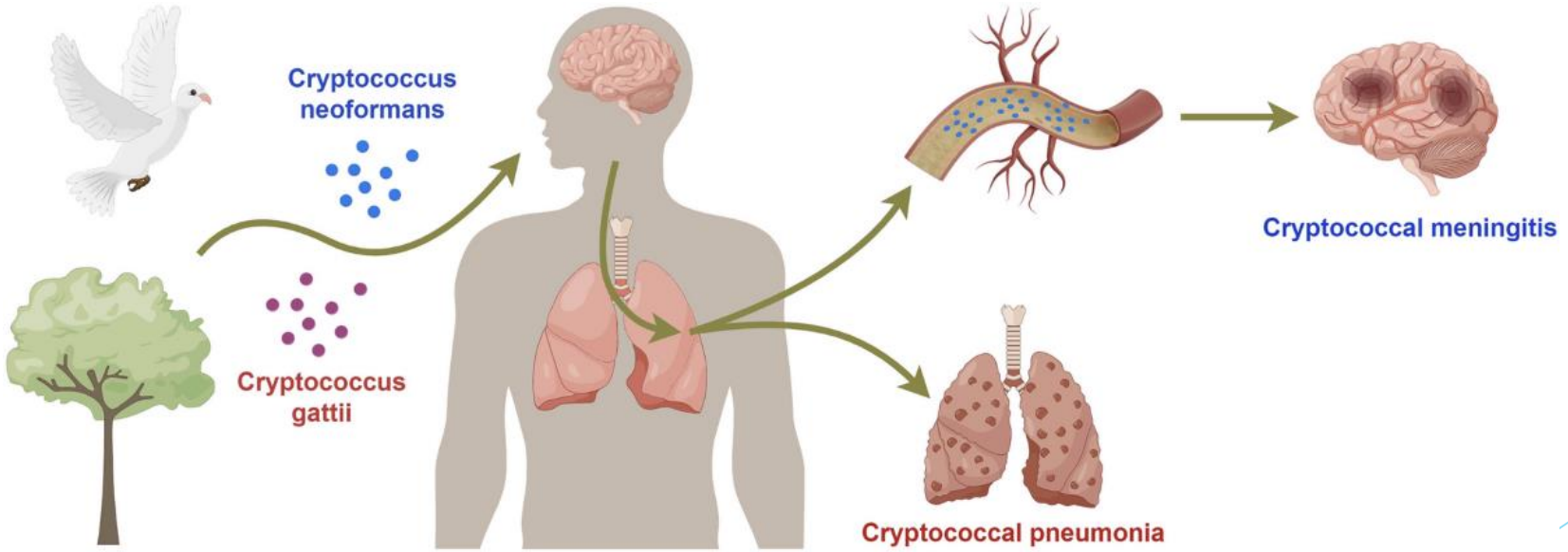
Cryptococcal meningoencephalitis in solid organ transplant



Cryptococcal meningitis (CM) is one of the leading causes of meningitis in regions heavily impacted by HIV, and it is the primary cause of HIV-related deaths in Africa and globally.

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

The inhalation of Cryptococcus gattii and C. neoformans yeasts can cause a wide range of symptoms, from asymptomatic infection to CNS involvement, during an incubation period of one to two weeks in HIV-positive patients and 6 to 12 weeks in other patients.

Cryptococcosis in SOT recipients

Cryptococcosis is the third most common invasive fungal infection in SOT recipients, with an incidence of 4·5–33·8% and causing considerable mortality.

Cryptococcosis is typically a late-occurring infection, with the median time to onset ranging from 16 to 21 months post-transplantation.

The time to onset is typically earlier (<12 months) for liver and lung compared to kidney transplant recipients.

Anti-rejection drugs vary in their degree of immunosuppression and heart and small bowel transplant recipients are at the highest cryptococcal meningitis risk.

CNS and pulmonary cryptococcosis dominate but unusual manifestations, including cutaneous disease and pericarditis, 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.

Fulminant meningoencephalitis occurs commonly in the setting of advanced immunosuppression and is uniformly fatal without antifungal therapy.

Skin involvement can appear as acneiform lesions, purpura, vesicles, nodules, abscesses, ulcers, granulomas, pustules, draining sinuses, and cellulitis.

Case Presentation

A 39-year-old man from Isfahan Iran, employed in the hospital service department, underwent kidney transplantation seven years ago. he developed fever, lethargy, headaches, and nausea. He was on immunosuppressive drugs (prograf and certican).

After one hour of hospitalization, the patient had a generalized seizure with decrease in the level of consciousness. diazepam was administered as needed. and due to loss of consciousness, he was intubated and transferred to the ICU.

During examination, the patient was unconsciousness and light-reactive pupils.

Which diagnostic methods suggest for a patient with suspected cryptococcosis?

Recommendations for yeast causing cryptococcosis and diagnostic methods

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:

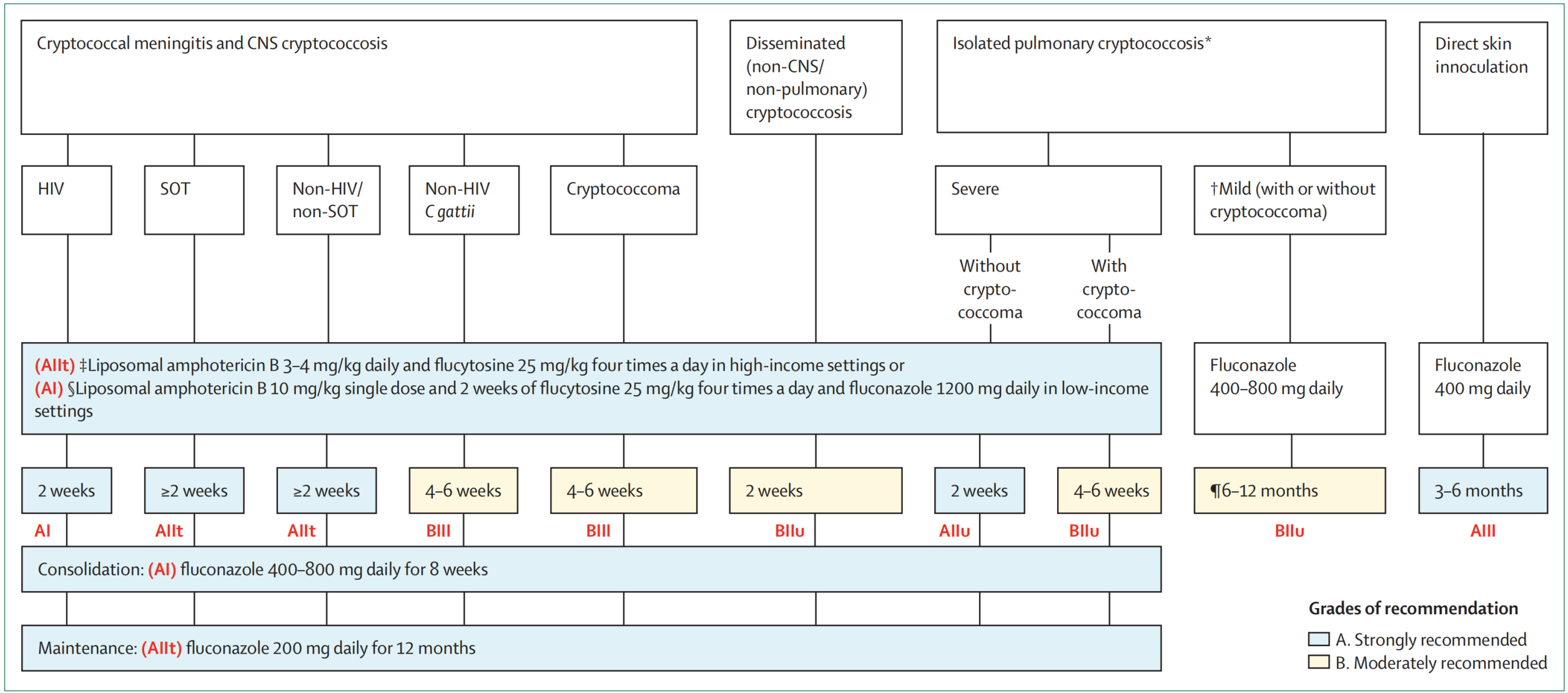
- Lumbar puncture with measurement of CSF opening pressure, glucose, protein, cell counts, microscopy, and culture and quantification of CSF cryptococcal antigen
- Quantification of blood cryptococcal antigen and cultures of blood, sputum (or other respiratory specimens), or other affected sites
- Brain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

a CSF India Ink preparation is positive in 70–90% of cases, but the use of this test depends on diagnostic laboratory facilities and expertise.

By contrast, the sensitivity and specificity of the CrAg lateral flow assay in the serum are up to 100% and 99·5%, respectively, and in the CSF 99·3% and 99·1%, respectively.

Thus, for diagnosis as well as pre-emptive screening, the availability of the CrAg lateral flow assay is essential to improve outcomes from cryptococcal meningoencephalitis.

Which treatment suggest for a patient with cryptococcal meningitis?


Cryptococcal meningitis and CNS cryptococcosis
Disseminated (non-CNS/ non-pulmonary) cryptococcosis
Isolated pulmonary cryptococcosis*
Direct skin innoculation
HIV
SOT
Non-HIV/ non-SOT
Non-HIV C gattii
Cryptococcoma
Severe
†Mild (with or without cryptococcoma)
Without crypto-coccoma
With crypto-coccoma
(AIIt) ‡Liposomal amphotericin B 3–4 mg/kg daily and flucytosine 25 mg/kg four times a day in high-income settings or
(AI) §Liposomal amphotericin B 10 mg/kg single dose and 2 weeks of flucytosine 25 mg/kg four times a day and fluconazole 1200 mg daily in low-income settings
Fluconazole 400–800 mg daily
Fluconazole 400 mg daily
2 weeks
≥2 weeks
≥2 weeks
4–6 weeks
4–6 weeks
2 weeks
2 weeks
4–6 weeks
¶6–12 months
3–6 months
AI
AIIt
AIIt
BIII
BIII
BIIu
AIIu
BIIu
BIIu
AIII
Consolidation: (AI) fluconazole 400–800 mg daily for 8 weeks
Maintenance: (AIIt) fluconazole 200 mg daily for 12 months
Grades of recommendation
A. Strongly recommended
B. Moderately recommended

Induction therapy

Multiple studies support the successful combination of amphotericin B (1 mg/kg daily) /liposomal amphotericin B (3–4 mg/kg Daily) plus flucytosine (25 mg/kg four times a day) as the induction treatment of choice in HIV-associated cryptococcal meningitis.

the addition of flucytosine to amphotericin B showed a trend towards improved CSF sterility at 2 weeks and reduced frequency of relapse.
this combination cleared cryptococci (measured as early fungicidal activity [EFA]) more rapidly than either amphotericin B alone or amphotericin B plus fluconazole.

B SOT recipients and people without HIV or SOT

First-line therapies

Induction (minimum 2 weeks)
(AIIt) Liposomal amphotericin B 3–4 mg/kg daily plus flucytosine 25 mg/kg four times a day

→

Consolidation (8 weeks)
(AIIt) Fluconazole 400–800 mg daily

→

Maintenance (12 months)
(AIIt) Fluconazole 200 mg daily

Alternative therapies

If liposomal amphotericin B is not available:
(BIIt) Amphotericin B lipid complex 5 mg/kg daily plus flucytosine 25 mg/kg four times a day

If liposomal amphotericin B and amphotericin B lipid complex are not available:
(BIIt) Amphotericin B 0·7–1·0 mg/kg daily plus flucytosine 25 mg/kg four times a day

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

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

(BIII) Posaconazole 300 mg daily (with TDM)

(BIII) Isavuconazole 200 mg daily

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

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[73,74]
- (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 anticryptococcal activity
- (CIII) 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 anticryptococcal treatment

Grades of recommendation

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

- Mycological success, defined as cryptococcocal culture negativity (also termed CSF sterility) has been associated with improved outcomes and reduced clinical relapse.
- 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.

- Consider prolonging induction therapy if CSF is persistently culture positive at 2 weeks. (CIIu)

- In Cryptococcus gattii CNS infection occurring in nonHIV patients or CNS cryptococcoma consider extending induction therapy to 4–6 weeks. (BIII)

Consolidation therapy

400 mg daily fluconazole for consolidation therapy.

With the accumulation of safety data of a 800 mg fluconazole daily dose and evidence of a fluconazole dose response effect, this regimen is the preferred consolidation dose in low-income settings, where suboptimal antifungal regimens are used.

Although this evidence could lend support for a higher consolidation dose of 800 mg daily of fluconazole in a gradual rise in median fluconazole minimum inhibitory concentrations (MICs)

maintenance therapy

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.

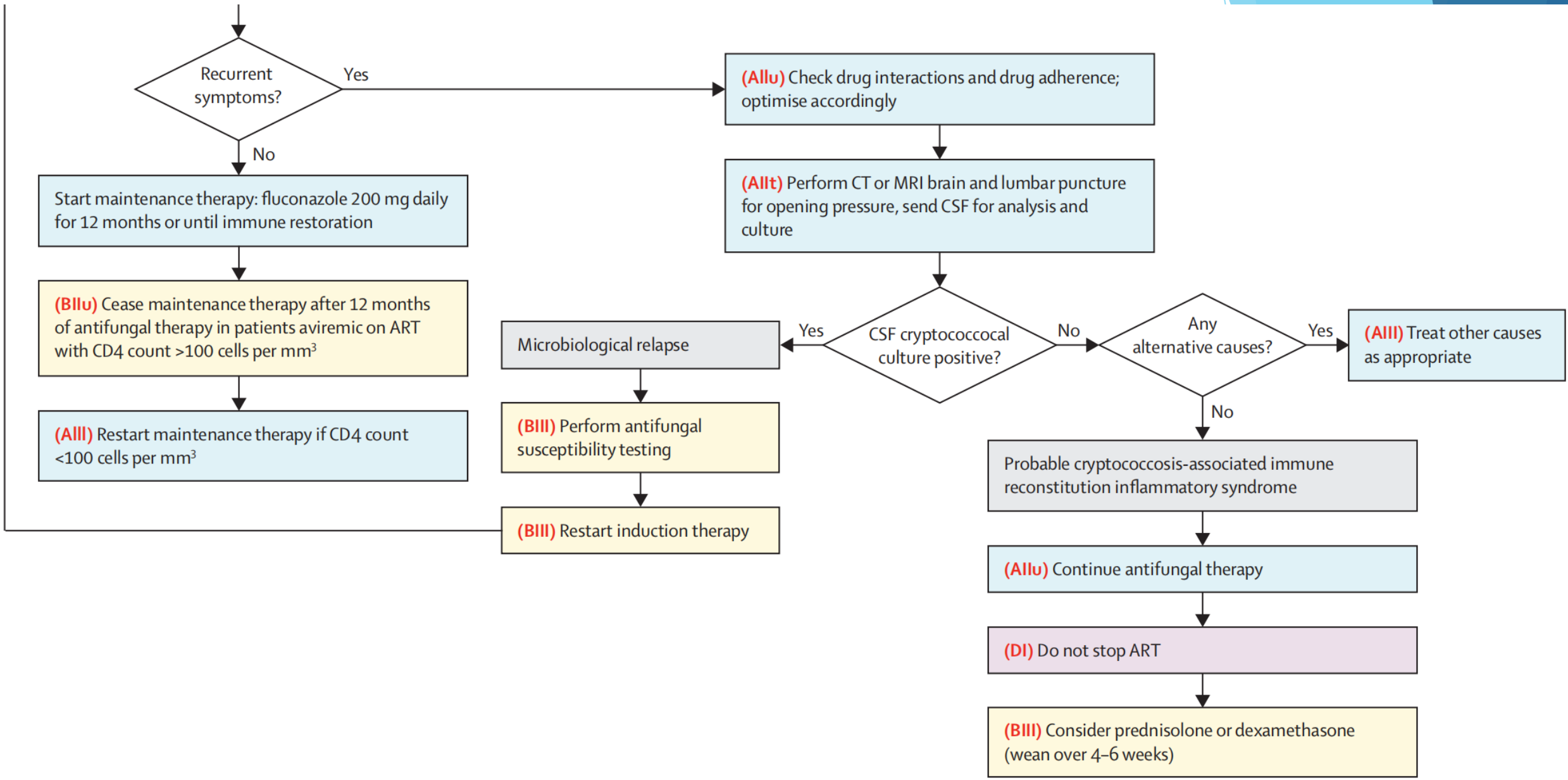
Rarely, triazoles, such as voriconazole, are used as alternatives to fluconazole due to concerns of posaconazole, or isavuconazole , fluconazole resistance, drug toxicity, or drug–drug interactions.

Notably, none of the newer triazoles have been formally trialled in cryptococcosis and none are readily available in low-income settings.

The disease complications include

- persistent infection (positive CSF culture four weeks after treatment)
- relapse,
- increased CSF pressure,
- post-treatment Immune Reconstitution Inflammatory Syndrome (IRIS)
- cerebral Cryptococcus hydrocephalus,
- dementia,
- chronic headache

Which treatment suggest for a patient with this complications ?


Recurrent symptoms?
Yes
No
(AIIu) Check drug interactions and drug adherence; optimise accordingly
(AIIt) Perform CT or MRI brain and lumbar puncture for opening pressure, send CSF for analysis and culture
Start maintenance therapy: fluconazole 200 mg daily for 12 months or until immune restoration
(BIIu) Cease maintenance therapy after 12 months of antifungal therapy in patients aviremic on ART with CD4 count >100 cells per mm3
(AIII) Restart maintenance therapy if CD4 count <100 cells per mm3
CSF cryptococcocal culture positive?
Yes
No
Microbiological relapse
(BIII) Perform antifungal susceptibility testing
(BIII) Restart induction therapy
Any alternative causes?
Yes
(AIII) Treat other causes as appropriate
No
Probable cryptococcosis-associated immune reconstitution inflammatory syndrome
(AIIu) Continue antifungal therapy
(DI) Do not stop ART
(BIII) Consider prednisolone or dexamethasone (wean over 4–6 weeks)

Recommendations for cryptococcal persistence, clinical relapse, and culture-positive (microbiological) relapse

- investigations should include brain CT or MRI, lumbar puncture for opening pressure, and CSF analyses, including microscopy and culture.

- Review adherence to antifungal therapy, ART, immunosuppressants, and other medications and consider drug–drug interactions; perform therapeutic drug monitoring if applicable.

- Consider escalating antifungal therapy while awaiting CSF results (and de-escalate if culture-negative)

- The use of follow-up blood or CSF cryptococcal antigen (including monitoring of titres) for clinical decision making is discouraged

- 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

Evaluate for drug adherence, drug–drug interactions, and drug resistance

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

- 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.

- Consider recommencing induction therapy with a more optimal regimen that is guided by antifungal susceptibility testing.

Manage raised intracranial pressure

Opening pressure should be measured at every lumbar puncture in patients with cryptococcal meningitis.

• Acute symptomatic elevation of the intracranial pressure (≥20 cm of CSF) should be managed by daily therapeutic lumbar punctures.

• 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.

Cryptococcal immune reconstitution inflammatory syndrome (IRIS)

- ✓ IRIS occurs in 10–20% of patients with cryptococcal meningoencephalitis during immunological restoration on ART.
- ✓ and in 5–12% of solid-organ transplantation recipients.
- ✓ Risk factors in the non-HIV population include rapid reduction in immunosuppressive therapy (in particular, discontinuation of calcineurin inhibitors) and resolution of immunosuppressive disorders.

- 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.

- Treatment of C-IRIS should include therapeutic lumbar puncture and symptomatic therapy, such as analgesia, antiemetics, and antiepileptics, if appropriate

- Continue antifungal therapy

- 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.


THANK YOU!