicities and effectiveness must be balanced against the potential rapid immune reconstitution of HAART impact on relapse rates without maintenance therapies and close monitoring. Intermittent AmBd should be reserved for patients who have had multiple relapses following azole therapy or who are intolerant of azoles. Oral itraconazole may be used if the patient is intolerant of fluconazole [42]. Limited experience suggests that a higher dosage of itraconazole (eg, 200 mg twice per day orally) may be more effective than 200 mg per day as maintenance therapy, and drug interactions must be considered.

The precision of when to start HAART in the treatment of coinfection with cryptococci and HIV to avoid IRIS remains uncertain. In our recommendations, there is a wide range of 2–10 weeks to accommodate this uncertainty. Recent studies suggest earlier initiation of HAART within 2 weeks may be possible without triggering an unacceptable increase in the frequency or severity of IRIS, but there was still a limited number of cryptococcosis cases, making it difficult to assess the impact of timing on outcome in cryptococcal infection [55, 56]. However, in some clinical settings, long delays in HAART can place

patients at risk of dying of other complications of HIV infection. It is also important to anticipate complications of drug interactions with HAART and antifungal drugs.

Until recently, life-long maintenance therapy to prevent disease relapse was recommended for all patients with AIDS after successful completion of primary induction therapy for cryptococcal meningoencephalitis. Specifically, risk factors for cryptococcal relapse in HIV-infected patients during the HAART era were found to be a CD4 cell count <100 cells/μL, receipt of antifungal therapy for <3 months during the previous 6 months, and serum cryptococcal antigen titer $\geq$1:512 [15]. However, several recent studies indicate that the risk of relapse is low provided patients have successfully completed primary therapy, are free of symptoms and signs of active cryptococcosis, and have been receiving HAART with a sustained CD4 cell count >100 cells/μL and an undetectable viral load. Several recent studies have examined the stopping of maintenance therapy and support our recommendations [57–61]. Results of the 2 largest studies are summarized. A prospective, multicenter trial conducted among 42 patients with AIDS in Thailand randomized subjects to continue or discontinue maintenance fluconazole therapy when the CD4 cell count had increased to >100 cells/μL and an undetectable HIV RNA level had been sustained for 3 months [58]. There were no episodes of relapse of cryptococcal meningitis in either group at a median of 48 weeks of observation after randomization. A second retrospective multicenter study was conducted among 100 patients with AIDS living in 6 different countries [57]. Inclusion criteria were a proven diagnosis of cryptococcal meningoencephalitis, a CD4 cell count of >100 cells/μL while receiving HAART, and the subsequent discontinuation of maintenance antifungal therapy. Primary end points or events were a confirmed diagnosis of relapse (recurrent cryptococcal meningoencephalitis), any other evidence of active cryptococcal disease, or death. No events occurred during a median period of 26.1 months when patients were receiving both HAART and maintenance therapy for cryptococcal meningitis (0% incidence per 100 person-years). After discontinuation of maintenance therapy, 4 relapses occurred (incidence, 1.53 cases per 100 person-years) during a median period of observation of 28.4 months. All relapses were among patients whose antifungal maintenance therapy was discontinued after they had a CD4 cell count of >100 cells/μL for $\geq$6 months, and 1 patient had a relapse with a positive culture result, which is consistent with our definition for relapse. It does illustrate that careful follow-up of these patients after termination of maintenance therapy is necessary. Collectively, results of these and other studies indicate that maintenance therapy for cryptococcal meningitis may be safely discontinued in most patients responding to HAART with a CD4 cell count >100 cells/μL, an undetectable or low HIV RNA level sustained for $\geq$3 months, and at least 1 year of antifungal drug exposure, with close patient follow-up and serial cryptococcal serum antigen tests. Reinstitution of fluconazole maintenance therapy should be considered if the CD4 cell count decreases to <100 cells/μL and/or the serum cryptococcal antigen titer increases [55].

Asymptomatic antigenemia is a well-documented clinical condition in advanced HIV disease; it has been noted to appear in 4%–12% of HIV-infected patients per year in certain populations [62–66]. Antigenemia preceded symptoms of meningitis by a median of 22 days in 1 study in Uganda [16], and if not detected, it makes appearance of disease unlikely over the next year. Cryptococcal antigenemia has been shown to be associated with increased mortality among those initiating HAART, and persons with asymptomatic antigenemia are at theoretical risk of the "unmasking" form of cryptococcal IRIS [67]. The precision of asymptomatic antigenemia management remains uncertain, but an aggressive diagnostic and preemptive therapeutic stance is warranted in high-incidence locales. Despite the possibility that a false-positive antigen test result has occurred with a negative diagnostic work-up, this high-risk group probably benefits from preemptive therapy.

Although fluconazole and itraconazole have been shown to reduce frequency of primary cryptococcal disease among those who have CD4 cell counts <50 cells/μL [68, 69], primary prophylaxis for crytococcosis is not routinely recommended in this group with advanced medical care. This recommendation is based on the relative infrequency of cryptococcal disease, lack of survival benefits, possibility of drug-drug interactions, creation of direct antifungal drug resistance, medication compliance, and costs. However, in areas in which the availability of HAART is limited, HIV-drug resistance is high, and the incidence of cryptococcal disease is very high, prophylaxis or preemptive strategies with the use of serum cryptococcal antigen might be considered [70].

Organ Transplant Recipients

Cryptococcosis has been documented in an average of 2.8% of solid-organ transplant recipients [71, 72]. The median time to disease onset is 21 months after transplantation; 68.5% of the cases occur > 1 year after transplantation. Approximately 25%–54% of organ transplant recipients with cryptococcosis have pulmonary infection, and in 6%–33%, the disease is limited to the lungs only [73, 74]. CNS involvement and disseminated infections (involvement of $\geq$2 sites) have been documented in 52%–61% of patients [71, 74]. Approximately 25% of the transplant recipients with *C. neoformans* disease have fungemia [71, 73].

Recommendations

14. For CNS disease, liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day in 4 divided doses) for at least 2 weeks for the

induction regimen, followed by fluconazole (400–800 mg [6–12 mg/kg] per day orally) for 8 weeks and by fluconazole (200–400 mg per day orally) for 6–12 months (B-II). If induction therapy does not include flucytosine, consider LFAmB for at least 4–6 weeks of induction therapy, and liposomal AmB (6 mg/kg per day) might be considered in high–fungal burden disease or relapse (B-III).

15. For mild-to-moderate non-CNS disease, fluconazole (400 mg [6 mg/kg] per day) for 6–12 months (B-III).

16. For moderately severe–to-severe non-CNS or disseminated disease (ie, >1 noncontiguous site) without CNS involvement, treat the same as CNS disease (B-III).

17. In the absence of any clinical evidence of extrapulmonary or disseminated cryptococcosis, severe pulmonary disease is treated the same as CNS disease (B-III). For mild-to-moderate symptoms without diffuse pulmonary infiltrates, use fluconazole (400 mg [6 mg/kg] per day) for 6–12 months (B-III).

18. Fluconazole maintenance therapy should be continued for at least 6–12 months (B-III).

19. Immunosuppressive management should include sequential or step-wise reduction of immunosuppressants, with consideration of lowering the corticosteroid dose first (B-III).

20. Because of the risk of nephrotoxicity, AmBd should be used with caution in transplant recipients and is not recommended as first-line therapy in this patient population (C-III). If used, the tolerated dosage is uncertain, but 0.7 mg/kg per day is suggested with frequent renal function monitoring. In fact, this population will frequently have reduced renal function, and all antifungal dosages will need to be carefully monitored.

Evidence summary. Given the risk of nephrotoxicity associated with concurrent use of AmBd and calcineurin inhibitors and the fact that ~25% of the transplant recipients with cryptococcosis have renal dysfunction (creatinine level, >2.0 mg/dL) at the time of diagnosis, LFAmB is preferable as induction therapy for CNS and severe non-CNS disease. Induction therapy should include flucytosine (100 mg/kg per day in 4 divided doses, adjusted for renal function). In patients with a positive CSF culture result at baseline, an additional lumbar puncture is recommended at 2 weeks, but lumbar puncture may be repeated earlier for increased intracranial pressure management or concern about potential microbiological failure. In a small prospective study of CNS cryptococcosis in transplant recipients, the median time to CSF sterilization was 10 days (mean, 16 days) [75]. A positive CSF culture result after 2 weeks of induction treatment identified a poor outcome in transplant recipients and supports a prolonged induction period with LFAmB in these patients [76]. CSF cryptococcal antigen titer in transplant recipients correlated neither with CSF sterilization at 2 weeks nor with outcome at 180 days [75]. Although initial CSF antigen titers did correlate with sterilization of CSF in HIV-infected individuals [27], serial evaluations of CSF or serum cryptococcal antigen titers were not precisely helpful in the acute management of either transplant recipients or HIV-infected patients [77].

Suggested therapy for the consolidation phase of treatment is fluconazole (400–800 mg [6–12 mg/kg] per day) for 8 weeks, adjusted for renal function, followed by fluconazole (200–400 mg [3–6 mg/kg] per day) for 6–12 months as maintenance therapy. A very low relapse rate has been documented with such an approach. A prospective study of 79 solid-organ transplant recipients who survived at least 3 weeks and in whom maintenance therapy was employed for a median of 183 days had a risk of relapse of 1.3% [75]. In contrast, the same group reported high rates of relapse in transplant recipients who did not receive maintenance therapy. Relapse was documented a median of 3.5 months after initial diagnosis and in all cases within 1 year after cessation of antifungal therapy [75]. This study also evaluated the risk of relapse in all previously reported cases of solid-organ transplant recipients with cryptococcosis ($n = 59$) in whom maintenance therapy was noted and who had been observed for a median of 12 months [75]. The antifungal agent used as primary therapy in 11 patients who experienced relapse included AmB preparations in 7 patients, fluconazole in 3 patients (with flucytosine in 1), and flucytosine alone in 1 patient [75]. The median duration of primary therapy was 8 weeks (range, 3–10 weeks). On the basis of these data, it can be concluded that most relapses occur within 6 months in patients who do not receive maintenance therapy, and continuation of maintenance antifungal therapy in solid-organ transplant recipients for at least 6 and up to 12 months is rational.

Although *C. neoformans* may be isolated from sputum samples of asymptomatic individuals [78], its identification in respiratory tract specimens in a transplant recipient should be considered as representing a pathogen and warrants an investigation for invasive pulmonary disease. A positive serum cryptococcal antigen titer has been documented in 33%–90% of transplant recipients with pulmonary cryptococcosis [78]. In a prospective study comprising 60 solid-organ transplant recipients with pulmonary cryptococcosis, 84% of those with any pulmonary involvement and 73% of those in whom the disease was limited only to the lungs had a positive serum cryptococcal antigen result [79]. However, a negative cryptococcal antigen result does not exclude the diagnosis of disseminated cryptococcosis. By comparison, patients with CNS disease (97%) or disseminated cryptococcosis (95%) were more likely to have a positive serum cryptococcal antigen result [73], and therefore, a positive serum cryptococcal antigen test in a transplant recipient warrants investigation for disseminated disease such as meningoencephalitis.

Stable patients, presenting with cavitary or nodular lung le-

sions and in whom the infection is limited to the lungs may be treated with fluconazole at a dose of 400 mg orally per day for the duration of induction and consolidation phases. For example, in a small prospective observational study, mortality in solid-organ transplant recipients with extraneural cryptococcosis who received an AmB-containing regimen (2 [11%] of 18) did not differ from those who received fluconazole (2 [10%] of 21). In a retrospective review of 19 solid-organ transplant recipients with cryptococcosis, 14 received fluconazole as primary therapy for a median of 60 days, and no therapeutic failures were documented in those with extraneural disease [9]. Successful outcome was also documented in 4 of 4 solid-organ transplant recipients who received fluconazole for treatment of pulmonary cryptococcosis and had no evidence of extrapulmonary disease. Patients with skin, soft-tissue, and osteoarticular infection without evidence of dissemination have also been treated successfully with fluconazole [75, 80]. Pulmonary cryptococcosis in transplant recipients occasionally presents with acute respiratory failure [81]. Patients who have extensive involvement on imaging studies and require mechanical ventilation have mortality rates exceeding 50% [81]. These patients and those with severe or progressive pulmonary infection should be treated in the same fashion as those with CNS cryptococcosis.

In the current era of organ transplantation, immunosuppressive regimens in a vast majority of the transplant recipients with cryptococcosis include a calcineurin inhibitor (eg, tacrolimus, cyclosporine, or sirolimus), and drug-drug interactions must be considered. Additionally, 80%–90% of these patients are receiving corticosteroids at the time of onset of cryptococcal disease [71]. Although a reduction in immunosuppressive therapy should be considered in transplant recipients with cryptococcosis, it has been proposed that abrupt withdrawal or reversal of immunosuppression could potentially lead to a shift towards a Th1 proinflammatory state. Although helpful in killing the yeast in tissue, it may pose a risk of IRIS [82] or organ rejection.

Transplant recipients who develop IRIS are more likely to have received a potent immunosuppressive regimen than those who do not develop IRIS. Renal transplant recipients with cryptococcosis may experience allograft loss temporally related to the onset of IRIS through TH1 up-regulation [82]. The overall probability of allograft survival after *C. neoformans* infection is significantly lower in patients who develop IRIS than in those who do not. In therapy-naive HIV-infected patients with opportunistic infection, deferring the start of antiretroviral therapy for 2–10 weeks until the infection seems to be microbiologically controlled has been proposed for several opportunists including cryptococcus (see recommendation 10). A similar rationale can also be applied to the management of immunosuppression in transplant recipients with these infections. Thus, careful adjustment of the reduction in posttransplantation immunosuppression by spacing the reduction of immunosuppressants over time and/or providing a step-wise elimination of immunosuppressants following initiation of antifungal therapy is a prudent approach to the management of transplant recipients with cryptococcosis [83]. In the careful reduction in immunosuppressives during management of severe cryptococcosis, it may be helpful to reduce the corticosteroids before the calcineurin inhibitors, because these inhibitors have direct anticryptococcal activity [70, 81].

Despite existing evidence suggesting that most cryptococcal disease in transplant recipients likely results from reactivation of a subclinical infection [84], because of the lack of precision in defining subclinical infection and in predicting subsequent disease, routine primary prophylaxis for cryptococcosis in transplant recipients is not recommended at present.

Non–HIV Infected, Nontransplant Hosts

In general, non-transplant patients with disseminated cryptococcosis have been screened with an HIV test and CD4 cell count determination. Recommendations for "presumably immunocompetent hosts" are limited, because the majority of patients in the 2 landmark studies of cryptococcal meningoencephalitis prior to the HIV epidemic were significantly immunosuppressed (eg, they had received steroids or had connective tissue diseases or cancer) [28, 29]. However, it is clear that those with apparently much less severe or variable host immune defects, compared with HIV infection or transplantation, can still present serious therapeutic challenges [85], and yet patients with idiopathic CD4 lymphocytopenia can frequently be managed successfully [86].

Recommendations

21. AmBd (0.7–1.0 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 4 weeks for induction therapy. The 4-week induction therapy is reserved for persons with meningoencephalitis without neurological complications and CSF yeast culture results that are negative after 2 weeks of treatment. For AmBd toxicity issues, LFAmB may be substituted in the second 2 weeks. In patients with neurological complications, consider extending induction therapy for a total of 6 weeks, and LFAmB may be given for the last 4 weeks of the prolonged induction period. Then, start consolidation with fluconazole (400 mg per day) for 8 weeks (B-II).

22. If patient is AmBd intolerant, substitute liposomal AmB (3–4 mg/kg per day IV) or ABLC (5 mg/kg per day IV) (B-III).

23. If flucytosine is not given or treatment is interrupted, consider lengthening AmBd or LFAmB induction therapy for at least 2 weeks (B-III).

24. In patients at low risk for therapeutic failure (ie, they

have an early diagnosis by history, no uncontrolled underlying disease or immunocompromised state, and excellent clinical response to initial 2-week antifungal combination course), consider induction therapy with combination of AmBd plus flucytosine for only 2 weeks, followed by consolidation with fluconazole (800 mg [12 mg/kg] per day orally) for 8 weeks (B-III).

25. After induction and consolidation therapy, use maintenance therapy with fluconazole (200 mg [3 mg/kg] per day orally) for 6–12 months (B-III).

Evidence summary. A comparative study convincingly showed that a combination of AmBd and flucytosine using low doses of the polyene and high doses of flucytosine is better than low doses of AmBd alone for non–HIV-infected patients with cryptococcal meningoencephalitis [28], and that 6 weeks of low-dose polyene and flucytosine are better than 4 weeks of therapy [29], but even in these combination studies mortality rate was ~24%. These studies were performed in the era preceding the availability of azole agents and LFAmB and predate the use of higher doses of AmBd with the concept of induction, consolidation, and maintenance therapy. To date, the information about these newer strategies for cryptococcal meningoencephalitis in non–HIV-infected and non-transplant patients remain limited, retrospective, and extrapolative. It is important to note that this is a very heterogeneous population ranging from hosts who are apparently normal to those with hematological malignancies and severe liver disease. Therefore, it is impossible to tailor a regimen that fits all patients. In fact, among the opinion leaders writing this document there remains no consensus regarding the length of induction therapy in this group, with some favoring the 2-week induction regimen, as for HIV-infected patients and transplant recipients (recommendation 24), and others supporting a 4–6-week induction therapy (recommendation 21).

Clinical experience with AmBd therapy is much more extensive than at the time of the Bennett and Dismukes trials [28, 29]. AmBd dosages of 0.7 mg/kg per day with adjunctive saline infusions are generally well tolerated for 2 weeks [21, 27, 87], and toxicity issues with prolonged use can be averted in some cases by substituting LFAmB for AmBd in the second 2–4 weeks of induction therapy. Furthermore, flucytosine dosages of 100 mg/kg per day are better tolerated than dosages of 150 mg/kg per day, thus leading to these modified recommendations [27, 35].

Alternative therapy to AmBd is liposomal AmB (3–4 mg/kg per day) in patients with initial or developing renal dysfunction or who are receiving other nephrotoxic agents. There are few reports of LFAmB treatment in non–HIV-infected and non-transplant patients, but in HIV-infected patients with primary cryptococcal meningoencephalitis, liposomal AmB (4 mg/kg per day) resulted in a significantly earlier CSF sterilization than did AmBd at 0.7 mg/kg per day. It was less toxic and had equivalent clinical efficacy [7, 20]. ABLC at 5 mg/kg per day has been successfully used for cryptococcal meningoencephalitis in salvage regimens and can also be considered in patients with AmBd nephrotoxicity [32]. This experience in severely immunosuppressed patients gives confidence for its success in this patient population.

Although there have been anecdotal reports or case series of fluconazole as primary therapy for cryptococcal meningoencephalitis in non–HIV-infected patients, these studies are nonrandomized and noncontrolled [88, 89]. Given the continuing high morbidity and mortality of cryptococcal meningoencephalitis in non–HIV-infected patients associated with suboptimal treatment regimens and the poor results of fluconazole alone for cryptococcal meningoencephalitis in HIV-infected patients, there is insufficient evidence to recommend fluconazole alone or combined with flucytosine as primary induction therapy for non–HIV-infected, nontransplant patients. A polyene should be part of an induction regimen for cryptococcal meningoencephalitis in this patient population.

The rate of relapse of cryptococcal meningoencephalitis in the non–HIV-infected patient ranged from 15% to 25% [29] prior to the AIDS epidemic and use of fluconazole. Relapses occurred primarily in the first year after initial treatment. Therefore, fluconazole is now recommended by the majority of experts as maintenance therapy in non–HIV-infected patients with cryptococcal meningoencephalitis during the first 6 months to 1 year after initial diagnosis and administration of primary induction therapy.

II. HOW ARE COMPLICATIONS MANAGED IN PATIENTS WITH CRYPTOCOCCOSIS?

Definition of Persistent or Relapsed Infection

The definition of persistent infection is somewhat arbitrary, but on a practical basis, persistently positive results of cultures of CSF after 4 weeks of proven antifungal therapy at an established effective dose is a reasonable starting point. Relapse of infection has 2 important features. First, the recovery of viable cryptococci from a previously checked sterile body site is essential; and second, recrudescence of signs and symptoms at the previous site of disease supports presence of disease. In a relapsed infection, both of these features have normalized and then recurred.

It is important to define persistence and relapse, because changing antigen titers, presence of positive India ink examination results, and abnormal cellular reactions or chemistries are insufficient to diagnose a microbiological relapse with an implied need to alter direct antifungal treatment strategies. Most cases of relapse are attributable to inadequate primary therapy (dose and/or duration) or failure of compliance with consolidation or maintenance of fluconazole dose.

Persistence

Recommendations

26. Check that adequate measures have been taken to improve immune status (eg, decrease immunosuppressants and introduce HAART) and optimize management of increased intracranial pressure (B-III).

27. Reinstitute induction phase of primary therapy for longer course (4–10 weeks) (B-III).

28. Consider increasing the dose if the initial dosage of induction therapy was ≤0.7 mg/kg IV of AmBd per day or ≤3 mg/kg of LFAmB per day (B-III), up to 1 mg/kg IV of AmBd per day or 6 mg/kg of liposomal AmB per day (B-III); in general, combination therapy is recommended (B-III).

29. If the patient is polyene intolerant, consider fluconazole (≥800 mg per day orally) plus flucytosine (100 mg/kg per day orally in 4 divided doses) (B-III).

30. If patient is flucytosine intolerant, consider AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg [12 mg/kg] per day orally) (B-III).

31. Use of intrathecal or intraventricular AmBd is generally discouraged and is rarely necessary (C-III).

32. Ideally, persistent and relapse isolates should be checked for changes in the MIC from the original isolate; a ≥3-dilution difference suggests development of direct drug resistance. Otherwise, an MIC of the persistent or relapse isolate ≥16 μg/mL for fluconazole or ≥32 μg/mL for flucytosine may be considered resistant, and alternative agents should be considered (B-III).

33. In azole-exposed patients, increasing the dose of the azole alone is unlikely to be successful and is not recommended (C-III).

34. Adjunctive immunological therapy with recombinant IFN-γ at a dosage of 100 $\mu g/m^2$ for adults who weigh ≥50 kg (for those who weigh <50 kg, consider 50 $\mu g/m^2$) 3 times per week for 10 weeks can be considered for refractory infection, with the concomitant use of a specific antifungal drug (B-III).

Relapse

Recommendations

35. Restart induction phase therapy (see "Persistence," above) (B-III).

36. Determine susceptibility of the relapse isolate (see "Persistence," above) (B-III).

37. After induction therapy and in vitro susceptibility testing, consider salvage consolidation therapy with either fluconazole (800–1200 mg per day orally), voriconazole (200–400 mg twice per day orally), or posaconazole (200 mg orally 4 times per day or 400 mg twice per day orally) for 10–12 weeks (B-III); if there are compliance issues and a susceptible isolate, prior suppressive doses of fluconazole may be reinstituted (B-III).

Evidence summary. Because no significant comparative trials/studies have been conducted to evaluate "salvage therapy" for patients for whom primary therapy fails or who experience relapse after successful primary therapy, our recommendations are based solely on clinical experience/personal preference and several small, open trial studies with refractory disease. For example, the use of IFN-γ treatment was tested during primary therapy and not salvage therapy, and even in this clinical setting, its positive impact on outcome was not definitive [42, 90]. There are no data regarding the newer azoles (voriconazole and posaconazole) as primary treatment of cryptococcal meningoencephalitis in HIV-infected or non–HIV-infected individuals. However, these azoles have been used as salvage therapy for HIV-infected individuals in open trials. For instance, small, open-label salvage trials suggest that voriconazole (200 mg twice per day orally) and posaconazole (400 mg twice per day orally) have therapeutic efficacy. Among patients with refractory cryptococcosis, voriconazole demonstrated success in 7 (39%) of 18 patients overall and led to stable disease in 10 (89%) of 11 patients. Among patients treated with posaconazole, 14 (48%) of 29 experienced success, and 6 (40%) of 15 had stable disease [18, 19]. In any relapse case, it is essential to determine whether compliance or drug interactions are an issue. If so, these will need to be addressed in the therapeutic strategy after reinduction therapy.

It is important to emphasize that CSF culture should represent at least 3–5 mL of fluid, and positive CSF India ink or Gram stain by itself is not sufficient for determining relapse. CSF and serum pronase-treated cryptococcal antigen titers are not precise indicators for relapse or for making therapeutic decisions except possibly for late relapses in HIV-infected patients taken off suppressive therapy. Finally, the 2-week lumbar puncture culture result is a test for determining fungicidal success of induction therapy. Generally, laboratories will keep fungal cultures for 3–4 weeks for detection of yeast growth, and most persistently positive cryptococcal cultures on therapy will grow within 2 weeks. In all non–HIV-infected and in most HIV-infected patients receiving combination antifungal therapy with AmBd plus flucytosine, negative cultures at 2 weeks of therapy should be a goal. Patients who do not reach this goal will need follow-up lumbar punctures until the CSF is sterile and will need more attention given to prolonging their induction therapy.

Elevated CSF Pressure

One of the most critical determinants of outcome for cryptococcal meningoencephalitis is control of CSF pressure. Approximately one-half of HIV-infected patients with cryptococcal meningoencephalitis have elevated baseline intracranial pressures (ie, >25 cm of CSF). This elevated CSF pressure level is generally linked to a high burden of yeast in the CSF [91].

This increased CSF pressure can be associated with increased morbidity and mortality, especially early in the treatment course, but its level in an individual patient is less precise. Also, development of classic hydrocephalus later during treatment and follow-up can occur.

If cryptococcal meningoencephalitis is suspected, opening pressure during the initial lumbar puncture should be measured. The presence of impaired mentation or focal neurologic signs may prompt radiographic imaging before the lumbar puncture, but most of these study findings are normal or show no focal lesions in cryptococcal disease, and the lumbar puncture can be safely performed. Acute elevated symptomatic CSF pressure with initial antifungal therapy should be managed aggressively by decompression, either via repeated lumbar punctures, temporary lumbar drainage catheter, or ventriculostomy in selected patients. There are much less data on treatment of HIV-negative patients with acute elevated intracranial pressure with regard to recommendations of pressure control, compared with HIV-positive patients.

Recommendations

38. Identify CSF pressure at baseline. A prompt baseline lumbar puncture is strongly encouraged, but in the presence of focal neurologic signs or impaired mentation, it should be delayed pending the results of a CT or MRI scan (B-II).

39. If the CSF pressure is ⩾25 cm of CSF and there are symptoms of increased intracranial pressure during induction therapy, relieve by CSF drainage (by lumbar puncture, reduce the opening pressure by 50% if it is extremely high or to a normal pressure of ⩽20 cm of CSF) (B-II).

40. If there is persistent pressure elevation ⩾25 cm of CSF and symptoms, repeat lumbar puncture daily until the CSF pressure and symptoms have been stabilized for >2 days and consider temporary percutaneous lumbar drains or ventriculostomy for persons who require repeated daily lumbar punctures (B-III).

41. Permanent VP shunts should be placed only if the patient is receiving or has received appropriate antifungal therapy and if more conservative measures to control increased intracranial pressure have failed. If the patient is receiving an appropriate antifungal regimen, VP shunts can be placed during active infection and without complete sterilization of CNS, if clinically necessary (B-III).

Evidence summary. The recommendations above are similar to those made in the 2000 IDSA guidelines [1]. Since then, the strength of these guidelines has been supported by reports of adverse consequences when they are not followed [2, 92].

Role of imaging. The most immediate determinant of outcome of cryptococcal meningoencephalitis is control of symptomatic increased intracranial pressure. This complication of increased intracranial pressure must be reduced without causing cerebral herniation. Patients without HIV disease may be at increased risk of cryptococcal cerebral mass lesions and more robust inflammatory responses in meninges, with the consequences of cerebral vasculitis and potential cerebral herniation. Cranial neuropathy, other focal neurologic signs, papilledema, and impaired mentation reflect this risk and should prompt CT or MRI to determine the risk of complications associated with lumbar puncture. MRI is more effective than CT in identifying CNS cryptococcal lesions in HIV-infected patients and can reflect the burden of yeasts at the start of therapy [93]. If there is evidence of obstruction that needs decompression, drainage may be done safely via ventriculostomy or VP shunt [94]. Patients with HIV disease generally do not have classic hydrocephalus or cryptococcal mass lesions on presentation, and radiographic images commonly show no abnormality or cerebral atrophy without obstruction or other pathology [95].

Reduction of CSF pressure. The National Institute of Allergy and Infectious Disease Mycoses Study Group published a large series of HIV-infected patients managed under specific treatment protocols for cryptococcal meningoencephalitis [95]. Of 221 patients receiving baseline CSF pressure recordings, one-half had recordings >25 cm of CSF and one-fourth had recordings >35 cm of CSF. This upper quartile had increased evidence of papilledema (29%) and impaired mentation (18%). Furthermore, patients who died (11 of 12) in the first 2 weeks of therapy had baseline intracranial pressures measured at ⩾25 cm of CSF. Of 161 patients treated by CSF lumbar drainage to reduce the pressure, there were fewer cases of clinical failure in those with controlled CSF pressure, compared with those who have persistently elevated pressure. CSF drainage was often immediately followed by relief of severe headaches and improved sense of well being. Recurrence of elevated intracranial pressure was often associated with worsening symptoms. In cases of very high pressure (>35 cm of CSF), some have suggested CSF pressure drainage to 35 cm of water initially with lumbar puncture, followed by lower levels later, but this is not uniformly accepted [96].

Consequence of failure to reduce elevated CSF pressure. In a retrospective series of 26 patients (19 of whom had AIDS), 14 had major deviations from IDSA 2000 guidelines, of whom 13 had failure to measure baseline CSF pressure and 9 did not undergo drainage for elevated CSF pressure [2] . Of these 14 patients, 7 developed new neurologic abnormalities during treatment, compared with 1 of 12 who were managed with no more than minor deviations from the 2000 IDSA Guidelines and developed new signs or symptoms.

Other medications for intracranial pressure. Medications other than antifungal drugs are not useful in the management of increased intracranial pressure in cryptococcal meningoencephalitis.

A randomized trial in Thailand found severe metabolic ac-

idosis and other complications associated with acetazolamide therapy and was stopped prematurely [97]. Despite not being included in the protocol, high-dose corticosteroids were used in 41 of 110 HIV-infected patients during initial therapy [95]. Ten of 13 patients with pressures >35 cm of CSF were treated with corticosteroids specifically for intracranial pressure elevation. Of all patients given high-dose corticosteroids, there was no benefit observed, and indeed, mortality and clinical deterioration were observed more commonly in recipients of corticosteroids.

Recurrence of signs and symptoms. In the case of the recurrence of symptoms and signs of increased intracranial pressure after initial improvement or elimination of signs and symptoms during initial management of cryptococcal meningoencephalitis, guidelines are less certain.

There is no general agreement on the timing of above, and there are no systematically collected data assessing effect of delay of re-initiating repeated lumbar punctures and other drainage procedures. With recurrence of symptoms, it will be necessary to restage the patient with brain imaging and lumbar puncture for CSF pressure measurements, culture, and other general CSF parameters and to reassess other potentially infected sites outside CSF to also rule out relapse and/or IRIS.

Long-term elevated intracranial pressure. When intracranial pressure remains elevated for an extended period of time, what is the most efficient therapeutic strategy?

Similar to VP shunts, data on the use of lumbar drains are limited to collections of case series. These vary in specific recommendations for type of drain and duration that they can safely be left in place [98]. In one report, a lumbar drain was used successfully for 13 days [99]. However, with these external lumbar drains, exogenous infections are possible, but bacterial superinfection occurred in <5% of cases in one case series [100]. Furthermore, some have recommended placing intracranial pressure monitors in patients with severe bacterial meningitis and using the pressure (>15 cm of CSF is considered elevated for ventricular pressures) to monitor the need for interventions [101]. This could also be applicable to patients with severe intracranial pressure issues with cryptococcal meningoencephalitis, but it has not been extensively evaluated. Ventricular shunts may also be used if pressure is uncontrolled by lesser measures [92, 94, 98]. In one series of 27 patients with obstructive hydrocephalus and cryptococcal meningoencephalitis, 63% had good outcomes following permanent shunt placement. Outcome was worse in those who had developed a Glasgow coma score <9; thus, early placement in difficult cases may be beneficial [94].

It should be noted that after management of cryptococcal meningoencephalitis, signs and symptoms of classical hydrocephalus can develop and placement of a VP shunt will be required. VP shunts can be placed during active infection as long as effective antifungal therapy has been introduced prior to shunt placement [98].

IRIS

IRIS caused by various microorganisms has emerged as a major complication in patients with AIDS since the introduction of HAART, and in persons with cryptococcal meningoencephalitis, it has potential for producing treatment failure [67, 102–105]. In cryptococcosis, IRIS can occur in 2 forms: (1) "unmasking" IRIS, in which cryptococcal symptoms first appear after the start of HAART; or (2) "paradoxical" IRIS during the treatment of cryptococcosis and administration of HAART. Cases of cryptococcosis-associated IRIS have also been reported as a complication in solid-organ transplant recipients [82] and in apparently healthy hosts [85]. During organ transplantation, it has occurred more frequently in patients receiving tacrolimus, mycophenolate mofetil, and prednisone than in patients receiving less-immunosuppressive regimens. Previous alemtuzumab therapy has also been recently recognized as a potential risk factor for IRIS.

IRIS can present in body sites that were not initially identified as infected. It consists of clinical manifestations compatible with exuberant tissue inflammation in patients experiencing rapid improvement in cellular immunity, and generally, results of cultures for the site of infection are negative. For example, this may occur following introduction of HAART in the setting of AIDS with the restoration of pathogen-specific CD4 cells or decreasing immunosuppressive therapy in transplant recipients with the reversal of a predominantly Th2 to a Th1 proinflammatory response or in those ceasing monoclonal antibody therapy with anti–tumor necrosis factor agents. IRIS has to be differentiated from microbiological progression of the disease (although both phenomena can appear simultaneously) or from other opportunistic infections, tumors, drug-related complications that may occur in these heavily immunocompromised patients [67, 83]. More-severe cryptococcal disease, including fungemia, an extremely low CD4 cell count, cryptococcosis revealing initial HIV infection, lack of previous antiretroviral therapy, lack of CSF sterilization at week 2, introduction of HAART during early part of induction therapy, and rapid initial decrease in HIV load in response to HAART have all been recognized as risk factors for IRIS [104]. Presence of cerebral lesions during the initial treatment phase of the disease is not predictive of the subsequent occurrence of symptomatic cerebral IRIS [93].

IRIS may either occur early (ie, within a few days) or late after the introduction of HAART, sometimes up to several months thereafter. Time of occurrence appears shorter in cases of cerebral IRIS. In solid-organ transplant recipients, IRIS has been described a mean of 6 weeks after the initiation of antifungal therapy. Manifestations of IRIS consist frequently of

fever with peripheral or mediastinal/abdominal lymphadenitis or CNS signs and/or symptoms of disease (meningitis or cerebral abscesses and their clinical consequences with or without an increase of CSF opening pressure), and these new symptoms can be construed as signs of treatment failure. Furthermore, in kidney transplant recipients, graft loss has appeared as a consequence of IRIS. Severe manifestations of IRIS can be lethal if not taken into consideration [102].

Recommendations

47. No need to alter direct antifungal therapy (B-III).

48. No definitive specific treatment recommendation for minor IRIS manifestations is necessary, because they will resolve spontaneously in days to weeks (B-III).

49. For major complications, such as CNS inflammation with increased intracranial pressure, consider corticosteroids (0.5–1.0 mg/kg per day of prednisone equivalent) and possibly dexamethasone at higher doses for severe CNS signs and symptoms. Length and dose of the corticosteroid taper are empirically chosen and require careful following of the patient, but a 2–6-week course is a reasonable starting point. The course should be given with a concomitant antifungal regimen (B-III).

50. Nonsteroidal anti-inflammatory drugs and thalidomide have been used but with too little experience to make a recommendation (C-III).

Evidence summary. In the clinical milieu associated with management of cryptococcosis, the appearance of IRIS is probably more common than clinicians appreciate. Many times, IRIS is considered to be treatment failure, and new antifungal regimens are considered when in fact, the essential immune reconstitution has simply overshot in its recovery; thus, IRIS causes persistent disease or recurrent symptoms, particularly in the CNS. Because there is no specific laboratory test for detection, IRIS becomes a clinical diagnosis. Specific recommendations for IRIS management are not robust and have not faced the scrutiny of clinical trials. The most important issues are clinical identification and prevention, and finally, when it is causing severe disease, IRIS management requires the use of an anti-inflammatory strategy to prevent further host damage and not a change in direct antifungal drug(s). It has been demonstrated, even in HIV-infected individuals, that corticosteroids can be safely administered for limited durations as long as viral load is controlled [106, 107].

Cerebral Cryptococcomas

Cerebral cryptococcomas can cause significant short- and long-term neurological morbidity, are difficult-to-treat, and require prolonged antifungal therapy [108, 109]. Antifungal drugs and relief of increased intracranial pressure are the mainstays of management. In severely immunosuppressed patients with nonresponding parenchymal brain mass, it is essential to consider that the mass may represent a second pathogen or tumor, and a brain biopsy or aspirate will be necessary for identification.

Recommendations

51. Induction therapy with AmBd (0.7–1 mg/kg per day IV), liposomal AmB (3–4 mg/kg per day IV), or ABLC (5 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for at least 6 weeks (B-III).

52. Consolidation and maintenance therapy with fluconazole (400–800 mg per day orally) for 6–18 months (B-III).

53. Adjunctive therapies include the following:

A. Corticosteroids for mass effect and surrounding edema (B-III).

B. Surgery: for large (≥3-cm lesion), accessible lesions with mass effect, consider open or stereotactic-guided debulkment and/or removal; also, enlarging lesions not explained by IRIS should be submitted for further tissue diagnosis (B-II).

Evidence summary. Lesions detected by CT are more common in apparently healthy hosts (>14%) than those compromised by AIDS (4%–5%) or for other reasons (10%) [110] and are usually associated with meningitis. Although probably more common in *C. gattii* infection [93, 107, 108], they are also caused by *C. neoformans* [85, 110]. For instance, in a recent study involving 62 patients coinfected with HIV and *C. neoformans,* MRI identified masses in 21% and dilated perivascular spaces in 46% [88]. In apparently healthy hosts, CT most commonly reveals small, ring-enhancing lesions. Nonenhancing "pseudocysts" are more common in immunosuppressed hosts [109, 111]. Presentations with single large lesions (≥3 cm) indistinguishable from acute pyogenic abscesses or with symptomatic hydrocephalus are less common but necessitate early consideration of surgery for partial removal, histopathology and culture for confirmation of diagnosis, and/or CSF VP shunt insertion [108, 112].

There are no prospective studies of therapy for cerebral cryptococcomas. Recommendations are derived from case reports [113, 114], retrospective analyses of HIV-negative patients with neurocryptococcosis [14, 108, 109, 115, 116], prospective observational studies of cryptococcosis [14, 89], randomized clinical trials in non–HIV-associated and HIV-associated meningoencephalitis [20, 27–29, 117], and expert opinion [1]. Some of these studies predated the introduction of azoles and HAART. The suggested treatment of choice is induction therapy with AmBd combined with flucytosine followed by consolidation therapy with fluconazole. Induction phase may be longer for cryptococcomas than for meningitis alone. The duration of induction and consolidation therapy depends on the clinical, imaging, and mycological responses. Reliance on imaging alone can be misleading, because some brain lesions persist for long periods of time [111] and/or develop surrounding edema during effective antifungal therapy, presumably because of an im-

munological response associated with control of the cryptococcal meningoencephalitis [118]. Prolonged therapy and repeated induction courses are required in some patients, even when fluconazole is used for consolidation therapy [89, 108, 115]. Therefore, unlike meningitis, for which the site can be routinely sampled, maintenance therapy with fluconazole is recommended for at least 6 months and preferably 12–18 months with cryptococcomas. Adjunctive therapies may be necessary. For example, a trial of corticosteroids is considered in patients with cryptococcomas with significant surrounding edema, especially if there are neurological deficits. Cryptococcus can also cause cerebral vasculitis, and there are no data specifically to address management of this condition and whether anti-inflammatory agents would improve outcome. If corticosteroids are used—especially in patients with cryptococcomas responding poorly to antifungal therapy—corticosteroid doses should be reduced gradually to prevent a "rebound" IRIS phenomenon with a too rapid steroid taper. Open or stereotactic-guided removal of a surgically accessible cryptococcoma may be required to reduce life-threatening cerebral mass effects if there is substantial surrounding edema (these cases resemble a pyogenic abscess). Surgery may also be needed to achieve cure in cases unresponsive to prolonged or repeated induction antifungal therapy [109, 111]. Shunting is indicated for symptomatic hydrocephalus with dilated cerebral ventricles [98, 108]. Surgery has not been complicated by contiguous or disseminated cryptococcosis in patients with active infection already receiving antifungal drugs [98]. With obstruction of the optic nerve, surgery may be required for local decompression via a window procedure to prevent the late development of blindness [119].

Adjunctive, recombinant IFN-γ is of unproven benefit in the management of cryptococcomas. It has been tried as one of multiple modalities in salvage therapy for cases of *C. gattii* infection unresponsive to multiple antifungal drugs. Although its specific contribution to outcome is uncertain, cytokine replacement therapy will need to be carefully considered in individual refractory cases including cryptococcomas.

III. WHAT ARE THE APPROPRIATE TREATMENT STRATEGIES FOR PATIENTS WITH NONMENINGEAL CRYPTOCOCCOSIS?

Pulmonary (Immunosuppressed)

Pulmonary cryptococcosis includes clinical entities ranging from asymptomatic pneumonia to severe ARDS [81, 89, 120]. In most cases cryptococcal lung disease is believed to result from reactivation of a dormant infection with the infecting propagules being acquired long before the diagnosis of cryptococcosis. However, lung disease can also follow recent inhalation of infectious propagules and produce acute symptoms. ARDS in the context of cryptococcosis and AIDS or severe immunosuppression is often associated with dissemination and high mortality and requires urgent treatment [81, 120]. ARDS can also be a symptom of IRIS in transplant recipients or HIV-infected individuals [82, 104]. There are no clinical or radiographic feature characteristics of cryptococcal pneumonia. However, the presence of diffuse interstitial pneumonia on chest radiographs and CT should probably be considered a sign of a poorer prognosis. In HIV-infected or other severely immunosuppressed patients, pulmonary cryptococcosis is associated with disseminated cryptococcosis that requires specific management. Thus, a systematic evaluation, including blood and CSF cultures and measurement of serum and CSF cryptococcal polysaccharide antigen, should be performed in an immunosuppressed patient for whom bronchoalveolar lavage or sputum culture results are positive for *C. neoformans* [14]. This recommendation is especially important in HIV-infected individuals with $CD4^+$ T lymphocyte counts <200 cells/μL. Isolated cryptococcal pneumonia can only be ascertained after this evaluation.

The objective of the treatment is to obtain control of signs and symptoms of cryptococcal pneumonia and to avoid dissemination to the CNS. The expected outcome is thus resolution of clinical symptoms, normalization of chest radiograph or CT findings, and negative results of fungal cultures of specimens of sputum and all infected body sites.

Recommendations

54. In immunosuppressed patients with pulmonary cryptococcosis, meningitis should be ruled out by lumbar puncture; the presence of CNS disease alters the dose and duration of induction therapy and the need for intracranial pressure monitoring (B-II).

55. Pneumonia associated with CNS or documented dissemination and/or severe pneumonia (ARDS) is treated like CNS disease (B-III).

56. Corticosteroid treatment may be considered if ARDS is present in the context of IRIS (B-III).

57. For mild-to-moderate symptoms, absence of diffuse pulmonary infiltrates, absence of severe immunosuppression, and negative results of a diagnostic evaluation for dissemination, use fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months (B-III).

58. In HIV-infected patients who are receiving HAART with a CD4 cell count >100 cells/μL and a cryptococcal antigen titer that is $\leqslant$1:512 and/or not increasing, consider stopping maintenance fluconazole after 1 year of treatment (B-II).

59. Surgery should be considered for either diagnosis or persistent radiographic abnormalities and symptoms not responding to antifungal therapy (B-III).

Evidence summary. There have been no prospective, randomized trials of the specific outcome of cryptococcal pneu-

monia treatment in HIV-infected or other immunosuppressed patients, because all recent controlled trials include only HIV-infected patients with CNS infection and do not deal specifically with pneumonia. Therefore, the optimal treatment for cryptococcal pneumonia has not been fully elucidated. Recommendations are based on current knowledge of cryptococcal pathogenesis and on prior data from treatment of CNS and pulmonary cryptococcal infections in HIV-infected and other immunosuppressed patients [75, 78, 88, 89, 121].

Pulmonary (Nonimmunosuppressed)

Although dissemination from an active pulmonary infection can occur in a nonimmunosuppressed patient, it is a much less likely occurrence than in immunocompromised patients. In general, symptoms are less severe, but there is substantial overlap between presentations in nonimmunocompromised and immunocompromised hosts.

Recommendations

60. For mild-to-moderate symptoms, administer fluconazole (400 mg per day orally) for 6–12 months; persistently positive serum cryptococcal antigen titers are not criteria for continuance of therapy (B-II).
61. For severe disease, treat similarly to CNS disease (B-III).
62. Itraconazole (200 mg twice per day orally), voriconazole (200 mg twice per day orally), and posaconazole (400 mg twice per day orally) are acceptable alternatives if fluconazole is unavailable or contraindicated (B-II).
63. Surgery should be considered for either diagnosis or persistent radiographic abnormalities and symptoms not responding to antifungal therapy (B-III).
64. In nonimmunocompromised patients with pulmonary cryptococcosis, consider a lumbar puncture to rule out asymptomatic CNS involvement. However, for normal hosts with asymptomatic pulmonary nodule or infiltrate, no CNS symptoms, and negative or very low serum cryptococcal antigen, a lumbar puncture can be avoided (B-II).
65. ARDS in the context of an inflammatory syndrome response may require corticosteroid treatment (B-III).

Evidence summary. There are no prospective studies that specifically address the management of pulmonary cryptococcosis in any patient population but only retrospective surveys and anecdotal reports [78, 81, 88, 89, 122]. The prospective data concerning the treatment of pulmonary cryptococcosis are limited to patients included in large comparative trials of treatment for CNS cryptococcosis in non–HIV-infected patients [28, 29] in which concomitant pulmonary disease was noted but was not an end point of therapy. Thus, specific treatment and the optimal duration of therapy have not been precisely elucidated for patients with this disease.

It is clear from recent retrospective reviews of patients with isolated pulmonary cryptococcosis that the majority receive some form of antifungal therapy, typically oral fluconazole (200–400 mg per day) or an induction course of AmB (or LFAmB) followed by oral fluconazole [81, 89, 123–127]. These reports provide a wide range (6 weeks to >1 year) for length of therapy. Most investigators have advocated the aggressive use of AmBd (or an LFAmB), with or without flucytosine, as initial therapy for patients with severe pulmonary cryptococcosis (including those with ARDS, with or without extrapulmonary involvement), and as with immunosuppressed patients, corticosteroids may be useful in severe cases, although this is not certain.

There are few data examining the use of itraconazole and the extended-spectrum triazoles, voriconazole and posaconazole, for treatment of the patient with pulmonary cryptococcosis [19, 128]. Most of the experience with these newer agents has been among patients who developed intolerance to or failure with another antifungal agent and were being treated with salvage therapy with either voriconazole or posaconazole [19, 128]. Nevertheless, they are acceptable alternatives to standard therapy with polyenes or fluconazole under these special circumstances (eg, persistent or progressive disease with conventional therapy, unacceptable drug toxicity, or significant drug-drug interactions).

Although all patients with proven or suspected pulmonary cryptococcosis should be considered for antifungal therapy, it is well documented that many immunocompetent, asymptomatic patients with positive results of cultures, serology, and/or histopathology have done clinically well with observation alone and without any specific antifungal therapy [78, 89, 122–124]. The question remains, "Should all patients with isolated pulmonary cryptococcosis be offered antifungal therapy?" Some experts suggest treating all patients who have viable cryptococci isolated from the lung or respiratory tract, whereas others recommend that many of these apparently immunocompetent patients can be observed without specific therapy, provided that they are asymptomatic, that the lesion has been resected, and that there is no clinical, serologic, or radiographic evidence of extrapulmonary disease [78]. Examination for dissemination with a lumbar puncture in the immunocompetent host with cryptococcus isolated from lungs prior to treatment is a clinical decision. However, there is support to not perform a lumbar puncture for patients with negative or low serum cryptococcal antigen test results, no CNS symptoms, and no risk factors for dissemination [129].

The role of surgery for patients with isolated pulmonary cryptococcosis is limited [78, 89, 124, 130]. The most common role for surgery is "accidental" and occurs among patients who undergo surgical excision of pulmonary nodule to rule out

malignancy but are determined to have isolated pulmonary cryptococcosis. Many of the patients in whom all parenchymal disease has been surgically excised, who are asymptomatic, and who have absent serum cryptococcal antigen titers may or may not require antifungal therapy (see previous paragraph). The other role for surgery in the immunocompetent patient population regards those patients who have persistent focal radiographic abnormalities despite conventional antifungal therapy. In this population with persistent symptoms or signs, some authorities have offered surgical resection to patients with focal pulmonary disease, rather than either continuing long-term antifungal therapy or observation without therapy. This approach has been curative in selected patients and may even identify another pathogen.

Nonmeningeal, Nonpulmonary Cryptococcosis

With rare exceptions, such as primary skin infection, nonmeningeal, nonpulmonary cryptococcosis represents the consequence of dissemination even if the clinical syndrome is confined to a single anatomical site. Treatment regimens are similar to those for disseminated or CNS disease, and drug selection and duration of therapy depend on severity of disease, response to therapy, and host immune status, because there are no substantial specific studies for individual body sites except for the lung and CNS. This is particularly relevant to duration of therapy. As with other forms of disseminated disease, it is important to specifically rule out CNS disease. Cryptococcemia is frequent in HIV-infected patients with disseminated infection.

Recommendations

66. For cryptococcemia or dissemination (involvement of at least 2 noncontiguous sites or evidence of high fungal burden based on cryptococcal antigen titer $\geqslant$1:512), treat as CNS disease (B-III).

67. If CNS disease is ruled out, fungemia is not present, infection occurs at single site, and there are no immunosuppressive risk factors, consider fluconazole (400 mg [6 mg/kg] per day orally) for 6–12 months (B-III).

Evidence summary. Patients infrequently present with cryptococcal disease in other body sites in the absence of pulmonary or CNS infection. Cryptococcal skin lesions are seen in up to 15% of patients with disseminated cryptococcosis and are most common in HIV patients, manifesting as papules, pustules, purpura, ulcer, cellulitis, superficial granulomas or plaques, abscesses, and sinus tracts [131]. In patients with AIDS, umbilicated papules resembling molluscum contagiosum are described, and in transplant recipients, cellulitis may occur without evidence of dissemination. Although the majority of cryptococcal skin lesions result from disseminated infection, primary cryptococcal skin infections by direct inoculation may occur [132].

Cryptococcal lesions of the skeletal system are rare, occurring in <10% of patients with disseminated disease [133]. The vertebrae are the most common bony site for disease. Radiography reveals a well-circumscribed osteolytic lesion resembling malignancy. Cryptococcal septic arthritis is rare, and drainage of the joint is generally not necessary except for diagnosis.

Cryptococcal infection can involve any body site or structure following dissemination, including liver, lymph nodes, peritoneum, adrenals, and eyes. The urogenital tract is an occasional target involving kidney and/or prostate. In particular, the prostate may serve as a major sanctuary and reservoir, with accompanying cryptococcuria persisting after conventional therapy [134]. Management of ocular infections requires an individualized therapeutic strategy depending on the extent of eye structure involvement. Therapies for ocular infections range from systemic combinations of polyene with high–eye penetration drugs, such as flucytosine and/or fluconazole, to adjunctive intravitreal AmBd in consult with an ophthalmologist.

IV. WHAT IS THE APPROPRIATE TREATMENT FOR CRYPTOCOCCOSIS IN SPECIAL CLINICAL SITUATIONS (PREGNANT WOMEN, CHILDREN, RESOURCE-LIMITED ENVIRONMENT, AND *C. GATTII* INFECTION)?

Pregnant Women with Cryptococcosis

Immunologic alterations associated with pregnancy may increase the severity of cryptococcosis in pregnant women. Cryptococcal disease during pregnancy manifests most frequently as meningoencephalitis or pneumonia [135]. The mortality rate in pregnant women with cryptococcal meningitis approaches 25%. Australian aboriginal women with cryptococcosis during pregnancy have been noted to have particularly poorer outcomes [135, 136]; the precise basis for this poor prognosis, however, is not understood.

Recommendations

68. For disseminated and CNS disease, use AmBd or LFAmB, with or without flucytosine (B-II). Flucytosine is a category C drug for pregnancy, and therefore, its use must be considered in relationship to benefit versus risk.

69. Start fluconazole (pregnancy category C) after delivery; avoid fluconazole exposure during the first trimester; and during the last 2 trimesters, judge the use of fluconazole with the need for continuous antifungal drug exposure during pregnancy (B-III).

70. For limited and stable pulmonary cryptococcosis, perform close follow-up and administer fluconazole after delivery (B-III).

71. Watch for IRIS in the postpartum period (B-III).

Evidence summary. AmBd is the preferred initial regimen for the treatment of cryptococcal meningoencephalitis, disseminated disease, or severe pulmonary cryptococcosis in pregnant patients. AmBd has a US Food and Drug Administration category B rating for use in pregnancy (ie, there is no evidence of risk in humans). AmBd is well distributed in the umbilical cord serum, amniotic fluid, and placenta [135, 137–139]. Umbilical cord blood concentrations range from one-third to ~100% of those found in maternal serum [135, 139]. Data from extensive clinical use of AmBd for coccidioidomycosis has documented no teratogenicity or undue toxicity related to electrolyte imbalance or renal dysfunction in the mother or fetus [137–139]. Although the optimal duration of AmBd therapy during pregnancy has not been determined, an induction treatment regimen similar to that for CNS disease in HIV-negative patients is reasonable, and duration should be tailored to trimester of treatment initiation to ensure antifungal drug treatment throughout pregnancy. A switch to fluconazole is appropriate after delivery. Although fluconazole should be avoided in the first trimester, it might be necessary to give it during the last 2 trimesters to ensure this continuous antifungal exposure. LFAmB is a suitable alternative in patients intolerant of AmBd. These agents have category B ratings for pregnancy, and their use as replacement for AmBd for the treatment of coccidioidomycosis has been deemed acceptable [140].

Flucytosine in combination with polyene has been used to treat cryptococcosis primarily in the second and third trimesters and has not been associated with adverse neonatal outcomes [141]. The literature describing flucytosine use in pregnancy, however, is limited to case reports and small series. Because of its mechanism of action and animal model studies that show potential for teratogenicity, flucytosine is classified as a pregnancy class C drug and should be used with caution in pregnancy on a case-by-case basis.

Fluconazole use is not advisable during pregnancy, particularly in the first trimester. Fluconazole has been associated with craniofacial ossification defects, thin wavy ribs, and renal pelvis defects [142]. Congenital malformations similar to those observed in animals have been reported in infants born to mothers who received fluconazole through or beyond the first trimester of pregnancy [143]. In patients with pulmonary cryptococcosis in whom the disease is limited to the lungs and who have no evidence of CNS or of disseminated infection or no significant symptoms, deferring antifungal therapy until after delivery (with careful observation during pregnancy) may be considered. Fluconazole is excreted in breast milk at concentrations similar to plasma.

A state of relative immunosuppression characterized by physiologic suppression of proinflammatory responses is critical for the maintenance of pregnancy [144]. This is established by the expression of Th2 and Th3 responses such as transforming growth factor–β by maternal tissue and simultaneous inhibition of Th1 or proinflammatory cytokines [144]. Rapid reversal of this immunological environment in the postpartum period can lead to overt clinical symptoms of previously stable infections [123, 145, 146]. Indeed, nearly 45% of the cases of cryptococcosis in pregnancy reported in the literature presented with symptomatic disease in the third trimester or postpartum period [135]. Recognition that patients may develop new onset or progressive disease in the postpartum period is critical, and understanding that this may be due to IRIS is important to management [146].

Children with Cryptococcosis

Cryptococcal disease occurs less frequently in children than in adults. For instance, among US children with AIDS, the incidence appears to be on the order of 0.5%–1% [147, 148]. A higher incidence among children with AIDS from Thailand and South Africa has been reported [149, 150]. Besides AIDS, cryptococcosis has been reported in children with a variety of underlying conditions. Although some of these conditions (ie, receipt of a solid-organ transplant and connective tissue disease) are risk factors for both adults and children, other conditions are more characteristic of childhood, including primary immunodeficiencies (eg, hyper–immunoglobulin M syndrome and severe combined immunodeficiency syndrome) and certain malignancies (eg, acute lymphoblastic leukemia and sarcomas). Both isolated pulmonary and CNS cryptococcosis have been described in children without a recognized immunodeficiency. Neonatal cryptococcosis has been reported, and vertical transmission has been proposed [151, 152].

Recommendations

72. Induction and consolidation therapy for CNS and disseminated disease is AmBd (1 mg/kg per day IV) plus flucytosine (100 mg/kg per day orally in 4 divided doses) for 2 weeks (for the non–HIV-infected, non-transplant population, follow the treatment length schedule for adults), followed by fluconazole (10–12 mg/kg per day orally) for 8 weeks; for AmB-intolerant patients, either liposomal AmB (5 mg/kg per day) or ABLC (5 mg/kg per day) (A-II).
73. Maintenance therapy is fluconazole (6 mg/kg per day orally) (A-II).
74. Discontinuation of maintenance therapy in children receiving HAART is poorly studied and must be individualized (C-III).
75. For cryptococcal pneumonia, use fluconazole (6–12 mg/kg per day orally) for 6–12 months (B-II).

Evidence summary. Literature concerning pediatric cryptococcosis is limited to case reports and small series. No clinical trials dedicated to children have been performed. Thus, the optimal dosing and duration of therapy for children with cryp-

tococcosis have not been precisely determined. Recommended therapy is based on the extrapolation of findings from studies performed in adults.

Specific considerations in the treatment of pediatric cryptococcosis include the need for pediatric dosing of antifungal agents. The dosage of AmBd reported in the treatment of pediatric cryptococcosis ranges from 0.5 to 1 mg/kg per day [148]. Children generally tolerate AmBd better than adults, and a dosage of 1 mg/kg per day for the treatment of cryptococcosis is commonly used [153–155]. Successful treatment with liposomal AmB has been reported in children with cryptococcosis at daily doses of 5–7.5 mg/kg per day [156, 157]. There are only a few cases of primary therapy with ABLC for pediatric cryptococcosis at 5 mg/kg per day [158]. Successful treatment of pediatric cryptococcosis using AmBd, with or without flucytosine, has been reported [148]. The combination of AmBd and flucytosine has also been used for the treatment of CNS candidiasis in the neonate [159]. Nonetheless, extensive treatment studies with flucytosine in children have not been performed, and flucytosine-related myelosuppression has been reported in adult patients during the 2-week induction phase of therapy [160]. Thus, monitoring of flucytosine levels and/or blood counts is recommended in children [161].

There are important differences in the pharmacokinetics of fluconazole in children versus those in adults. The volume of distribution for fluconazole is larger and the clearance is more rapid in children than in adults [162, 163]. This necessitates higher dosages in children. During consolidation treatment with fluconazole, a dosage of 10–12 mg/kg per day divided in 2 doses is recommended. A dosage of 6 mg/kg per day is recommended for maintenance therapy in HIV-infected children with cryptococcosis. The safety of discontinuing fluconazole in the context of immune reconstitution following HAART has been documented in several studies of adult patients [57, 59, 164–166], and these studies included adolescent patients [57]. If fluconazole maintenance therapy is discontinued following a successful response to HAART (ie, a CD4 T cell count $\geqslant$100 cells/uL and an undetectable or low viral load), clinical monitoring for relapse of infection and serial monitoring of serum cryptococcal antigen and CD4 T cell counts are recommended.

IRIS associated with cryptococcosis has recently been described in children [167], although no treatment data exist. Current recommendations for the treatment of IRIS in adults are described previously and should be considered in children.

Cryptococcosis in a Resource-Limited Health Care Environment

In many areas of the world where cryptococcosis is common, the resources to give extended-length IV drugs, such as AmBd or LFAmB, or flucytosine are not available. On a practical basis, there needs to be adjustments in management which optimize the care of patients in these clinical settings. There have been some studies and experiences in these resource-limited health care environments, and recommendations can be made to help clinicians.

Recommendations

76. For CNS and/or disseminated disease where flucytosine is not available, induction therapy is AmBd (1 mg/kg per day IV) for 2 weeks or AmBd (0.7 mg/kg per day IV) plus fluconazole (800 mg per day orally) for 2 weeks, followed by consolidation therapy with fluconazole (800 mg per day orally) for 8 weeks (A-I).

77. Maintenance therapy is fluconazole (200–400 mg per day orally) until immune reconstitution (A-I).

78. With CNS and/or disseminated disease where polyene is not available, induction therapy is fluconazole ($\geqslant$800 mg per day orally; 1200 mg per day is favored) for at least 10 weeks or until CSF culture results are negative, followed by maintenance therapy with fluconazole (200–400 mg per day orally) (B-II).

79. With CNS and/or disseminated disease when polyene is not available but flucytosine is available, induction therapy is fluconazole ($\geqslant$800 mg per day orally; 1200 mg per day is favored) plus flucytosine (100 mg/kg per day orally) for 2–10 weeks, followed by maintenance therapy with fluconazole (200–400 mg per day orally) (B-II).

80. With use of primary fluconazole therapy for induction, both primary or secondary drug resistance of the isolate may be an issue, and MIC testing is advised (B-III).

81. For azole-resistant strains, administer AmBd (1 mg/kg per day IV) until CSF, blood, and/or other sites are sterile (B-III).

Evidence summary. Evidence suggests AmB has concentration-dependent activity [168], and outcomes of more recent trials using AmBd (0.7 mg/kg per day IV) are better than in previous studies of lower doses [26, 27]. An even higher dosage of 1.0 mg/kg per day IV of AmBd has been used for the initial 2 weeks in cryptococcal meningitis with good results but without any comparative data [169]. A recent study of 64 randomized HIV-infected patients with cryptococcal meningoencephalitis showed that AmBd at 1.0 mg/kg per day was more fungicidal than at 0.7 mg/kg per day with the use of flucytosine [30]. Of note, in the setting of HIV-associated cryptococcal meningitis, both the dosages 0.7 mg/kg per day and 1.0 mg/kg per day IV of AmBd for 2 weeks have been well-tolerated, suggesting that, at least in this patient population, there is potential to increase the dose of AmBd without intolerable nephrotoxicity or anemia [21, 27]. In practice, in many resource-limited settings, 1 mg/kg per day IV of AmBd is currently used, given the average weight of HIV-infected patients and the 50-mg vial size [25, 170] and the lack of availability of flucytosine to boost fungicidal activity [21]. In Thailand, the combinational

use of AmBd plus 800 mg per day of fluconazole was an acceptable fungicidal regimen, compared with polyene alone [38].

If resources preclude a 2-week induction with AmBd, shorter courses, prior to switching to fluconazole, may still be of benefit. In an unselected, prospective series with nearly complete follow-up in South Africa, the 10-week mortality rate was 33% with 1-week induction therapy with AmBd alone at 1 mg/kg per day IV [25], less than that reported for fluconazole therapy alone in Africa. In a small, randomized study in Thailand that compared 1-week and 2-week induction therapy with AmBd alone, the proportion of patients achieving negative CSF culture results by 6 weeks appeared to be similar, although more patients in the 1-week arm were lost to follow-up [171]. When AmBd is given in resource-limited areas, frequent laboratory monitoring and fluid supplementation are still essential.

Where AmBd is not available or affordable, where facilities for admission and IV therapy do not exist, or where renal and potassium monitoring are not sufficiently rapid or reliable to allow safe use of AmBd, fluconazole is often the only treatment option. At dosages up to 400 mg per day, it is essentially a fungistatic drug, and outcomes are poor, with 10-week mortality of ~50% [25, 26, 39, 172, 173]. The prolonged period with a high viable yeast burden resulting from the slow rates of clearance of infection with fluconazole at 400 mg per day may also predispose to the development of fluconazole resistance and possibly increased risk of IRIS when antiretroviral therapy is started [50]. Data from animal studies suggest increased fungicidal response with increasing fluconazole dosage [174]. There is a linear plasma concentration–dose relationship with fluconazole dosages up to 2 g per day [175]. While acknowledging that such comparisons are very unreliable, the results of several small studies do suggest a dose response in patients with cryptococcal meningitis, with median times to CSF sterilization of 64 days with dosages of 200–400 mg per day [6], a mean of 41 days with a dosage of 400 mg per day [39], and a mean of 21–33 days with a dosage of 800 mg per day [40, 176]. In one study from the United States, there appeared to be a dose-response effect with fluconazole at least up to 1600 mg per day [37]. On this basis and given the unsatisfactory results of treatment at lower doses, the safety of fluconazole, and a study showing that a dosage of 1200 mg per day is more rapidly fungicidal than a dosage of 800 mg per day [177], pending further studies, a starting dosage of 1200 mg per day is favored. This recommendation will need to be further reviewed in the light of dose-escalation studies of fluconazole therapy currently underway in Africa, in which even higher dosages (ie, >1200 mg per day) may prove to be optimal, as has been observed in the United States.

Data on the interaction of fluconazole and nevirapine or efavirenz are incomplete and inconclusive. Small pharmacokinetic studies from South Africa and Thailand suggest a 75%–100% increase in nevirapine exposure with use of fluconazole at 400 mg per day. This finding appeared to be associated with an increased rate of hepatotoxicity in South Africa, but this association was not found in a separate investigation conducted in Thailand [178], and most studies have not yet found a close relationship between nevirapine levels and hepatotoxicity [179]. Efavirenz levels may also be raised (16% increase in the area under the curve) with coadministration of fluconazole at 200–400 mg per day [180], but at higher dosages of fluconazole, the impact on efavirenz is not certain. However, if high-dose fluconazole is used, efavirenz would be preferred to nevirapine on the basis of a less significant interaction. Finally, with concomitant infections like tuberculosis, rifampin accelerates clearance of fluconazole, which may lead to suboptimal dosing; thus, fluconazole doses may need to be increased.

The combination of fluconazole plus flucytosine improves outcomes in murine models [181, 182] although not in a rabbit study [174]. A clinical study from Uganda suggested a benefit with the addition of flucytosine to fluconazole, although the dosage of fluconazole was low (200 mg per day) [36]; and in a small series from the United States, the combination of flucytosine (at 150 mg/kg per day) and fluconazole (at 400 mg per day) resulted in a relatively short median time to CSF sterilization of 23 days, although adverse effects with the combination, which was given for 10 weeks, appeared to be frequent [35]. For instance, 28% of study participants had to stop flucytosine therapy, mainly because of gastrointestinal adverse effects or cytopenias, but >95% of participants did tolerate flucytosine therapy for ⩾2 weeks [35]. More recently published work suggested using fluconazole at ⩾800 mg per day with flucytosine at 100 mg/kg per day [37].

Obstructive hydrocephalus is rare in HIV-related cryptococcal meningoencephalitis in resource-limited environments, and clinical head scans rarely demonstrate contraindications to lumbar puncture [95]. Although controlled trials are lacking, there is extensive clinical experience suggesting the benefit of mechanical drainage of CSF in patients with symptomatically raised CSF opening pressure by repeated lumbar punctures.

Secondary fluconazole resistance is an emerging problem when fluconazole is used as initial therapy [50]. Patients who re-present with signs of meningitis after starting antiretroviral therapy may have IRIS or fluconazole resistance or both. In addition, when fluconazole is used as initial therapy, the long time taken to sterilize the CSF means that CSF culture results may still be positive when disease is primarily caused by IRIS. Therefore, in this setting, susceptibility testing of relapse isolates—and, ideally, comparison with initial isolates—is important to rule out direct fluconazole resistance. In addition, quantitative cultures of CSF may be helpful in differentiating the low organism load expected in IRIS from the rising organism load seen with the development of fluconazole resistance.

C. gattii Infection

Infections caused by *C. gattii* occur predominantly in apparently healthy hosts [108, 110, 183, 184]. They have been reported rarely in patients with AIDS, although ~2% of HIV-associated cases in the Gauteng province of South Africa are caused by *C. gattii.* Clinically, these cases resembled *C. neoformans* infection [185]. In HIV-negative hosts, intracranial infection with *C. gattii* is associated with more neurological complications, a delayed response to therapy, and a higher incidence of neurosurgical intervention [108] than is disease due to *C. neoformans* [108, 109, 186], despite similar susceptibility of the 2 species to antifungal drugs when tested in vitro in some reports [110, 186, 187]. Mortality of meningoencephalitis with *C. gattii* ranged from 0%–20% in 3 Australian series to 41% in Papua New Guinea, with abnormal mental status at presentation being a poor prognostic indicator [108, 109, 116, 188].

Recommendations

82. For CNS and disseminated disease due to *C. gattii,* induction, consolidation, and suppressive treatment are the same as for *C. neoformans* (A-II).

83. More diagnostic focus by radiology and follow-up examinations are needed for cryptococcomas/hydrocephalus due to *C. gattii* than that due to *C. neoformans,* but the management principles are the same (B-II).

84. Pulmonary cryptococcosis (same as *C. neoformans*): single, small cryptococcoma suggests fluconazole (400 mg per day orally); for very large and multiple cryptococcomas, consider a combination of AmBd and flucytosine therapy for 4–6 weeks, followed by fluconazole for 6–18 months, depending on whether surgery was performed (B-III).

85. Consider surgery if there is compression of vital structures, failure to reduce size of cryptococcoma after 4 weeks of therapy, or failure to thrive (B-III).

86. Recombinant IFN-γ use remains uncertain (C-III).

Evidence summary. The slow response to therapy is largely because *C. gattii* infection causes a disproportionate number of cryptococcomas in the brain (up to 30% of cases) and/or lung, compared with *C. neoformans* [110]. Cerebral cryptococcomas respond slowly and relatively poorly to antifungal therapy [108, 109]. Most of this difference, but not all, is explained by the propensity of *C. gattii* to infect apparently healthy hosts, with containment of foci of infection by the immune response. However, some isolates of *C. gattii* from Vancouver, British Columbia, Spain, and Latin America have high azole MICs, and thus, the role of direct drug resistance in management difficulties of some cases needs to be investigated [189, 190].

Management of CNS cryptococcosis caused by *C. gattii* is best guided by the appearance of the following on cerebral CT: no abnormality (meningitis alone; still the most common presentation), multiple ring-enhancing lesions with meningitis, a single mass lesion resembling acute pyogenic abscess (CSF may be normal), or hydrocephalus with dilated ventricles and meningitis [109]. Meningitis alone responds to the same therapy as *C. neoformans* meningitis. Large, single mass lesions are typically diagnosed after surgical excision for presumed pyogenic abscess, in which case they respond better to shorter courses of antifungal therapy than if not excised. Multiple cryptococcomas require prolonged therapy, with or without corticosteroids. An apparent relapse during antifungal therapy must be distinguished from the development of IRIS [118]. Hydrocephalus requires placement of a VP shunt combined with antifungal therapy [112].

In Papua New Guinea, cryptococcal meningitis due to *C. gattii* presents with a relatively high prevalence of papillitis or papilledema, leading to visual loss, with or without optic atrophy [188, 191]. This complication has been attributed to immune-mediated optic nerve dysfunction rather than late presentation of disease [191]. Corticosteroids have been used in some cases, but there is no proven benefit [191].

Recombinant IFN-γ has been tried as one of multiple modalities in salvage therapy for patients with cerebral cryptococcomas unresponsive to multiple antifungal drugs, although its specific contribution to outcome is uncertain. There are also case reports of very low levels of proinflammatory cytokines (IFN-γ, tumor necrosis factor-α, and interleukin-6) and high levels of the anti-inflammatory cytokine interleukin-10 in *C. gattii* meningitis in nonimmunocompromised hosts that were associated with slowed clearance of cryptococcus from the CSF [117, 118].

PERFORMANCE MEASURES

1. When available, all patients should receive a polyene in the induction treatment regimen for cryptococcal meningoencephalitis.
2. Patients with symptomatic increased intracranial pressure should be aggressively identified, treated, and monitored.
3. Relapse of symptoms and signs during or after treatment needs to be carefully studied to determine whether this represents failure to control fungal growth (drug resistance or compliance issues) or represents IRIS.
4. Patients with disseminated cryptococcosis or meningoencephalitis should be tested for HIV infection.

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