



# Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM

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Cryptococcosis is a major worldwide disseminated invasive fungal infection. Cryptococcosis, particularly in its most lethal manifestation of cryptococcal meningitis, accounts for substantial mortality and morbidity. The breadth of the clinical cryptococcosis syndromes, the different patient types at-risk and affected, and the vastly disparate resource settings where clinicians practice pose a complex array of challenges. Expert contributors from diverse regions of the world have collated data, reviewed the evidence, and provided insightful guideline recommendations for health practitioners across the globe. This guideline offers updated practical guidance and implementable recommendations on the clinical approaches, screening, diagnosis, management, and follow-up care of a patient with cryptococcosis and serves as a comprehensive synthesis of current evidence on cryptococcosis. This Review seeks to facilitate optimal clinical decision making on cryptococcosis and addresses the myriad of clinical complications by incorporating data from historical and contemporary clinical trials. This guideline is grounded on a set of core management principles, while acknowledging the practical challenges of antifungal access and resource limitations faced by many clinicians and patients. More than 70 societies internationally have endorsed the content, structure, evidence, recommendation, and pragmatic wisdom of this global cryptococcosis guideline to inform clinicians about the past, present, and future of care for a patient with cryptococcosis.

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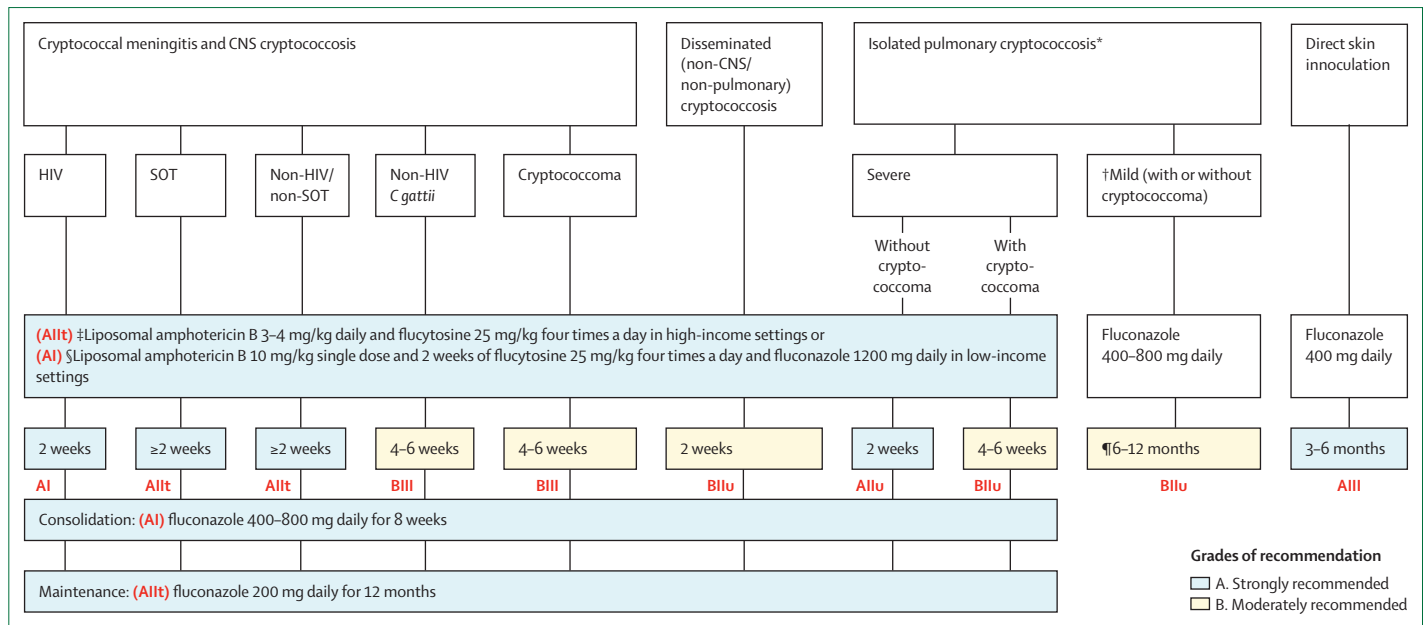
## Introduction

Cryptococcosis accounts for substantial morbidity and mortality globally. In 2022, WHO listed *Cryptococcus neoformans* as a top fungal priority pathogen.<sup>1</sup> Cryptococcosis often involves the CNS or the lungs, but disseminated disease can affect any organ, yet appear localised. Despite the knowledge gained and improvements in clinical outcomes generated by multiple interventional trials<sup>2–7</sup> done primarily in low-income settings with insufficient resources, mortality from cryptococcal meningoencephalitis is high, ranging from 24 to 47% at 10 weeks.<sup>2,4,7,8</sup> The highest burden of disease is in low-income and middle-income countries, especially in sub-Saharan Africa,<sup>9</sup> where HIV and AIDS are the dominant risk factor, although new non-HIV immunocompromised risk groups and putatively immunocompetent individuals are increasingly reported in high-income settings with sufficient resources.

Complementary diagnostic and management guidelines for cryptococcosis exist.<sup>10–21</sup> This comprehensive management guideline serves primarily to facilitate clinical decision making while also providing an overview of the uncertainties in cryptococcosis management. With contributors across the globe, this guideline gives voice to expertise and challenges from diverse settings in a globally relevant Review. General principles and treatment recommendations are provided, and clinicians are urged to use careful clinical judgement when formulating

## Key points

- Accurate delineation of the cryptococcosis clinical syndrome is important as it guides antifungal treatment choice and duration; cryptococcosis syndromes are divided into CNS, disseminated disease, isolated pulmonary disease, or direct skin inoculation (figure 1)
- Liposomal amphotericin B 3–4 mg/kg daily and flucytosine 25 mg/kg four times a day is the most optimal induction therapy option for cryptococcal meningitis, disseminated cryptococcosis, and severe isolated pulmonary cryptococcosis in high-income settings
- In low-income settings, patients with HIV-associated cryptococcal meningitis are best treated with liposomal amphotericin B 10 mg/kg as a single-dose, with 14 days of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily as induction therapy; this induction therapy has not been trialled in non-HIV-associated cryptococcal meningitis or other non-CNS cryptococcosis syndromes
- Optimise outcomes by providing the most effective antifungal therapy while preventing, monitoring, and managing potential toxicity; do not stop or switch to an inferior regimen too early or unnecessarily
- Expect and monitor for clinical relapse and investigate thoroughly for causality; review adherence to antifungal therapy and consider drug–drug interactions; during treatment follow-up, do not escalate antifungal therapy for persistent blood antigenemia (blood cryptococcal antigen), persistently positive CSF cryptococcal antigen, visible cryptococci in CSF (without culture positivity), or abnormal CSF microscopy or biochemistry, as they are not necessarily indicators of microbiological failure
- Adapt and adopt these ECMM global guidelines to suit local practices, while constantly advocating for better antifungal access, scrutinising new trial data, and reviewing local data to improve patient outcomes



**Figure 1: Recommended first-line antifungal therapy by cryptococcosis syndrome**

Grading of recommendation and level of evidence in bolded red letters. Recommendation grading by shading: blue (strongly recommended; A) and yellow (moderately recommended; B). SOT=solid organ transplantation. *C gattii*=*Cryptococcus gattii*. w=weeks. \*Isolated *Cryptococcus neoformans* or *Cryptococcus gattii* pulmonary cryptococcosis, mild is defined as asymptomatic or mildly symptomatic patients or with a solitary small nodule (<2 cm); whereas severe is defined as multiple lesions, large lesions (≥2 cm), lobar consolidation, cavitation, multi-lobe involvement, or hypoxaemic. †If the presence of *Cryptococcus* spp in respiratory specimens is deemed to be airway colonisation after careful evaluation and no treatment is elected, regular follow-up is recommended, especially in the setting of future immunosuppression. ‡Strongly preferred in cryptococcal meningitis and CNS cryptococcosis in SOT and non-HIV non-SOT patient populations, disseminated cryptococcosis, and severe pulmonary cryptococcosis. §Has not been directly compared against §. §Has only been trialled in people with cryptococcal meningitis and there are no supporting data of its use in SOT or non-HIV non-SOT patients or in other cryptococcosis syndromes. ¶Can consider a shorter duration (eg, 3 months) in immunocompetent individuals with mild isolated pulmonary cryptococcosis.

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treatment plans for the individual patient. See the appendix for more detailed text, tables, and panels relevant to each section. A summary of the first-line treatment for the different cryptococcosis syndromes is in figure 1.<sup>3</sup> An explanation of the evidence grading system used for the recommendations throughout is in panel 1.

### Populations at high risk, clinical presentations, and outcomes

Primarily acquired via inhalation but occurring mainly upon reactivation after a period of latency, cryptococcosis has protean manifestations, with cryptococcal meningitis being the most common severe presentation. Pulmonary cryptococcosis is underdiagnosed and often subclinical. Disseminated cryptococcosis can involve any organ of the body, thus a thorough clinical assessment is required, even in individuals who appear asymptomatic.<sup>24,25</sup> Although classic patient populations at high risk include people living with HIV and solid organ transplant (SOT) recipients, individuals with other immunosuppressive conditions or receiving immunosuppressant drugs and people putatively immunocompetent are also affected by cryptococcosis (appendix pp 6, 79). Those who survive cryptococcosis report substantial morbidity, ranging from 10–70% depending on the disease syndrome and severity, underlying predisposing conditions of the host, and the health-care system in which the patient is managed<sup>26–29</sup> (panel 2; appendix pp 8, 39).

### Yeasts causing cryptococcosis and diagnostic methods

*C neoformans* species complex is the predominant causative agent of cryptococcosis in people living with HIV, and *Cryptococcus gattii* species complex more commonly causes disease in people who appear immunocompetent. Although both can cause a similarly broad range of cryptococcosis syndromes, *C neoformans* has a predilection for CNS disease and *C gattii* is more often associated with pulmonary disease and large cryptococcomas.<sup>30–32</sup>

Diagnostic methods used to establish the diagnosis, extent, severity, and prognosis of cryptococcosis are constantly evolving (appendix pp 10, 41). Microscopy and culture of cerebrospinal fluid (CSF) pellet after centrifugation and blood culture, accompanied by CSF and blood (ie, serum, plasma, or whole blood) cryptococcal antigen testing (most commonly by lateral flow assay) and radiological studies, are central to the diagnosis of cryptococcosis (panel 3; appendix pp 10, 35, 41).<sup>33,34</sup>

### Screening, primary prophylaxis, and pre-emptive therapy

Supportive evidence for cryptococcal screening is limited to people living with HIV and depends on blood cryptococcal antigen by lateral flow assay (panel 4; appendix p 49).

### Panel 1: Grade of recommendation and level of evidence

This guideline follows the structure and definitions of previous European Confederation of Medical Mycology guidelines on invasive fungal infections,<sup>22,23</sup> which are in accordance with the Grading of Recommendations Assessment, Development and Evaluation and Appraisal of Guidelines for Research & Evaluation systems, as previously described. Strength of recommendation and quality of evidence are provided.

#### Grade of recommendation

- A: the guideline group strongly supports a recommendation for use
- B: the guideline group moderately supports a recommendation for use
- C: the guideline group marginally supports a recommendation for use
- D: the guideline group supports a recommendation against use

#### Level of evidence

- I: evidence from at least one well-designed randomised controlled trial (RCT)
- II: evidence from at least one well-designed clinical trial, without randomisation; from cohort or case-controlled analytic studies (preferably from >1 centre); from multiple time series; or from results of uncontrolled experiments
- III: evidence from opinions of respected authorities, based on clinical experience, descriptive case studies, or reports of expert committees

#### Added index for source of level II evidence

- r: meta-analysis or systematic review of RCT
- t: transferred evidence (ie, results from different patient cohorts or similar immune-status situations)
- h: historical control as control group
- u: uncontrolled trials
- a: for published abstract presented at an international symposium or meeting

## HIV-associated cryptococcal meningitis

### Induction therapy

Multiple studies support the successful combination of amphotericin B plus flucytosine as the induction treatment of choice in HIV-associated cryptococcal meningitis. First trialled by van der Horst and colleagues, the addition of flucytosine to amphotericin B showed a trend towards improved CSF sterility at 2 weeks and reduced frequency of relapse.<sup>35</sup> In a subsequent trial, this combination cleared cryptococci (measured as early fungicidal activity [EFA]) more rapidly than either amphotericin B alone or amphotericin B plus fluconazole.<sup>5</sup> Importantly, the combination of amphotericin B 1 mg/kg daily plus flucytosine 25 mg/kg four times a day showed a survival advantage at day 70, compared with amphotericin B alone in the treatment of cryptococcal meningitis.<sup>2</sup> The nephroprotection of

### Panel 2: Recommendations for populations at high risk, clinical presentations, and outcomes

- (AIII) Cryptococcosis should be considered in any patient presenting with compatible symptoms or microbiology, regardless of their immune status.
- (AIII) Among patients without known predisposition to cryptococcosis, exclusion of an underlying immunodeficiency (eg, performing HIV serology and CD4 T-cell count) is recommended

### Panel 3: Recommendations for yeast causing cryptococcosis and diagnostic methods

(AII) All patients with suspected or confirmed cryptococcosis (including cryptococcal antigenemia) require clinical assessment for CNS, pulmonary, and other body site involvement.

Investigations for disseminated disease should include:

- Lumbar puncture with measurement of CSF opening pressure, glucose, protein, cell counts, microscopy, and culture and quantification of CSF cryptococcal antigen
- Quantification of blood cryptococcal antigen and cultures of blood, sputum (or other respiratory specimens), or other affected sites
- Brain imaging (preferably MRI) and chest imaging (preferably CT)

liposomal amphotericin B compared with amphotericin B is long recognised and the accessibility of liposomal amphotericin B in high-income settings led to the establishment of liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day for 2 weeks as the standard.

In low-income settings, challenges with antifungal access, adverse effects, and difficulty of monitoring and safely managing 2 weeks of amphotericin B induction treatment led to phase 2 studies exploring alternative regimens. Fluconazole monotherapy, even at doses up to 1200 mg daily, was associated with approximately 50% mortality at 10 weeks and up to 75% mortality at 1 year.<sup>36–38</sup> An oral combination of fluconazole 1200 mg daily plus flucytosine 25 mg/kg four times a day was associated with a significant improvement in EFA compared with fluconazole alone.<sup>39</sup> The addition of a short, 5–7 day course of amphotericin B at 1 mg/kg daily to oral fluconazole or combined oral fluconazole and flucytosine showed improved rates of cryptococcal clearance,<sup>40,41</sup> similar to rates observed with 14 days of amphotericin B.

In the phase 3 ACTA trial conducted in centres in Africa the oral combination of fluconazole 1200 mg daily and flucytosine 25 mg/kg four times a day for 2 weeks was compared with 1 week of amphotericin B 1 mg/kg daily and 2 weeks of amphotericin B 1 mg/kg daily as induction therapy, with the amphotericin B groups

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#### Panel 4: Recommendations for screening, primary prophylaxis, and pre-emptive therapy

Adults living with HIV who are antiretroviral therapy (ART)-naïve or after a period of ART discontinuation with less than 200 CD4 cells per mm<sup>3</sup> must have:

- (AI) A lateral flow assay of blood cryptococcal antigen for the screening of cryptococcosis and the cryptococcal antigen titre should be measured if positive
- (AII) All patients with cryptococcal antigenaemia should be carefully assessed and investigated for cryptococcosis and treated as appropriate
- (AIII) In people living with HIV who have asymptomatic cryptococcal antigenaemia but without clinical cryptococcosis after thorough investigation (including at least a lumbar puncture), fluconazole 1200 mg daily for 2 weeks (when ART can be initiated), followed by fluconazole 800 mg daily for 8 weeks, and 200 mg daily thereafter for 6 months is recommended (guidance might be updated contingent on results of prospective trials)
- (BII) In clinical settings where cryptococcal antigen lateral flow antigen screening is not available (despite WHO's strong recommendations), universal primary prophylaxis with fluconazole 100 mg daily in people living with HIV in high endemic areas with a CD4 count of less than 200 cells per mm<sup>3</sup> is recommended

In patients without HIV:

- (DII) Routine blood cryptococcal antigen screening, primary prophylaxis, and pre-emptive therapy are not recommended

being further randomly assigned to either fluconazole 1200 mg daily or flucytosine 25 mg/kg four times a day.<sup>7</sup> 1 week of amphotericin B 1 mg/kg daily plus flucytosine followed by fluconazole 1200 mg daily in the second week was the best-performing induction group, with a 24% 10-week mortality rate. This regimen was adopted as the preferred 10-week induction regimen by WHO and southern African guidelines until the AMBITION-cm study.<sup>16,18</sup>

In the AMBITION-cm phase 3 study, which had sites across Africa, a single initial 10 mg/kg dose of liposomal amphotericin B with oral fluconazole 1200 mg daily plus flucytosine 25 mg/kg four times a day for 2 weeks was compared with the WHO recommendation of 1 week of amphotericin B 1 mg/kg daily plus flucytosine followed by 1 week of fluconazole 1200 mg daily.<sup>6</sup> This new regimen met non-inferiority criteria (10-week mortality 24·8% vs 28·7%) with similar EFAs and was significantly better tolerated. The WHO guidelines now recommend the AMBITION-cm regimen as the preferred antifungal therapy in people living with HIV and cryptococcal meningitis.<sup>10</sup>

The applicability of the ACTA and AMBITION-cm trials to high-income settings and in non-HIV

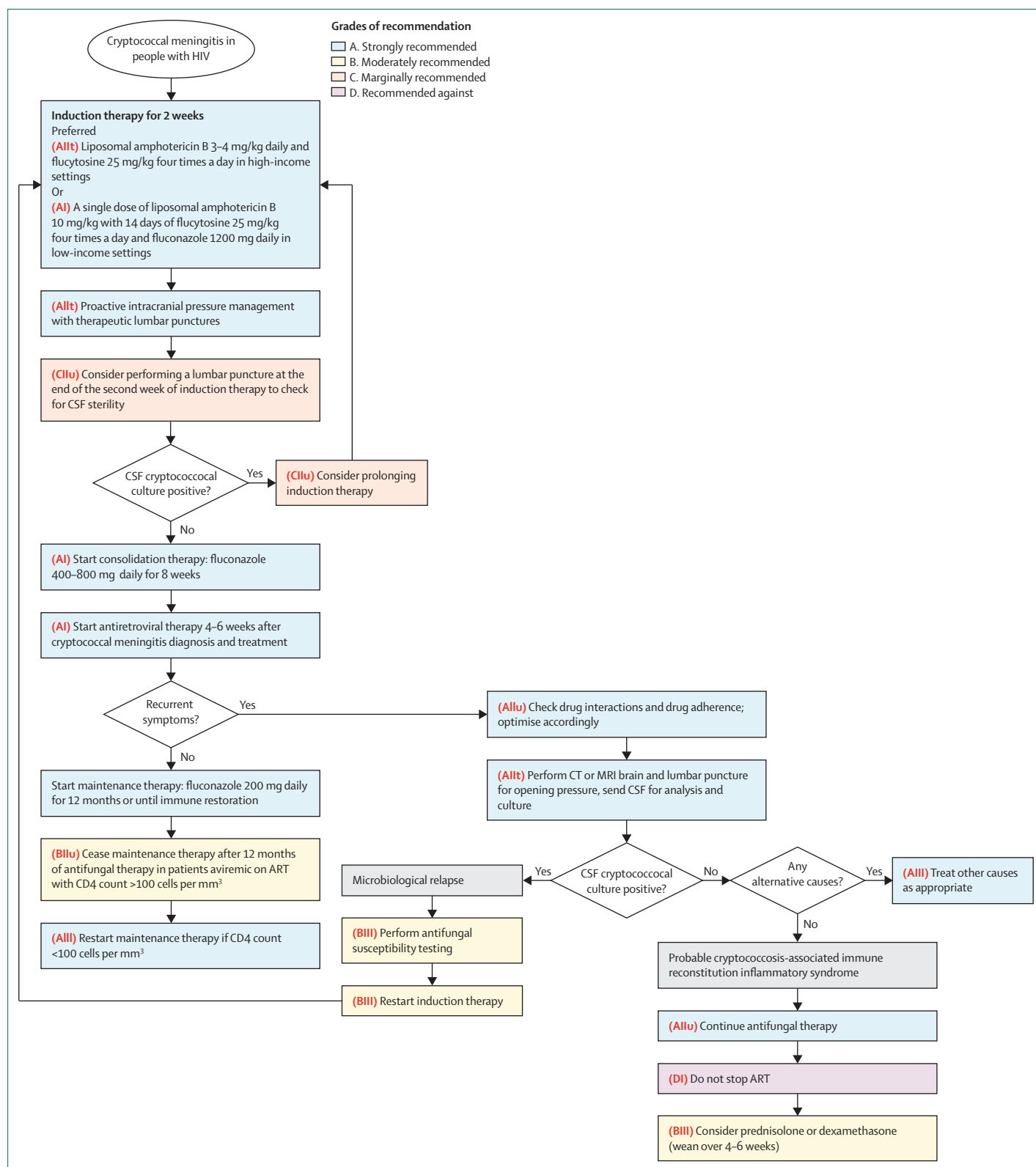
populations is contentious. The standard regimen is liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day for 2 weeks, which is different to the comparators used in the trials. Retrospective database reviews in the USA showed low rates of acute inpatient mortality from cryptococcal meningitis (10·5% in HIV-cryptococcal meningitis and 13·3% in non-HIV cryptococcal meningitis) and a remarkably low mortality rate at 1 year of 11·6% in the past two decades.<sup>42,43</sup> The reliance on high-dose fluconazole and flucytosine as the basis of induction therapy in the AMBITION-cm study might not be pragmatic in high-income settings, where more comorbidities occur, potential drug–drug interactions need to be carefully considered, and the risk of hepatotoxicity is less tolerated than in low-income settings. In the USA, only a third of patients completed the 14 days of flucytosine.<sup>44</sup> Although some experts support the inclusion of the AMBITION-cm triple regimen as a primary option in high-income settings, other experts call for further comparative trials in high-income settings to assess the regimen's effect in patients with HIV and patients without HIV (in whom no supporting data exist). Regardless of the induction antifungal regimen used, the complications of cryptococcal meningitis, such as increased intracranial pressure, require intense clinical monitoring, and most patients with cryptococcal meningitis require inpatient care for 1–2 weeks or more.

Mycological success, defined as cryptococcal culture negativity (also termed CSF sterility) has been associated with improved outcomes and reduced clinical relapse.<sup>45</sup> In people living with HIV and cryptococcal meningitis, CSF sterility before ART commencement has been shown to be associated with reduced occurrence of neurological deterioration, microbiological relapse, and cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS).<sup>45</sup> Some treatment guidelines advocate performing a lumbar puncture after 2 weeks of induction therapy (before changing to consolidation therapy) to assess CSF culture sterility as a marker of successful induction.<sup>11,15,18,20</sup> Other guidelines—particularly those focused on low-income settings—do not.<sup>10,16</sup>

#### Consolidation and maintenance therapy

There have been no trials of consolidation and maintenance therapy in cryptococcal meningitis within the past two decades. Two early studies established 400 mg daily fluconazole for consolidation therapy.<sup>35,46</sup> With the accumulation of safety data of a 800 mg fluconazole daily dose and evidence of a fluconazole dose-response effect,<sup>36,47</sup> this regimen is the preferred consolidation dose in low-income settings, where suboptimal antifungal regimens are used.<sup>16,18</sup> A gradual rise in median fluconazole minimum inhibitory concentrations (MICs) in cryptococcal isolates collected





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### Panel 5: Ten principles of cryptococcal meningitis management

The key principles in cryptococcal meningitis management are best read in context (see relevant sections in main text). Although most evidence and recommendations are derived from cryptococcal meningitis in people living with HIV, many of these principles are translatable to non-HIV settings.

#### 1) Selectively screen, risk-stratify, and investigate for cryptococcosis

This principle is specific to people with HIV and cryptococcal meningitis (panel 4).

#### 2) Provide best fungicidal induction regimen possible

- (Allt) Liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day for 2 weeks (preferred in high-income settings and strongly recommended in SOT and non-HIV non-SOT settings); or (AI) a single dose of liposomal amphotericin B 10 mg/kg with 14 days of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily (note: only trialled in people living with HIV in low-income settings).
- (CIlu) Consider performing a lumbar puncture at the end of the first or second week of induction therapy to check for CSF sterility before ART commencement.
- (CIlu) Consider prolonging induction therapy if CSF is persistently culture positive at 2 weeks.
- (BIII) In *Cryptococcus gattii* CNS infection occurring in non-HIV patients or CNS cryptococcoma consider extending induction therapy to 4–6 weeks.

#### 3) Monitor for and minimise drug toxic effects

- (Allu) In-hospital care for the first 1–2 weeks is encouraged to manage the major early complications seen with cryptococcal meningitis management.
- (Allu) The use of amphotericin B and liposomal amphotericin B should be accompanied by pre-hydration and aggressive potassium and magnesium replacement therapy.
- (Allu) Frequent (at least every alternate day) complete blood counts, renal function tests, and electrolyte measurements are recommended to assess for therapy-related nephrotoxicity and bone marrow, fluid, and electrolyte changes. Liver function tests at baseline and at least weekly are recommended.
- See appendix pp 16, 30.

#### 4) Manage raised intracranial pressure

- (Allu) Opening pressure should be measured at every lumbar puncture in patients with cryptococcal meningitis.
- (Allt) Acute symptomatic elevation of the intracranial pressure ( $\geq 20$  cm of CSF) should be managed by daily therapeutic lumbar punctures (ie, removal of sufficient CSF, usually around 20–30 mL) to reduce the pressure to 50% of opening pressure or to a normal pressure of  $\leq 20$  cm of CSF (documented as a closing pressure).

- (BIIlu) Perform a scheduled therapeutic lumbar puncture 48–72 h after initial lumbar puncture or 7 days, regardless of initial opening pressure.
- (Allt) Persistent raised symptomatic intracranial pressure despite therapeutic lumbar punctures should be managed by surgical decompression via temporary lumbar drainage, shunting, or ventriculostomy, depending on local expertise and resources.

#### 5) Look for an underlying immunosuppressive state

Exploring for an immunosuppressive state—particularly, but not limited to, HIV infection—is important in the management of cryptococcosis.

- (AIII) Among patients without known predisposition to cryptococcosis, exclusion of an underlying immunodeficiency (including performing HIV serology and CD4 T-cell count) is recommended in all patients with cryptococcosis.
- (BIII) Individuals without a known risk factor for disseminated cryptococcosis, particularly those with a history of other atypical fungal, mycobacterial, or bacterial infections, should be considered for evaluation of an undiagnosed immunodeficiency, preferably in consultation with a clinical immunologist (appendix pp 6, 79).

#### 6) Provide and ensure adherence to consolidation and maintenance therapy

- Consolidation (8 weeks): (AI) Fluconazole 400–800 mg daily. 800 mg is preferred in low-income settings.
- Maintenance (12 months or until immune restoration): (Allt) Fluconazole 200 mg daily.
- (Allu) Check for drug–drug interactions and adjust the dose as necessary.
- (AIII) Close therapeutic drug monitoring of tacrolimus, cyclosporine, and sirolimus levels and dose reduction of these agents are recommended when azoles are co-administered.<sup>73,74</sup>

#### 7) Optimal commencement of ART in people with HIV

This principle is specific to people with HIV and cryptococcal meningitis.

- (DI) Immediate or very early commencement of ART is not recommended.
- If there is inadequate access to antifungal induction therapy, (AI) delay ART for 4–6 weeks.
- If there is adequate access to antifungal induction therapy, (BIIlu) consider further individualisation, taking into consideration resolution of symptoms and signs of cryptococcal meningitis and intracranial pressure (including normalisation of opening pressure), attainment of CSF cryptococcal sterility, successful identification and management of concurrent co-infections and other AIDS-defining illnesses, the patient's readiness for ART, and

(Continues on next page)

(Panel 5 continued from previous page)

local experience of cryptococcal meningitis and cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS) management (usual range is 4–6 weeks).

#### 8) Monitor for clinical relapse and investigate causality

- (Allt) Investigate thoroughly for causality (ie, CNS and non-CNS and infective and non-infective) in cases of apparent clinical relapse. Investigations should include CT or MRI of the brain, lumbar puncture for opening pressure, and CSF analyses including microscopy and culture.
- (Allu) Review adherence to antifungal therapy, ART, immunosuppressants, and other medications and consider drug–drug interactions. Perform therapeutic drug monitoring if applicable. Optimise control of underlying diseases.
- (Dllu) The use of follow-up blood or CSF cryptococcal antigen (including monitoring of titres) for clinical decision making is discouraged.
- (Dllu) Do not escalate antifungal therapy for persistent blood antigenemia, persistently positive CSF cryptococcal antigen, visible cryptococci in CSF (without culture positivity), or abnormal CSF microscopy or biochemistry. These are not necessarily indicators of microbiological failure.

#### 9) Evaluate for drug adherence, drug–drug interactions, and drug resistance

This principle is specific to people with culture-positive (microbiological) persistence or relapse.

- (BIII) Antifungal susceptibility testing should be done concurrently on all initial and relapse isolates (if stored and available). An increase in fluconazole minimum inhibitory concentration of >2 dilutions is concerning for the potential development of drug resistance.
- (BIII) Consider recommencing induction therapy with a more optimal regimen that is guided by antifungal susceptibility testing.

#### 10) Carefully exclude alternative diagnoses before attributing clinical relapse to C-IRIS

- (Allt) For patients with suspected paradoxical C-IRIS, carefully exclude recurrent cryptococcal disease or new infective or non-infective conditions before attributing symptoms and signs to C-IRIS. Perform a brain MRI and lumbar puncture to measure opening pressure and get CSF for microbiological, cellular, and biochemical analyses.
- (Allu) Treatment of C-IRIS should include therapeutic lumbar puncture and symptomatic therapy, such as analgesia, antiemetics, and antiepileptics if appropriate.
- (Allt) Continue antifungal therapy.
- (BIII) High-dose prednisolone or prednisone (usually 0.5–1.0 mg/kg daily) or dexamethasone (usually 0.2–0.3 mg/kg daily), weaned over 4–6 weeks can be considered in those with persistent symptoms who are unresponsive to therapeutic lumbar punctures. Rarely, a second steroid course with taper is needed.
- (DIII) Do not stop ART.

during initial cryptococcal meningitis presentation have been reported in South Africa and Uganda.<sup>48,49</sup> Although this evidence could lend support for a higher consolidation dose of 800 mg daily of fluconazole in these settings, whether this regimen is required across all patient groups and settings is contentious. Widespread fluconazole use could also perpetuate further rises in MICs.

Maintenance therapy with fluconazole 200 mg daily has been shown to be highly effective at preventing relapse, superior to weekly amphotericin B and itraconazole capsules.<sup>50–52</sup> Rarely, triazoles, such as voriconazole,<sup>53–60</sup> posaconazole,<sup>61–63</sup> or isavuconazole,<sup>64,65</sup> are used as alternatives to fluconazole due to concerns of fluconazole resistance, drug toxicity, or drug–drug interactions. Notably, none of the newer triazoles have been formally trialled in cryptococcosis and none are readily available in low-income settings (appendix p 30).

A low incidence of cryptococcal meningitis relapse is observed after a minimum of 1 year of antifungal therapy in people living with HIV established on ART, who are virologically suppressed or have a CD4 count more than 100 cells/mm<sup>3</sup>.<sup>66–72</sup>

A management algorithm is described in figure 2 and key principles are discussed in panel 5. Recommendations

for cryptococcal meningitis treatment in people living with HIV are based on the availability of antifungal drugs. Preferred and alternative strategies are offered in (figure 3 and figure 4A).


#### Adjunctive therapy

In the past decade, trials of adjunctive treatment in HIV-associated cryptococcal meningitis have all been shown to be ineffective, and in some cases harmful. These include high-dose dexamethasone,<sup>75</sup> sertraline,<sup>76,77</sup> and tamoxifen.<sup>78</sup> The debate regarding adjunctive exogenous interferon(IFN)- $\gamma$  is unresolved. IFN- $\gamma$  has been studied in two randomised trials of HIV-associated cryptococcal meningitis, which suggested faster clearance of yeasts in the CSF,<sup>79,80</sup> but further studies are needed. There is no trial evidence supporting its use in non-HIV-associated cryptococcal meningitis (appendix p 65).

#### Cryptococcal meningitis in SOT recipients

Cryptococcosis is the third most common invasive fungal infection in SOT recipients, with an incidence of 4.5–33.8%<sup>26,28,29</sup> and causing considerable mortality.<sup>12</sup> SOT recipients encompass a third of non-HIV-related cryptococcosis in the USA.<sup>81</sup> The majority of cryptococcosis

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Antifungal availability			
	All available	*Liposomal amphotericin B 3–4 mg/kg daily and flucytosine 25 mg/kg four times a day for 2 weeks <b>Allt</b>	
	No liposomal amphotericin B available	†Single dose 10 mg/kg liposomal amphotericin B with 14 days of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily <b>AI</b>	
	No liposomal amphotericin B or amphotericin B lipid complex available	Amphotericin B lipid complex 5 mg/kg daily and flucytosine 25 mg/kg four times a day for 2 weeks <b>BII</b>	
	No flucytosine available	‡Amphotericin B 0.7–1 mg/kg daily and flucytosine 25 mg/kg four times a day for 2 weeks <b>BI</b>	‡Amphotericin B 1 mg/kg daily and flucytosine 25 mg/kg four times a day for one week, followed by fluconazole 1200 mg for one week <b>BI</b>
	No †polyene antimycotic available	Liposomal amphotericin B 3–4 mg/kg daily and §fluconazole 800–1200 mg daily for 2 weeks <b>BIII</b>	Amphotericin B lipid complex 5 mg/kg daily and §fluconazole 800–1200 mg daily for 2 weeks <b>BIII</b>
	Only fluconazole available	§Fluconazole 800–1200 mg daily for 2 weeks <b>CI</b>	†Amphotericin B 0.7–1 mg/kg daily and §fluconazole 800–1200 mg daily for 2 weeks <b>BI</b>

## Grades of recommendation

- A. Strongly recommended  
 B. Moderately recommended  
 C. Marginally recommended

**Figure 3: HIV-cryptococcal meningitis antifungal induction treatment recommendations by antifungal drug availability**

Grading of recommendation and level of evidence in bolded red letters. \*Has not been compared with †. †Has only been trialled in HIV-cryptococcal meningitis. ‡Amphotericin B: 1 mg/kg showed earlier fungicidal activity than 0.7 mg/kg, but some institutions use the low dose due to toxicity concerns. §Fluconazole induction doses of up to 1200 mg daily have been trialled but caution is advised; consider drug–drug interaction and liver toxicity. †Polyene antimycotic includes amphotericin B formulations such as conventional deoxycholate amphotericin B, liposomal amphotericin B, and amphotericin B lipid complex.

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in SOT occurs late (ie, months or years after transplantation) and is due to reactivated disease; however, acute donor-derived infections have been described.<sup>14,82,83</sup>

Anti-rejection drugs vary in their degree of immunosuppression and heart and small bowel transplant recipients are at the highest cryptococcal meningitis risk.<sup>84</sup> CNS and pulmonary cryptococcosis dominate but unusual manifestations, including cutaneous disease<sup>85,86</sup> and pericarditis,<sup>87</sup> have been reported. Notably, blood cryptococcal antigen can be negative in SOT recipients with cryptococcosis, particularly those with single pulmonary nodules or in lung transplant recipients.<sup>88</sup>

There are no randomised treatment trials targeted specifically at SOT recipients; hence, recommendations are extrapolated from evidence in people living with HIV. The use of lipid-formulations in SOT recipients with CNS cryptococcosis was independently associated with reduced mortality compared with amphotericin B.<sup>89</sup> The AMBITION-cm regimen has not been studied in non-HIV patients, and the evidence for high dose fluconazole (with the ensuing potential toxicity and drug–drug interactions) in this group is absent. A precipitous reduction in dosing of immunosuppressants, particularly calcineurin inhibitors, can lead to C-IRIS.<sup>90</sup> Figure 4B contains recommendations for treatment in SOT recipients (appendix p 62).

### Cryptococcal meningitis in people without HIV or SOT

The group of people without HIV or SOT is heterogeneous, ranging from apparently healthy people to those with haematological malignancies or liver cirrhosis. There is

no single therapeutic regimen or duration that meets all patients' needs, but the therapeutic principles mirror cryptococcal meningitis treatment in high-income settings, with liposomal amphotericin B 3–4 mg/kg daily and flucytosine 25 mg/kg four times a day as induction therapy. Induction therapy can be extended in those with persistently positive CSF cultures or persistent symptoms at 2 weeks. In 2022, the combination of liposomal amphotericin B and flucytosine was shown to have a low acute mortality of 6% in a nationwide observational study of non-HIV-associated cryptococcal meningitis in Japan.<sup>91</sup> Figure 4B contains recommendations for treatment in people without HIV or SOT (appendix pp 18, 62).

### Pulmonary cryptococcosis

There are no randomised treatment studies in pulmonary cryptococcosis. Case series and clinical knowledge suggest that for patients with cryptococcaemia and evidence of CNS involvement, those with blood cryptococcal antigen titres more than 1:512 by latex agglutination (or ten-fold higher by lateral flow assay),<sup>92</sup> or severe pulmonary disease should be treated as cryptococcal meningitis.<sup>33,35,93,94</sup> Patients with mild isolated pulmonary disease without cryptococcoma have been successfully treated with fluconazole monotherapy of

**Figure 4: Antifungal treatment recommendations for cryptococcal meningitis**

(A) Recommendations for people with HIV. (B) Recommendations for SOT recipients and patients without HIV or SOT. SOT=solid organ transplant. CSF=cerebrospinal fluid. TDM=therapeutic drug monitoring.



**A People with HIV****First-line therapies****Induction (2 weeks)**

**(AIIIt)** Liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day (preferred in high-income settings); or  
**(AI)** Single dose liposomal amphotericin B 10 mg/kg and 14 days of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily (recommended in low-income settings)

**Consolidation (8 weeks)**

**(AI)** Fluconazole 400–800 mg daily (800 mg preferred in low-income settings)

**Maintenance (12 months or until immune restoration)**

**(AIIIt)** Fluconazole 200 mg daily

**Alternative therapies****If liposomal amphotericin B is not available:**

**(BIIIt)** Amphotericin B lipid complex 5 mg/kg daily plus flucytosine 25 mg/kg four times a day

**(BIII)** Voriconazole 200 mg twice a day (with TDM)

**(BIII)** Posaconazole 300 mg daily (with TDM)

**If liposomal amphotericin B and amphotericin B lipid complex are not available:**

**(BI)** Amphotericin B 0.7–1.0 mg/kg daily plus flucytosine 25 mg/kg four times a day; or  
**(BI)** Amphotericin B 1 mg/kg daily and 5-flucytosine 25 mg/kg four times a day for 1 week, followed by fluconazole 1200 mg daily for 1 week

**(BIII)** Isavuconazole 200 mg daily

**(CIIt)** Itraconazole 200 mg twice a day (with TDM)

**If flucytosine is not available:**

**(BIII)** Liposomal amphotericin B 3–4 mg/kg daily plus fluconazole 800–1200 mg daily;  
**(BIII)** Amphotericin B lipid complex 5 mg/kg daily plus fluconazole 800–1200 mg daily; or  
**(BI)** Amphotericin B 0.7–1 mg/kg daily plus fluconazole 800–1200 mg daily

**Comments:**

- **(Allu)** Opening pressure should be measured at every lumbar puncture in patients with cryptococcal meningitis
- **(Allu)** The use of amphotericin B and liposomal amphotericin B should be accompanied by pre-hydration and aggressive potassium and magnesium replacement therapy
- **(Allu)** In-hospital care for the first 1–2 weeks is encouraged to manage the early complications of cryptococcal meningitis therapy
- **(BIII)** Monitoring of flucytosine drug concentration is recommended, where available and if timely; particularly with renal dysfunction
- **(Allu)** Check for drug–drug interactions and adjust doses as necessary
- **(CIlu)** Consider performing a lumbar puncture at the end of the first or second week of induction therapy to check for CSF sterility before antiretroviral therapy (ART) commencement
- **(CIlu)** Consider prolonging induction therapy if CSF is persistently culture positive at 2 weeks
- **(CIIt)** Adjunctive recombinant interferon- $\gamma$  might be considered for persistently positive CSF yeast cultures in people with HIV-associated cryptococcal meningitis who have evidence of poor inflammatory responses or persistently positive cryptococcal CSF culture after prolonged antifungal therapy
- **(DI)** The routine use of high-dose dexamethasone in cryptococcal meningitis is not recommended
- **(CIIt)** A short course of dexamethasone can be considered for specific indications such as symptomatic space-occupying lesions in the CNS with surrounding oedema or mass effect and cerebral vasculitis
- **(BIlu)** Cease maintenance therapy after 12 months of antifungal therapy in patients aviraemic on ART with a CD4 count more than 100 cells per mm<sup>3</sup>
- **(AIII)** Restart maintenance therapy if CD4 count drops to less than 100 cells per mm<sup>3</sup>

**B SOT recipients and people without HIV or SOT****First-line therapies****Induction (minimum 2 weeks)**

**(AIIIt)** Liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day

**Consolidation (8 weeks)**

**(AIIIt)** Fluconazole 400–800 mg daily

**Maintenance (12 months)**

**(AIIIt)** Fluconazole 200 mg daily

**Alternative therapies****If liposomal amphotericin B is not available:**

**(BIIIt)** Amphotericin B lipid complex 5 mg/kg daily plus flucytosine 25 mg/kg four times a day

**(BIII)** Voriconazole 200 mg twice a day (with TDM)

**(BIII)** Posaconazole 300 mg daily (with TDM)

**If liposomal amphotericin B and amphotericin B lipid complex are not available:**

**(BIIIt)** Amphotericin B 0.7–1.0 mg/kg daily plus flucytosine 25 mg/kg four times a day

**(BIII)** Isavuconazole 200 mg daily

**(CIIt)** Itraconazole 200 mg twice a day (with TDM)

**If amphotericin B-based therapies are not able to be used:**

**(CIIt)** flucytosine 25 mg/kg four times a day plus fluconazole 800–1200 mg daily

**Comments:**

- Recommendations in HIV patient population are also applicable
- **(AIII)** Induction therapy with liposomal amphotericin B and flucytosine should be considered for any disseminated disease or isolation from a sterile site (even in the absence of CNS manifestations)
- **(AIII)** Close monitoring of tacrolimus, cyclosporine, and sirolimus concentrations (TDM) and dose reduction of these agents are recommended when azoles are co-administered<sup>73,74</sup>
- **(BIII)** Immunosuppressant doses need to be carefully adjusted to allow effective killing of yeasts but should be reduced slowly to avoid precipitating cryptococcosis-associated immune reconstitution inflammatory syndrome; consider a sequential or stepwise reduction of immunosuppressants with careful lowering of corticosteroids early and eliminating mycophenolate before considering reduction of the calcineurin inhibitors because of their direct anticytotoxic activity
- **(CIIt)** In a patient treated for cryptococcosis, retransplantation or a new organ transplant can be considered, provided viable yeasts have been cleared from CSF and the patient is asymptomatic after receiving 12 months of anticytotoxic treatment

**Grades of recommendation**

- ☐ A. Strongly recommended  
☐ B. Moderately recommended  
☐ C. Marginally recommended

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See Online for appendix

#### Panel 6: Recommendations for pulmonary cryptococcosis

- Stratify treatment by disease severity and presence of pulmonary cryptococcoma (appendix pp 22, 67, 84)
- Isolated pulmonary cryptococcosis in immunocompetent or immunocompromised host:
  - (Allu) Severe disease: as for CNS disease
  - (Bllu) Mild disease: fluconazole 400 mg daily for 6–12 months (range guided by symptom resolution)
- Pulmonary cryptococcosis with CNS manifestations or other evidence of dissemination (eg, cryptococcaemia or skin lesions)
  - (Allt) as for CNS disease
- (Alll) If the presence of *Cryptococcus* spp in respiratory specimen is deemed as airway colonisation after careful evaluation and no treatment is elected, regular follow-up is recommended, especially in the setting of future immunosuppression
- Pulmonary cryptococcoma (see cryptococcoma section)

#### Panel 7: Recommendations for non-pulmonary non-CNS disease

- (Allu) The recommendation for cryptococcaemia is to treat the same as for CNS disease
- (Alll) The recommendation for primary cutaneous (skin) cryptococcosis, attributed to direct inoculation without evidence of dissemination, is fluconazole 400 mg daily for 3–6 months or until healed
- (Bllu) For all other non-CNS non-pulmonary disseminated disease treat the same as CNS disease
- (Bllu) Cryptococcal eye disease should be managed in collaboration with an ophthalmologist

400 mg daily.<sup>93,95,96</sup> Some clinicians consider watchful-waiting and elect not to treat asymptomatic immunocompetent people who incidentally culture any *Cryptococcus* spp in their sputum and have no radiological features of pulmonary cryptococcosis, as they consider this presentation to be airway colonisation.<sup>97</sup> Criteria for distinguishing colonisation from infection is uncertain (panel 6; appendix pp 22, 67).

#### Non-pulmonary non-CNS disease

Cryptococcosis can affect any organ following haematogenous dissemination. Clinical presentation of non-CNS non-pulmonary disease without fungaemia is rare, but possible. The absence of documented fungaemia does not exclude dissemination. Barring direct inoculation into the skin following trauma, extra-pulmonary disease is by definition disseminated disease and generally requires consideration for aggressive induction therapy. There are no clinical treatment trials for non-pulmonary non-CNS cryptococcosis.

Importantly, visual changes noted in cryptococcal meningitis are frequently related to raised intracranial

pressure and do not necessarily indicate direct eye involvement. Ocular cryptococcosis can occur<sup>98,99</sup> but is unusual and requires formal ophthalmological documentation and management. Isolated skeletal osteomyelitis is rare and often requires a combined surgical and medical approach.<sup>100–102</sup> Skin lesions might be polymorphic (panel 7; appendix p 67).

#### Specific management issues

##### Raised intracranial pressure

Increased intracranial pressure has been associated with a high burden of cryptococci, leading to both acute and chronic symptoms and signs (eg, visual and hearing loss) and decreased short-term survival. Clinical experience has shown that CSF outflow obstruction can be improved by removal of CSF; observational studies suggested that scheduled therapeutic lumbar punctures result in substantial improvement in survival, regardless of opening pressure.<sup>103,104</sup> For prolonged control of acute increased intracranial pressure, use of lumbar drains in cases without hydrocephaly or ventriculostomies in cases with hydrocephaly might be required.<sup>105–107</sup> Medical therapies including acetazolamide, mannitol, and corticosteroids can be detrimental (panel 8; appendix p 79).<sup>108,109</sup>

##### Timing of ART commencement

The optimal time to commence ART for HIV infection during cryptococcosis is controversial. Four randomised trials<sup>3,110–112</sup> to find out the optimal timing of ART initiation in HIV-cryptococcal meningitis co-infection have been done in low-income settings, using induction regimens that are not currently preferred, including fluconazole (800 mg daily) monotherapy,<sup>110</sup> amphotericin B 0.7 mg/kg daily,<sup>111</sup> and amphotericin B 0.7–1 mg/kg daily and fluconazole 800 mg daily for 2 weeks. These data seem to suggest that initiating ART within 2 weeks of cryptococcal meningitis presentation is too early in the setting of suboptimal antifungal therapy, and that delaying ART initiation for 4–6 weeks reduces the incidence of C-IRIS and death. CSF sterility before ART commencement might be another factor.<sup>45</sup> A retrospective analysis of combined cohorts in high-income settings did not show higher mortality in those receiving early ART in the first two weeks of antifungal therapy compared with those with delayed therapy.<sup>113</sup> Early ART in high-income settings will need careful justification and close monitoring; further randomised studies might be helpful.<sup>114</sup>

There are no studies for timing ART initiation in other forms of cryptococcosis, those with cryptococcal antigenemia, or those recommencing ART after a period of interruption. Early concerns that potent integrase inhibitors pose an increased risk of C-IRIS have been disproven.<sup>115</sup> Whether those presenting with cryptococcal meningitis within 2 weeks of starting ART require withholding of ART is uncertain (panel 9; appendix p 70).<sup>116–118</sup>

**Panel 8: Recommendations for raised intracranial pressure**

- (Allu) Opening pressure should be measured at every lumbar puncture in patients with cryptococcal meningitis
- (AIII) A brain CT should be done (if CNS imaging not already done) to exclude CNS outflow obstruction
- (Allt) Acute symptomatic elevation of the intracranial pressure ( $\geq 20$  cm of CSF) should be managed by daily therapeutic lumbar punctures (ie, removal of sufficient CSF, usually around 20–30 mL), to reduce the pressure to 50% of opening pressure or to a normal pressure of  $\leq 20$  cm of CSF (documented as a closing pressure)
- (BIIlu) Perform a scheduled therapeutic lumbar puncture 48–72 h after initial lumbar puncture or 7 days, regardless of initial opening pressure
- (Allt) Persistent raised symptomatic intracranial pressure, despite therapeutic lumbar punctures, should be managed by surgical decompression via temporary lumbar drainage, shunting, or ventriculostomy, depending on local expertise and resources
- (BIII) Consider ventriculoperitoneal (preferential) and lumboperitoneal shunts (alternative) to control both acute and chronic hydrocephalus if temporary measures are not successful. Ideally, insert shunts after institution of effective antifungal therapy

**Resistance to antifungals**

Developing secondary resistance to flucytosine is common when given as monotherapy, necessitating its use with a partner drug in cryptococcosis. Acquired resistance to polyenes, such as amphotericin B, is rare, but the emergence of fluconazole resistance is concerning.<sup>48,49,119</sup> Fluconazole monotherapy as induction therapy has been associated with secondary resistance.<sup>120–123</sup>

There are no clinical MIC breakpoints for fluconazole against *Cryptococcus* spp and insufficient data to suggest that high MICs imply worse outcomes. Interpretation of epidemiological cutoff values with the Clinical and Laboratory Standards Institute (CLSI) method for fluconazole requires accurate species identification. The epidemiological cutoff values is 8 ug/mL for *C. neoformans* VNI, 16 ug/mL for *C. gattii* VGI, and 32 ug/mL for *Cryptococcus deuterogattii* VGII.<sup>124</sup> In principle, a higher than two-fold increase in MIC during treatment could suggest development of resistance and the need for closer clinical monitoring. There are no European Committee on Antimicrobial Susceptibility Testing (EUCAST) epidemiological cutoff values available for fluconazole (panel 10; appendix p 72).

**Cryptococcal persistence, clinical relapse, and culture-positive (microbiological) relapse**

Distinguishing clinical relapse from persistent cryptococcal infection is challenging. Clinical relapse can be due to a microbiological relapse, C-IRIS, raised intracranial pressure (whether related to C-IRIS or not), or other

**Panel 9: Recommendations for the timing of ART commencement**

- (DI) Immediate or very early commencement of ART is not recommended.
- (AI) If suboptimal antifungal induction therapy is used, delay ART for 4–6 weeks.
- (BIIlu) If optimal antifungal induction therapy was used, consider further individualisation, taking into consideration resolution of symptoms and signs of cryptococcal meningitis, intracranial pressure (including normalisation of opening pressure), attainment of CSF cryptococcal sterility, successful identification, management of concurrent co-infections and other AIDS-defining illnesses, the patient's readiness for ART, and local experience of cryptococcal meningitis and C-IRIS management (usual range is 4–6 weeks).
- (CIIt) If possible, ensure CSF is cryptococcal culture negative before ART commencement.
- (BIII) For people who have had ART who develop cryptococcal meningitis and might need to switch to second-line ART or recommence ART, a delay of 4–6 weeks is recommended.
- (CIII) Pending further studies, consider withholding ART and restarting at 4–6 weeks in those presenting with cryptococcal meningitis within 2 weeks of starting ART.
- (BIII) Patients with isolated pulmonary cryptococcosis or those with asymptomatic cryptococcal antigenemia can commence ART earlier (eg, at 2 weeks).

**Panel 10: Recommendations for antifungal resistance**

For those with fluconazole resistance or emerging fluconazole resistance:

- (BIII) Consider a long (eg, 4 weeks) course of induction treatment with amphotericin B (1 mg/kg daily) or high dose of liposomal amphotericin B (3–6 mg/kg daily) together with flucytosine
- (BIII) Consider amphotericin B 1 mg/kg weekly or liposomal amphotericin B 3–6 mg/kg weekly as consolidation or maintenance therapy. Consider daily voriconazole, posaconazole, isavuconazole, or itraconazole for isolates without evidence of pan-azole resistance, as guided by antifungal susceptibility testing
- (CIII) If amphotericin B or liposomal amphotericin B are not available, adding flucytosine to high-dose fluconazole (1200 mg daily) could be considered

infective and non-infective (CNS and non-CNS) causes (figure 2). Cryptococcal antigen persists in the CSF and blood, thus it has little clinical utility in distinguishing clinical responders from non-responders.<sup>125</sup> Most cases of culture-positive (microbiological) relapse occur early and result from inadequate or suboptimal induction therapy or early discontinuation of consolidation or maintenance therapy (figure 2; panel 11; appendix p 74).

#### Panel 11: Recommendations for cryptococcal persistence, clinical relapse, and culture-positive (microbiological) relapse

- (Allt) Think broadly and investigate thoroughly for causality (CNS or non-CNS and infective or non-infective) in cases of apparent clinical relapse; investigations should include brain CT or MRI, lumbar puncture for opening pressure, and CSF analyses, including microscopy and culture
- (Allu) Review adherence to antifungal therapy, ART, immunosuppressants, and other medications and consider drug–drug interactions; perform therapeutic drug monitoring if applicable. Optimise control of underlying diseases
- (CIII) Consider escalating antifungal therapy while awaiting CSF results (and de-escalate if culture-negative)
- (DIIu) The use of follow-up blood or CSF cryptococcal antigen (including monitoring of titres) for clinical decision making is discouraged
- (DIIu) Do not escalate antifungal therapy for persistent blood antigenemia, persistently positive CSF cryptococcal antigen, visible cryptococci in CSF (without culture positivity), or abnormal CSF microscopy or biochemistry; these are not necessarily indicators of microbiological failure

For culture-positive (microbiological) persistent or relapsed infection (figure 1):

- (BIII) Antifungal susceptibility testing should be done concurrently on all initial and relapse isolates (if stored and available); an increase in fluconazole MIC of more than two dilutions is considered concerning for the potential development of drug resistance
- (BIII) Consider reinduction with a more optimal regimen (guided by antifungal susceptibility testing)

#### Panel 12: Recommendations for C-IRIS

- (Allt) For patients with suspected paradoxical C-IRIS, carefully exclude recurrent cryptococcal disease or new infective or non-infective conditions before attributing symptoms and signs to C-IRIS; perform a brain MRI and lumbar puncture to measure opening pressure and get CSF for microbiological and biochemical analyses
- (Allu) Treatment of C-IRIS should include therapeutic lumbar puncture and symptomatic therapy, such as analgesia, antiemetics, and antiepileptics, if appropriate
- (AIII) Continue antifungal therapy
- (BIII) High-dose prednisolone or prednisone (usually 0.5–1.0 mg/kg daily) or dexamethasone (usually 0.2–0.3 mg/kg daily), weaned over 4–6 weeks, can be considered in those with persistent symptoms who are unresponsive to therapeutic lumbar punctures; rarely a second steroid course with taper is needed
- (DIII) Do not stop ART
- (BIII) Cases of steroid-refractory or recurrent C-IRIS should be discussed with experts in the field
- (BIIu) Steroids could be considered for PIIRS

#### Panel 13: Recommendations for *C gattii*

In *C gattii* CNS disease:

- (AIII) Treat the same as *C neoformans* CNS infection
- (BIII) In non-HIV patients, consider extending induction therapy to 4–6 weeks
- (AIII) Early CSF shunting is indicated for obstructive chronic hydrocephalus

Treatment of *C gattii* lung disease is summarised in the appendix (p 17).

#### C-IRIS

C-IRIS has been described in people with HIV usually between 2 weeks and 3 months after commencement of ART. Patients develop exaggerated symptoms and signs or atypical inflammation, reminiscent of a paradoxical recurrence,<sup>126,127</sup> but C-IRIS can also occur in the setting of immune recovery or withdrawal of immunosuppressants. It has also been observed in seemingly immunocompetent individuals, including in *C gattii* infections, as a post-infectious inflammatory immune response syndrome (PIIRS).<sup>90,128</sup> There is no diagnostic biomarker for C-IRIS. It is diagnosed by diagnosis of exclusion (figure 2).

There have been no therapeutic trials in C-IRIS. Management strategies include therapeutic lumbar puncture and symptomatic therapies. In severe C-IRIS, corticosteroids are commonly used to dampen inflammation, although their efficacy has not been rigorously examined in clinical trials. In steroid-refractory C-IRIS, there are case reports on the use of tumour necrosis factor- $\alpha$  blockers, such as adalimumab<sup>129–132</sup> or thalidomide,<sup>133–135</sup> with mixed success. Corticosteroids can also be beneficial in PIIRS (panel 12; appendix p 76).<sup>136</sup>

#### *C gattii*

About 50–70% of *C gattii* infections occur in putatively immunocompetent hosts,<sup>137–139</sup> compared with 2–30% in people with HIV.<sup>140–144</sup> Autoantibodies to granulocyte-macrophage colony-stimulating factor and idiopathic CD4 lymphopenia are reported risk factors.<sup>137,145–147</sup> Notably, not all commercial lateral flow assays are able to detect *C gattii* disease.<sup>148</sup> Antifungal agents used for treatment are the same as for *C neoformans*.<sup>30,32,141</sup> However, 4–6 weeks of induction therapy might be required in some cases of non-HIV-associated meningitis with *C gattii* (panel 13; appendix p 81).<sup>149</sup>

#### Cryptococcomas

Cryptococcomas occur predominantly in the lungs and brain and are more frequent in *C gattii* infection.<sup>140,150</sup> CNS cryptococcomas can manifest as neurological deficits or raised intracranial pressure,<sup>140</sup> which requires urgent management. Corticosteroids and surgical resection can be of value.<sup>149,151,152</sup> Radiological lesions can persist indefinitely despite clinical and microbiological cure (panel 14; appendix p 84).<sup>32,153</sup> Recommendations for cryptococcomas are in.

#### Non-*C neoformans* and non-*C gattii* strains of cryptococcus

There are individual case reports and small case series of non-*C neoformans* and non-*C gattii* cryptococcus infections, predominantly in immunosuppressed patients. *Papiliotrema laurentii* (previously *Cryptococcus laurentii*)<sup>154</sup> and *Naganishia albida* (previously *Cryptococcus albidus*)<sup>155</sup> account for about 80% of the invasive infections in this group and usually involve the skin, lungs, bloodstream, or CNS.<sup>156</sup> Colonisation, especially of the skin, respiratory, and



**Panel 14: Recommendations for cryptococcomas**

- (AIII) Perform a biopsy or aspirate to exclude a secondary pathogen or an underlying tumour in non-responding cryptococcomas (particularly in immunosuppressed patients)
- (BIII) Consider surgical resection for accessible brain lesions more than 3 cm, lesions at risk of compressing critical structures, or large lesions not responding to therapy
- (DIII) During follow-up, do not prolong or escalate therapy for persistent radiological findings in the absence of new or worsening symptoms or signs

For CNS cryptococcoma:

- (BIII) Consider prolonging CNS antifungal induction therapy to 4–6 weeks
- (BIII) Consider corticosteroids for large cryptococcomas with surrounding mass effect or if neurological symptoms and cerebral imaging signs worsen despite a good microbiological response

The appendix (pp 22, 84) summarises treatment of lung cryptococcoma.

gastrointestinal tracts must be distinguished from true disease. In some cases, the laboratory might misidentify another yeast as *P. laurentii* or *N. albida* on the basis of non-definitive commercial identification methods.<sup>157</sup> Elevated MICs against flucytosine, fluconazole, and other azoles for some isolates have been documented but are of uncertain clinical significance (panel 15; appendix p 85).<sup>158,159</sup>

**Pregnancy**

The majority of cases of cryptococcosis in pregnancy occur in the third trimester or postpartum.<sup>160,161</sup> Maternal mortality from disseminated cryptococcosis is approximately 25%, and less than 50% of women carry their pregnancy to term.<sup>161</sup> Extensive clinical experience suggests that amphotericin B and liposomal amphotericin B are safe during pregnancy (Category B drug), and thus are the cornerstone of treatment.<sup>161,162</sup> Flucytosine is rated by the USA Food and Drug Administration as a Category C drug because of its direct effects on RNA and DNA metabolism. Fluconazole is a Category D drug due to its increased risk of musculoskeletal malformations, tetralogy of Fallot, and spontaneous abortions (panel 16; appendix p 86).<sup>163–167</sup>

**Paediatrics**

There is a clear need for paediatric-specific studies in cryptococcosis. CNS disease seems to predominate in paediatrics, but non-CNS disease is probably under-reported.<sup>168–174</sup> Clinical efficacy trials and studies to validate diagnostic tests and therapies for cryptococcosis in children are scarce. Recommendations are extrapolated from studies in adult populations. Dosing of antifungal agents needs particular attention for the paediatric patient (panel 17; appendix p 87).

**Panel 15: Recommendations for non-*C. neoformans* and non-*C. gattii* strains of cryptococcus**

- (AIII) As non-*C. neoformans* and non-*C. gattii* *Cryptococcus* spp are rarely pathogenic, careful assessment of the laboratory identification and clinical context is required to ascertain clinical significance
- (CIII) For CNS or disseminated disease, treat the same as *C. neoformans* CNS infection

**Panel 16: Recommendations for cryptococcosis in pregnancy**

- (AIII) Use liposomal amphotericin B or amphotericin B in induction, consolidation, and maintenance therapy and for the treatment of isolated cryptococcal antigenemia
- (DII) Avoid the use of flucytosine and fluconazole in pregnancy, particularly in the first trimester; their use in the second and third trimester requires careful individualised risk–benefit assessment
- (BIII) Fluconazole can be used after delivery despite its excretion into breastmilk
- (AIII) Apply clinical judgement when considering initiation of antifungal therapy and duration of therapy, factoring in trimester of pregnancy and severity of illness
- (CIII) For asymptomatic cryptococcal antigen in pregnancy, consider intermittent polyene therapy, especially in the first trimester

**Panel 17: Recommendations for paediatric cryptococcosis**

For the treatment of CNS or disseminated disease:

- (AII) Induction: amphotericin B 1 mg/kg daily or liposomal amphotericin B 3–4 mg/kg daily plus flucytosine (100–150 mg/kg daily in 4 divided doses) for 2 weeks
- (AII) Consolidation: fluconazole 12 mg/kg (maximum 800 mg) daily for 8 weeks
- Maintenance: fluconazole 6 mg/kg daily (maximum 800 mg) for 6–12 months
  - (AII) Should be provided for people who live with HIV and are immunocompromised
  - (BII) Can be provided for people who are immunocompetent
- (AIII) For the treatment of severe isolated pulmonary diseases: treat the same as CNS disease
- (AIII) Treatment of mild isolated pulmonary disease: fluconazole 12 mg/kg daily (maximum 800 mg) for 6–12 months
- (AIII) Screening is recommended for children older than 10 years living with HIV in high disease prevalence areas

**Conclusions**

Cryptococcosis and its management is complex and challenging. Adherence to clinical practice guidelines can improve outcomes.<sup>44,175</sup> Although there has been substantial development of evidence from randomised controlled trials over the past 20 years, there are considerable unmet needs (appendix pp 23, 91). Addressing these challenges is particularly crucial in low-income settings, where the burden of disease is high and access to antifungal therapy is inadequate. Equally, more clinical research needs to be done in high-income settings, where host risk profiles are changing and an increasing array of presentations of cryptococcosis are being recognised, necessitating more nuanced and individualised treatment plans.

**Contributors**

JRP guided the structure, content, and development of the guideline. OAC contributed to the conceptual planning, management, and supervision of the project. CCC and JRP coordinated the work of the

authors. TAB, CCC, MC, FH, TSH, OL, RO, JRP, TCS, AS, and AW contributed to the coordination of data collection, data visualisation, and participants' contributions and communication and wrote the first manuscript draft. All authors contributed towards the literature review, collection and preparation of data, creation of tabled recommendations, and critical review of the manuscript.

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AA reports grants from the Agence Nationale de la Recherche; serving as a consultant to Gilead Sciences; receiving speaking honoraria from Gilead Sciences and PR Edition; travel support from Gilead Sciences and Pfizer; and patents with the Institut Pasteur. J-WA reports grants or contracts from WHO (fungal priority pathogens list) and receipt of equipment and materials from the Westmead Hospital Foundation. JB reports support from the Australian National Health and Medical Research Council and receipt of honoraria from Gilead. TAB reports a personal research fellowship from Gilead Sciences; investigator-led research grant from Pfizer; lecture honoraria and participation in advisory boards for Gilead Sciences, Mundipharma, and Pfizer; and participation in the Trial Steering Committee for a phase 2 trial of inhaled opelconazole (Pulmocide). FC reports speaker honoraria from, and being part of, an advisory board for Pfizer and United Medical. CCC reports receipt of an Early Career Fellowship from the Australian National Health and Medical Research Foundation, receipt of a speaker travel support for IDweek 2024, being a principal investigator in an early phase clinical trial unit, and was a recipient of the Australian National Health and Medical Research Council Early Career Fellowship (APP 1092160). MC reports grants from Cidara, F2G, Pfizer, and Janssen; receipt of honoraria from Pfizer MSD and Gilead; and travel support from Pfizer. SCC reports untied educational grants from MSD Australia and F2G and is on the antifungal advisory boards of MSD Australia, Gilead Sciences, and F2G. OAC reports grants or contracts from BMBF, Cidara, EU-DG RTD (101037867), F2G, Gilead, MedPace, MSD, Mundipharma, Octapharma, Pfizer, and Scynexis; consulting fees from AbbVie, AiCuris, Biocon, Cidara, Gilead, IQVIA, Janssen, Matinas, MedPace, Menarini, Moderna, Molecular Partners, MSG-ERC, Noxxon, Octapharma, Pfizer, PSI, Scynexis, and Seres; honoraria for lectures from Abbott, AbbVie, Al-Jazeera Pharmaceuticals, Hikma, Gilead, Grupo Biotoscana/United Medical/Knight, MedScape, MedUpdate, Merck/MSD, Noscendo, Pfizer, Shionogi, and streamedup!; payment for expert testimony from Cidara; participation on a data safety monitoring board or advisory board from Boston Strategic Partners, Cidara, IQVIA, Janssen, MedPace, PSI, Pulmocide, Shionogi, and The Prime Meridian Group; a patent at the German Patent and Trade Mark Office (DE 10 2021 113 007-7); stocks from CoRe Consulting and EasyRadiology; other interests from Wiley; support from the German Federal Ministry of Research and Education; and funding by the Deutsche Forschungsgemeinschaft under Germany's Excellence Strategy (Cologne Cluster of Excellence on Cellular Stress Responses in Aging-associated Diseases, EXC 2030—390661388). J-PG reports speaker honoraria from Gilead, Mundipharma, and Pfizer. NPG reports grants from National Institutes of Health (USA), National Institute of Health and Care Research (UK), Medical Research Council (MRC; UK), Centers for Disease Control and Prevention (CDC; USA), and National Health Laboratory Service Research Trust (South Africa); participation in the ACACIA trial as part of the data safety monitoring board, project committee of DREAMM, project advisory committee for 5FC Crypto, and leadership roles in the Federation of Infectious Diseases Societies of Southern Africa. AHG reports grants from Gilead Sciences; personal fees from Amplyx, Astellas, Basilea, F2G, Gilead Sciences, Merck Sharp & Dohme, Mundipharma, Pfizer, and Scynexis; speaker honoraria from Gilead Sciences and MSD; and participation in an advisory board for Astellas, Mundipharma, Partner Therapeutics, and Pfizer. FH reports grants from Health Holland and European Society for Clinical Microbiology and Infectious Diseases; leadership roles as treasurer of the Netherlands Society for Medical Mycology, Chair of the Division Microbial Genomics of the Royal Netherlands Society for Microbiology, Vice-President International Society for Human and Animal Mycology (ISHAM); and receipt of evaluation kits from Bruker and Pathonostics. TSH reports receipt of an investigator award from Gilead Sciences, honoraria from Pfizer and Gilead Sciences, and participation in a data safety monitoring board or advisory board for Viamet and F2G.

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