

Guideline



Chinese Guideline on the Diagnosis and Treatment of Cryptococcosis in Adults (2026)

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Abstract

Objective To develop an evidence-informed, immune-risk-stratified clinical practice guideline for the diagnosis, treatment, and follow-up of adult cryptococcosis in China.

Methods A multidisciplinary panel formulated clinical questions; reviewed the available evidence; graded evidence certainty using the Grading of Recommendations Assessment, Development and Evaluation framework, and used a modified Delphi process combining anonymous online voting through Wenjuanxing with face-to-face consultation.

Results Forty-four recommendations address immune-risk stratification, targeted screening, pathogen detection, pulmonary and central nervous system cryptococcosis, disseminated and other-site disease, antifungal therapy, intracranial hypertension, immune reconstitution inflammatory syndrome, treatment response, treatment nonresponse, and follow-up.

Conclusion This clinical practice guideline complements existing Chinese guidance by providing a unified, disease-specific framework for adult cryptococcosis across immune states and anatomical sites, supporting simultaneous Chinese and English dissemination.

Key words: Cryptococcosis; Cryptococcal meningitis; Pulmonary cryptococcosis; Cryptococcal antigen

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INTRODUCTION

Cryptococcosis is an important invasive fungal disease in China. The major pathogenic species include *Cryptococcus neoformans* (*C. neoformans*) and *Cryptococcus gattii* (*C. gattii*) species complexes^[1]. In 2022, the World Health Organization (WHO) published the fungal priority pathogens list^[2], in which *C. neoformans* was placed in the critical-priority group and *C. gattii* in the medium-priority group. Cryptococcosis mainly includes pulmonary cryptococcosis (PC), central nervous system (CNS) cryptococcosis, disseminated cryptococcosis, and cryptococcosis at other sites. Since 2010, Chinese expert consensus documents and specialty guidelines have supported clinical diagnosis and treatment^[3]. As evidence has evolved, screening,

diagnosis, treatment, and response assessment need to be updated and harmonized for high-risk populations and major disease forms.

GUIDELINE DEVELOPMENT METHODOLOGY

This guideline was jointly initiated by Xuanwu Hospital, Capital Medical University; the Respiratory Diseases Branch of the Beijing Medical Association; the Multidisciplinary Diagnosis and Treatment Branch of the Chinese Antituberculosis Association; and the Medical Professional Committee of the China Patent Protection Association. A Guideline Development Steering Group was established, under which the Guideline Expert Group, Writing Expert Group, Methodology Expert Group, and Evidence Evaluation Group were formed. The Guideline Expert

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Group comprised 95 members from multiple disciplines, including respiratory medicine, infectious diseases, neurology, surgery, radiology, pathology, dermatology, and clinical pharmacology. Guideline development was initiated on November 8, 2025, and the final draft was completed on March 10, 2026. The guideline has been registered with the Global Practice Guidelines Registry Platform (GPGRP; registration No. PREPARE-2025CN1585).

The target population is Chinese adults with cryptococcosis, including PC, central nervous system cryptococcosis, disseminated cryptococcosis, and cryptococcosis at other sites, covering immunocompetent patients and those with mild-to-moderate or severe immunocompromise. The intended users are clinicians working in related fields, clinical pharmacists, nurses, laboratory personnel, and pathology professionals at healthcare institutions at all levels; public health prevention and control personnel may also use the guideline as a reference.

During guideline development, the working groups first reviewed existing domestic and international guidelines, management recommendations, expert consensus statements, and diagnostic and treatment standards related to cryptococcosis. Informed by the characteristics of clinical practice in China, 39 candidate clinical questions were initially identified. These questions cover risk assessment, microbiological and pathological diagnosis, treatment of central nervous system and PC, pharmacotherapy in special populations, and surgical intervention. The clinical

questions were structured using the population, intervention, comparator, and outcome (PICO) framework, and the Evidence Evaluation Group conducted literature searches and evidence appraisal according to a prespecified strategy. Draft recommendations were developed on the basis of the evidence synthesis, and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess certainty of evidence and strength of recommendations. After multiple rounds of expert review, anonymous voting, face-to-face consultation, and external review, 44 recommendations were finalized.

Recommendation review and consultation were conducted using a modified Delphi process that combined anonymous voting through Wenjuanxing with face-to-face consultation. A five-point scale was used, assigning scores of 5, 4, 3, 2, and 1 to “agree,” “mostly agree,” “uncertain,” “needs further discussion,” and “disagree,” respectively. Recommendations reaching an agreement rate of $\geq 80\%$ were accepted; those with agreement rates of 67% to $< 80\%$ underwent face-to-face consultation, revision, and repeat voting; and those with agreement rates $< 67\%$ were considered not to have reached consensus. Three rounds of voting and consultation were completed. In the final round, 95 valid questionnaires were returned (response rate, 100%), and the expert authority coefficient was 0.79. All 44 recommendations achieved agreement rates of $\geq 90\%$; the coefficient of variation was < 0.20 for 43 recommendations

Table 1. Definitions of GRADE certainty of evidence and strength of recommendations

Certainty of evidence	Definition	Common starting evidence
High	We are very confident that the true effect is close to the estimated effect.	Randomized controlled trials, or a well-evaluated body of high-quality evidence.
Moderate	We have moderate confidence in the effect estimate; the true effect is likely to be close to the estimate but may differ importantly.	Randomized controlled trials with one or more downgrading factors, or higher-quality observational studies.
Low	Our confidence in the effect estimate is limited; the true effect may differ importantly from the estimate.	Observational studies, or randomized controlled trials with multiple downgrading factors.
Very low	We have very little confidence in the effect estimate; the true effect is very likely to differ importantly from the estimate.	Case series, case reports, or evidence with serious methodological limitations.
Strength of recommendation	Strong recommendation: clear net benefit or net harm and applicable to most of the target population.	Conditional/weak recommendation: important uncertainty exists regarding benefits and harms, values and preferences, resources, or certainty of evidence.
GPS	Not graded as certainty of evidence or strength of recommendation; used only when action is necessary and the evidence is difficult to quantify directly, with the rationale stated.	GPS should not be misrepresented as high-quality evidence.

Note. RCT, randomized controlled trial; GPS, good practice statement.

and 0.20–0.25 for one recommendation, indicating good consensus. The draft guideline was reviewed by the Guideline Expert Group and subsequently by external experts and was revised in response to their feedback.

This guideline addresses the general considerations of cryptococcosis (including areas of ongoing uncertainty or controversy such as risk assessment and immune-status stratification, screening and prophylactic treatment for high-risk populations, pathogen detection techniques, pathological testing techniques, and medication strategies for special populations), neurological cryptococcosis, PC, cryptococcosis of other organs, follow-up, and future perspectives. It aims to provide standardized and actionable guidance for clinical diagnosis and treatment, ultimately improving diagnostic and therapeutic practice and patient outcomes. During guideline development, all members of the expert groups and working groups declared that they had no conflicts of interest related to pharmaceutical companies relevant to this guideline.

Clinical Questions and the PICO Framework

Clinical questions were structured according to the PICO framework: P represents the target population; I, the intervention or diagnostic test; C, the comparator; and O, patient-important outcomes, diagnostic-accuracy outcomes, or implementation outcomes. A single PICO question could support multiple recommendations addressing the same topic. Table 2 summarizes the core PICO frameworks used in this guideline.

Critical Outcome Measures

Critical outcomes were discussed by clinical and methodology experts with consideration of disease severity, clinical decision relevance, and importance to patients, and were prioritized using the GRADE 1–9 scale: 1–3, not important; 4–6, important; and 7–9, critical. Mortality, recurrence, culture conversion to negative, neurological function, serious drug-related adverse events, and the clinical consequences of false-negative or false-positive diagnostic results were prioritized as patient-important or critical outcomes.

Evidence Retrieval, Appraisal, and Synthesis

The Evidence Evaluation Group developed standardized search strategies for the final clinical questions and critical outcomes according to the population, PICO framework. Searches combined

controlled vocabulary terms, including Medical Subject Headings (MeSH) where applicable, with free-text terms. International bibliographic databases and trial registries included PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov; Chinese databases and registries included the Chinese Clinical Trial Registry, Wanfang Data, the Chinese Biomedical Literature Database (SinoMed/CBM), China National Knowledge Infrastructure (CNKI), and the VIP Database. Each source was searched from inception through October 12, 2025. No language restrictions were applied, and non-human studies were excluded. The Chinese-language searches used corresponding terms for cryptococcosis, *Cryptococcus neoformans*, *Cryptococcus gattii*, pulmonary cryptococcosis, central nervous system cryptococcosis, disseminated cryptococcosis, clinical practice guidelines, diagnostic criteria, treatment regimens, China, and adults. Major English terms included “Cryptococcosis,” “*Cryptococcus neoformans*,” “*Cryptococcus gattii*,” “Pulmonary cryptococcosis,” “Central nervous system cryptococcosis,” “Disseminated cryptococcosis,” “Clinical practice guideline,” “Diagnostic criteria,” “Treatment regimen,” “China,” and “Adult.” Search syntax was adapted to the indexing system and search interface of each database. The above search was a systematic search. Given that the guideline was finalized on March 10, 2026, the guideline evidence review group conducted a targeted update search of PubMed before finalization. The search topics included “cryptococcosis,” “pulmonary cryptococcosis,” “voriconazole,” “fluconazole treatment failure,” “CrAg,” and “diagnostic testing.”

Eligible evidence included randomized controlled trials, cohort studies, case-control studies, systematic reviews and meta-analyses, narrative reviews, clinical practice guidelines, management recommendations, and expert consensus statements. Evidence from Chinese populations and studies of higher methodological quality was prioritized. For duplicate publications, only the most recent report or the report with the largest sample size was retained. Conference abstracts, dissertations that had not undergone peer review, studies involving participants younger than 18 years, and animal studies were excluded. Randomized controlled trials underwent additional methodological quality assessment. The types of evidence prioritized varied according to the clinical question. For intervention questions, randomized controlled trials and systematic reviews were

prioritized; diagnostic questions were informed primarily by diagnostic-accuracy studies; prognostic and risk-factor questions could include cohort and case-control studies; and case series could be considered for rare disease sites, with their limitations explicitly reflected in the evidence appraisal. Quality or risk-of-bias tools were selected according to study design and included RoB 2, ROBINS-I, QUADAS-2, AMSTAR 2, QUIPS, or the

Newcastle-Ottawa Scale, as appropriate. Meta-analysis was performed when the evidence was sufficiently homogeneous; otherwise, structured narrative synthesis was used, and sources of heterogeneity were described.

GRADE and Evidence-to-Decision

Certainty of evidence was rated as high, moderate, low, or very low using the GRADE

Table 2. PICO framework for the core clinical questions

No.	P (Population)	I (Intervention/Test)	C (Comparator)	O (Key outcomes)
1	Adults with HIV/AIDS and CD4 < 200/ μ L	Routine serum CrAg screening	No screening or testing only after symptoms develop	Occurrence of CM, mortality, initiation of preemptive treatment, cost-effectiveness
2	Adults with non-HIV SID	Risk-stratified serum CrAg screening	No routine screening	Detection of dissemination/CM, overtesting, treatment delay
3	Asymptomatic adults with IC/MID	Routine CrAg screening	Testing triggered by clinical indications	Detection rate, false positives, lumbar puncture/treatment burden
4	Adults with suspected cryptococcosis	CrAg LFA	LA/EIA/CLIA/culture	Sensitivity, specificity, turnaround time, accessibility
5	Adults with high CrAg titers or suspected CM	Lumbar puncture + CSF CrAg/culture	Serum CrAg only or imaging follow-up	Definitive diagnosis of CM, early treatment, complications
6	Highly suspected cases with negative conventional pathogen testing	mNGS/tNGS/PCR	Repeat conventional testing	Diagnostic yield, misdiagnosis, interpretation of contamination, cost
7	Suspected PC with insufficient noninvasive evidence	BALF CrAg/culture/molecular testing	Serum testing or imaging follow-up	Diagnostic accuracy, invasive-procedure risk
8	Peripheral/subpleural lesions suspicious for PC	TBLB/TBCB/PTNB	Noninvasive follow-up	Histological confirmation, complications, differentiation from lung cancer
9	Cryptococcus isolates or cases of treatment failure	Antifungal susceptibility testing with reporting of MIC/ECV	No susceptibility testing or empiric treatment only	Regimen adjustment, recurrence, detection of resistance
10	Adults with CNS cryptococcosis	L-AmB + 5-FC induction	Other AmB regimens or fluconazole regimens	Mortality, culture conversion to negativity, nephrotoxicity, neurologic outcomes
11	Adults with non-HIV CNS cryptococcosis	Standard induction + consolidation + maintenance	Shortened or alternative regimens	Recurrence, mortality, drug toxicity
12	Adults with HIV-associated CM	Delay ART initiation by 4–6 weeks	Early initiation at 1–2 weeks	Mortality, IRIS, viral control
13	Adults with CM and elevated intracranial pressure	Repeated lumbar puncture/continuous drainage/shunting	Pharmacologic dehydration alone or no intervention	Mortality, vision/hearing, neurologic function, infection risk
14	Adults with mild PC	Fluconazole 400–800 mg/day for 6–12 months	Observation or other antifungal agents	Cure, progression, recurrence, adverse reactions
15	Adults with severe PC or risk of extrapulmonary dissemination	AmB + 5-FC induction followed by consolidation and maintenance	Fluconazole monotherapy	Dissemination, mortality, radiographic resolution, toxicity
16	Adults with inadequate response to or intolerance of fluconazole	Voriconazole or AmB substitution/escalation	Continue fluconazole	Clinical improvement, resistance, TDM-related safety
17	Localized PC with poor response to medication / need to differentiate from lung cancer	Surgical resection + course of antifungal therapy	Continue medical therapy or follow-up	Diagnostic confirmation rate, recurrence, complications, quality of life
18	Adults with cutaneous or genitourinary cryptococcosis	Systemic evaluation for dissemination + site-specific treatment	Local treatment only	Missed dissemination, recurrence, mortality, functional outcomes

Note. BALF, bronchoalveolar lavage fluid; CM, cryptococcal meningitis; CrAg, Cryptococcal Antigen; IC, immunocompetent; MIC, minimum inhibitory concentration; MID, mild-to-moderate immunodeficiency; PICO, population, intervention, comparator, and outcome; PTNB, percutaneous transthoracic needle biopsy; TBCB, transbronchial cryobiopsy; TBLB, transbronchial lung biopsy; TDM, therapeutic drug monitoring.

approach. Randomized studies generally started at high certainty and observational studies at low certainty. Evidence could be downgraded for risk of bias, inconsistency, indirectness, imprecision, or publication bias and, when appropriate, upgraded for factors such as a large effect, a dose-response relationship, or residual confounding that would be expected to reduce the observed effect. For diagnostic evidence, sensitivity, specificity, and the potential consequences of false-positive and false-negative results for patient outcomes were also considered.

Recommendations were formulated in accordance with GRADE Evidence-to-Decision principles, integrating certainty of evidence, anticipated benefits and harms, patient values and preferences, resource use, equity, acceptability, and feasibility rather than relying on expert agreement alone. Recommendation strength was classified as strong or conditional/weak. Good practice statements were used when direct quantification of the evidence was difficult but a clinical action was considered clearly necessary.

Recommendation Development, Voting, and External Review

Recommendations were developed using a modified Delphi process combining anonymous voting through Wenjuanxing with face-to-face consultation. The questionnaire used a five-point scale, assigning scores of 5, 4, 3, 2, and 1 to “agree,” “mostly agree,” “uncertain,” “needs further discussion,” and “disagree,” respectively. Recommendations reaching an agreement rate of $\geq 80\%$ were accepted; those with agreement rates of 67% to $< 80\%$ underwent face-to-face consultation, revision, and repeat voting; and those with agreement rates $< 67\%$ were considered not to have reached consensus.

Three rounds of voting and consultation were completed. In the final round, 95 valid questionnaires were returned (response rate, 100%), and the expert authority coefficient was 0.79. All 44 final recommendations achieved agreement rates of $\geq 90\%$; the coefficient of variation was < 0.20 for 43 recommendations and 0.20–0.25 for one, indicating good consensus.

The draft guideline was reviewed by the Guideline Expert Group and subsequently underwent external expert review. The working group discussed the external comments and revised the recommendations and related text in response to the feedback before finalization.

Patient and Public Involvement, Conflicts of Interest, and Updating

Patients and caregivers were involved in the guideline development process to incorporate patient perspectives and improve the clinical relevance and acceptability of the recommendations. Patient and caregiver representatives were invited to provide input on disease burden, diagnostic delays, treatment experience, medication tolerability, follow-up needs, health education, and preferences regarding shared decision-making. Their feedback was considered by the writing group and expert panel during the refinement of key clinical questions, recommendation wording, and patient education content.

All members of the guideline development group, expert panel, writing group, evidence-evaluation group, methodology group, and secretariat completed conflict-of-interest declarations before participating in the consensus process. No member reported conflicts of interest with pharmaceutical companies or other commercial entities directly relevant to the scope of this guideline. Potential conflicts, if identified during the development process, were reviewed and managed according to the requirements of the organizing societies and standard guideline methodology.

This guideline is planned to be updated every 3 years. An earlier update may be initiated if new evidence emerges that could alter key recommendations, if major safety alerts occur, or if important changes arise in diagnostic technologies, antifungal treatment options, drug availability, epidemiology, or antifungal resistance patterns.

CLINICAL ASSESSMENT AND DIAGNOSIS

Clinical spectrum and outcomes of cryptococcosis vary by immune status, anatomical involvement, and pathogen burden. This section summarizes only the background necessary for clinical risk stratification and decision-making.

Host Immune Status and Cryptococcosis

According to the location of the disease, cryptococcosis can be divided into CNS cryptococcosis, PC, disseminated cryptococcosis and other sites of cryptococcosis.

Classification of the Host Immune Status: An operational immune-risk stratification framework

has been developed for clinical use in this guideline. The framework comprises severe immunodeficiency (SID), mild-to-moderate immunodeficiency (MID), and IC categories. This framework is not intended to represent an internationally established classification system but rather to support clinical decisions regarding screening, lumbar puncture, assessment of dissemination, treatment intensity, and follow-up. The distinction among these categories is supported by studies demonstrating significant differences in the clinical characteristics of cryptococcosis across immune statuses^[4-10].

SID Population: SID includes hematological malignancy, solid-organ or bone-marrow transplantation, intensive immunosuppression, or advanced HIV infection^[9-17]. The degree and duration of immune impairment should be documented because they influence screening, dissemination risk, treatment intensity, and follow-up.

MID Population: MID includes any of the following conditions^[10,18]: (1) diabetes; (2) chronic liver disease or cirrhosis, or chronic kidney disease (KDIGO stage G2 or above); (3) autoimmune disease treated with low-dose glucocorticoids (daily dose < 20 mg prednisone equivalent and cumulative dose < 700 mg prednisone equivalent in the preceding 3 weeks); or (4) recent chemotherapy for solid tumors. Cryptococcosis in the MID population is predominantly pulmonary (approximately 80%); 18.6–19.5% of patients have CNS or disseminated infection, and the mortality rate is approximately 12%^[10,19].

IC Population: IC refers to patients without underlying diseases or with conditions that do not materially impair immune function, such as hypertension^[10]. IC patients typically have the PC form of cryptococcosis; lesions are usually localized, and most patients are asymptomatic or mildly symptomatic. CNS involvement and disseminated infection are rare. The prognosis of PC in IC patients is generally favorable, and fluconazole monotherapy can cure or substantially improve disease in most patients^[9,18].

Screening for Cryptococcosis in High-Risk Populations: Serum cryptococcal antigen (CrAg) screening is recommended for people with advanced HIV infection^[13,14,20-23] and should be considered in other high-risk populations according to immune status, symptoms, and local epidemiology.

In apparently IC patients, cryptococcosis may present with pulmonary or CNS disease; a negative initial test does not exclude disease when clinical suspicion remains high^[8,10,18,24].

Antigenic Detection of Cryptococcosis

The diagnostic approach combines cryptococcal antigen testing, microscopy, culture, molecular assays, and—when clinically indicated—susceptibility testing. The choice of the appropriate test should be guided by the suspected site of infection, immune status, disease severity, and the need for rapid treatment decisions.

CrAg Test: CrAg testing is the core rapid diagnostic test for suspected cryptococcosis. LFA is preferred for routine screening because it is rapid, simple, and highly accurate; LA, EIA, and CLIA may be used according to local availability. CrAg titers may support risk assessment and follow-up, but persistent antigen positivity alone should not be used to define treatment failure or cure^[25-32].

In LA, latex particles coated with antibodies against cryptococcal capsular glucuronoxylomannan are mixed with patient specimens, such as cerebrospinal fluid (CSF) or serum. Visible agglutination indicates the presence of CrAg. This assay can be used with multiple specimen types; in CSF, sensitivity exceeds 90% and specificity approaches 100%. High antigen concentrations may cause a high-dose “hook effect” and false-negative results. Because LFA is faster and simpler, LA is now used less often in routine clinical practice^[25].

Ink Staining: India ink staining may be used as a rapid CSF test when cryptococcal meningitis (CM) is suspected, but its limited sensitivity means that a negative result does not exclude disease. Results should be interpreted together with CSF CrAg, culture, and clinical findings^[33].

Cryptococcal Culture: Cryptococcal culture remains the reference standard for etiological diagnosis and should be performed on CSF, blood, respiratory specimens, or tissue whenever clinically feasible. Culture is especially important for species identification, susceptibility testing, treatment failure, and relapse assessment^[31,33-36].

Molecular Diagnostic Techniques: Molecular diagnostic techniques include polymerase chain reaction (PCR) and next-generation sequencing (NGS).

PCR Detection: PCR is suitable when conventional pathogen detection is negative despite persistent clinical suspicion. Its sensitivity is generally higher than that of India ink staining or culture, and specificity approaches 100%^[33]. Multiplex PCR assays that include *Cryptococcus*, *Aspergillus*, and *Pneumocystis jirovecii* can improve pathogen detection and identification^[37]. Compared with

mNGS, multiplex PCR may provide shorter turnaround time and lower resource use when the suspected pathogen spectrum is narrow.

NGS: NGS includes metagenomic NGS (mNGS) and targeted NGS (tNGS). It is mainly used when conventional testing does not establish the diagnosis, especially in suspected severe PC, disseminated cryptococcosis, or CNS cryptococcosis. tNGS or mNGS can serve as supplementary diagnostic methods when conventional etiological tests are negative^[37-39]. Reported NGS sensitivity is 78.3% in BALF and 76.9% in CSF^[40]. Blood NGS may help diagnose disseminated cryptococcosis and can support species identification. For the usual sterile specimens, even a low number of *Cryptococcus*-specific reads may be diagnostically meaningful. For nonsterile specimens, such as sputum or BALF, low read counts should be interpreted cautiously because contamination is possible. PCR and NGS are not recommended as stand-alone tests for treatment-response assessment.

Recommendation 1 It is strongly recommended to initiate serum CrAg screening in HIV/AIDS patients with CD4⁺ T lymphocyte count < 200/μL. [High-quality evidence, strong recommendation]

Recommendation 2 For SID (non-HIV/AIDS) patients, it is suggested to conduct a risk assessment based on types and intensities of underlying diseases, glucocorticoid dosage and immunosuppressive drugs, and to start individualized serum CrAg screening as appropriate. [GPS]

Recommendation 3 When cryptococcal infection is suspected, LFA is recommended as the preferred screening method. [Moderate-quality evidence, strong recommendation]

Recommendation 4 When CNS cryptococcosis is suspected, CSF CrAg testing is recommended as the preferred screening method. [High-quality evidence, strong recommendation]

Recommendation 5 Positive culture of *Cryptococcus* from an uncontaminated sample is sufficient for a diagnosis of cryptococcosis. [High-quality evidence, strong recommendation]

Recommendation 6 When severe PC, CNS cryptococcosis and disseminated cryptococcosis are suspected but traditional pathogen detection is negative, molecular biological testing can be used as a supplementary diagnostic technique. [High-quality evidence, strong recommendation]

Drug Susceptibility Test: Clinical breakpoints for antifungal susceptibility testing of *Cryptococcus* have not been established. Laboratories should report

minimum inhibitory concentration (MIC) values with the relevant epidemiological cut-off values, and clinicians should interpret results in the context of species, infection site, drug exposure, host status, and clinical response^[41-44].

Susceptibility testing should be reserved for treatment failure, relapse, persistent culture positivity, or suspected resistance. Results should be interpreted with epidemiological cut-off values because clinical breakpoints are not established.

Broth microdilution is recommended when susceptibility testing is indicated. Testing should be prioritized for treatment failure, relapse, persistent culture positivity, or suspected resistance; MIC results should guide, but not replace, clinical judgment^[44].

Recommendation 7 Antifungal susceptibility testing is recommended for the following patients: Patients with cryptococcosis who have received standardized antifungal therapy but show a poor clinical or microbiological response; Patients with recurrent cryptococcal infection; Patients with cryptococcosis and prolonged exposure to azole antifungal agents, particularly previous prophylactic use; Patients infected with *C. gattii*. [Low-certainty evidence; conditional recommendation]

Recommendation 8 When antifungal susceptibility testing is performed, MIC and the corresponding epidemiological cutoff value (ECV) range should be reported because clinical breakpoints for *Cryptococcus* have not been established. Persistently or substantially elevated MIC values relative to the ECV may suggest acquired resistance. [Low-certainty evidence; conditional recommendation]

When PC cannot be confirmed non-invasively, early biopsy of an active or representative lesion should be considered, with culture, special stains, and molecular testing performed in parallel.

Histopathology should be interpreted with special stains, culture, CrAg testing, molecular testing, and clinical-radiologic findings. Atypical or scant organisms require confirmation using the same representative specimen whenever possible^[45-48].

Recommendation 9 In principle, the biopsy sampling site should be preferentially selected from active lesions or the main lesion area. Whenever possible, at least 2–3 valid histological specimens should be obtained. [GPS]

Recommendation 10 For surgically resected specimens, it is recommended to include, whenever possible, the interface between the lesion and the surrounding normal tissue. [GPS]

Recommendation 11 If fungal organisms are identified in lesional tissue and both cellular morphology and special stains are consistent with the characteristics of *Cryptococcus*, accompanied by corresponding histopathological changes, a pathological diagnosis of cryptococcal infection can be made. If organisms are scarce or exhibit atypical morphology, further molecular biological testing is recommended^[45-48]. [High-certainty evidence, strong recommendation]

Pharmacotherapy of Cryptococcosis

Commonly Used Drugs for the Treatment of Cryptococcosis *Amphotericin B (AmB)*^[49,50]: AmB is the key induction agent for severe, CNS, and disseminated cryptococcosis. Formulation selection should be based on disease severity, renal function, electrolyte status, toxicity risk, and local availability.

Flucytosine (5-FC)^[51-53]: Interestingly, 5-FC should be used in combination with amphotericin B during induction therapy when available. Renal function, blood counts, and drug exposure should be monitored to reduce toxicity.

Triazole Antifungal Agents^[51,52]: Triazoles are mainly used for consolidation, maintenance, and selected non-severe pulmonary disease. Fluconazole is the preferred oral agent; voriconazole^[54,55], isavuconazole^[56], or posaconazole^[57,58] should be reserved for selected cases after considering drug interactions, therapeutic drug monitoring, CNS penetration, and limited supporting evidence.

Management of Adverse Drug Events

Drug-Drug Interactions: Before prescribing an azole, clinicians should review concomitant medications and adjust doses or monitoring for high-risk substrates such as warfarin, sulfonyleureas, and calcineurin inhibitors. Potent enzyme inducers, especially rifampicin, should generally be avoided with voriconazole and used cautiously with fluconazole; therapeutic drug monitoring is recommended when available^[51,59,60].

Adverse Drug Reactions: During amphotericin B therapy, renal function, potassium, magnesium, complete blood count, infusion reactions, and cumulative toxicity should be monitored. L-AmB is preferred in patients with renal insufficiency when available. If AmB-D must be used, consider gradual dose escalation, adequate hydration, electrolyte replacement, and close monitoring. During 5-FC therapy, monitor renal function and blood counts, especially when other myelosuppressive drugs are used^[49,51,53,59-61].

Principles of Management of Cryptococcosis

Asymptomatic Infected Individuals: (1) Asymptomatic infected individuals with HIV/AIDS (CD4⁺ T-lymphocyte count < 200 cells/ μ L): Lumbar puncture and CSF examination are recommended. If the CSF CrAg test is positive, prompt induction therapy with L-AmB plus 5-FC is recommended (see the section on CNS cryptococcosis for the treatment regimen). If the CSF CrAg test is negative in asymptomatic infected individuals, preemptive therapy with fluconazole is recommended^[20-22]. The specific regimen is fluconazole 800 mg/day orally for 2 weeks, followed by 400 mg/day orally for at least 8 weeks, and then 200 mg/day for maintenance until the CD4⁺ T-lymphocyte count rises above 200 cells/ μ L and remains stable, at which point treatment may be discontinued. Among HIV/AIDS patients receiving antiretroviral therapy (ART), the annual incidence of CM in those with CD4⁺ T-lymphocyte count $\geq$ 200 cells/ μ L is low^[23]. Routine lumbar puncture and CSF examination are not recommended for such patients based solely on a positive serum CrAg, nor is there evidence to support benefit from preemptive fluconazole therapy. Close monitoring of clinical changes is advised. In regions with the necessary resources, dynamic monitoring of CrAg titers may be used, and more aggressive interventions may be considered for high titers (e.g., $\geq$ 1:160).

(2) Non-HIV/AIDS asymptomatic infected individuals: An individualized approach based on risk stratification is recommended, particularly for solid organ transplant recipients and patients with SID receiving long-term high-dose glucocorticoids or other potent immunosuppressants^[62-65]. For those with a positive serum CrAg alone, lumbar puncture and CSF examination should be performed whenever possible to exclude CM^[62,66]. For high-risk asymptomatic infected individuals with SID, preemptive therapy with fluconazole is recommended. The specific regimen is fluconazole 800 mg/day orally for 2 weeks, followed by 400 mg/day orally for at least 8 weeks, and then 200 mg/day for maintenance; the duration of treatment depends on the treatment status of the underlying disease^[62]. For asymptomatic infected individuals without SID, the decision to perform lumbar puncture and CSF examination should be made by an MDT. In principle, routine preemptive therapy is not recommended for such patients; individualized assessment and close clinical monitoring remain essential^[63-65,67].

Various Types of Cryptococcosis**Evaluation of Therapeutic Efficacy for Cryptococcosis:**

Treatment response should be assessed using symptoms, microbiological results, imaging, and

—when relevant—CrAg trends. No single parameter should be used in isolation. The criteria for evaluating treatment response are summarized in Table 6.

Table 3. Critical outcome measures and importance levels

Outcome category	Examples of critical outcomes	Suggested importance
Efficacy	All-cause mortality, disease-related mortality, CSF culture conversion to negativity, dissemination or occurrence of CM, recurrence	7–9
Safety	Kidney injury, bone marrow suppression, electrolyte disturbances, liver injury, drug–drug interactions	7–9
Diagnostic accuracy	Sensitivity, specificity, consequences of false negatives, overtreatment caused by false positives	7–9
Patient-important outcomes	Headache, vision or hearing, neurologic function, quality of life, length of hospital stay, financial burden	6–9
Implementation outcomes	Test accessibility, reporting timeliness, feasibility in primary care, TDM, and drug supply	6–8

Note. CM, cryptococcal meningitis; CSF, cerebrospinal fluid; TDM, therapeutic drug monitoring.

Table 4. Key judgement domains in the EtD framework

EtD domain	Judgement question	Documentation
Priority of the problem	Is the problem common, serious, or associated with important variation in decision-making?	High, moderate, or low, with rationale.
Benefits and harms	Do the expected benefits outweigh the risks and treatment burden?	List key effect estimates or structured narrative evidence.
Certainty of evidence	What is the overall certainty of evidence, and what are the main reasons for downgrading?	High, moderate, low, or very low.
Values and preferences	How do patients weigh mortality, neurologic harm, drug toxicity, lumbar puncture burden, and cost?	Results of patient or caregiver involvement.
Resources and equity	Are medications, tests, TDM, hospitalization, and surgical resources accessible?	Options for the Chinese context and low-resource settings.
Acceptability and feasibility	Can patients and healthcare professionals accept and implement the recommendation?	Implementation conditions, barriers, and quality indicators.

Note. EtD, Evidence-to-Decision; TDM, therapeutic drug monitoring.

Table 5. Comparison of commonly used laboratory detection methods for cryptococcosis [24-27,32-34,36-40,44]

Detection methods	Specimen type	Sensitivity	Specificity	Main features
CrAg	Serum	70%–80%	95%–98%	Minimally invasive and rapid (15–30 min). It is the core screening method for cryptococcosis. CrAg test of CSF is of great value in the diagnosis of CNS cryptococcal infection.
	CSF	98.8%	99.3%	
Culture	Sputum / BALF / blood / CSF / biopsy tissue	Sputum/BALF: 5.69%; Others: 35%–79%	Nearly 100%	Non-invasive and low-cost, a positive result can directly confirm the diagnosis. Disadvantage: relatively low sensitivity.
PCR	Sputum / BALF / blood / CSF / biopsy tissue	65%–98%	Nearly 100%	Short detection period (24 to 48 hours). Suspected cases of cryptococcosis with negative results in traditional pathogenology.
mNGS/tNGS	BALF / blood / CSF / biopsy tissue	76%–92%	82%–100%	Mainly used for the diagnosis of difficult cases and can serve as a supplementary test when traditional pathogen detection is negative.
Ink staining	CSF / rash secretions	CSF: 63%–82.5%; No data available for rash secretions for the time being.	Nearly 100%	Extremely fast and inexpensive, but with low sensitivity and dependent on the operator's experience.

Note. BALF, bronchoalveolar lavage fluid; CNS, central nervous system; CrAg, Cryptococcal Antigen; CSF, cerebrospinal fluid.

MANAGEMENT OF TREATMENT-NONRESPONSIVE CRYPTOCOCCOSIS

Treatment nonresponse should prompt a structured reassessment of diagnostic accuracy, adherence and drug exposure, immune status, drug interactions, resistance, complications, and alternative diagnoses.

Recommendation 12 L-AmB combined with 5-FC is the core regimen for induction therapy in patients with disseminated cryptococcosis, CNS cryptococcosis, and severe PC. Fluconazole is the foundation drug for mild PC and for consolidation and maintenance therapy after the induction phase. [High-certainty evidence, strong recommendation]

Recommendation 13 When fluconazole is poorly effective or poorly tolerated for the treatment of cryptococcosis, amphotericin B or voriconazole may be used as alternative therapeutic agents^[44,68]. [Moderate-certainty evidence, conditional recommendation]

Recommendation 14 Voriconazole is metabolized by CYP2C19, CYP2C9, and CYP3A4. Rifampicin and other potent inducers of these hepatic enzymes significantly reduce voriconazole plasma concentration; concomitant use should be

avoided. [High-certainty evidence, strong recommendation]

Recommendation 15 Fluconazole is primarily excreted by the kidneys and partially metabolized by CYP3A4. Caution is needed when co-administering fluconazole with rifampicin; if concomitant use is necessary, the dose of fluconazole should be increased and the therapeutic response closely monitored. [High-certainty evidence, strong recommendation]

Recommendation 16 Azole drugs are moderate to potent inhibitors of the pharmacokinetic enzyme CYP450, which can increase the plasma concentrations of substrates. Therapeutic drug monitoring is recommended to adjust the dosage of substrates to ensure the safety of treatment for comorbid conditions. [High-certainty evidence, strong recommendation]

Recommendation 17 Negative conversion of cryptococcal culture and trends in CrAg titers are recommended as laboratory indicators for evaluating therapeutic efficacy in CNS cryptococcosis, but comprehensive assessment integrating clinical findings remains necessary. [Moderate-certainty evidence, strong recommendation]

Table 6. Criteria for evaluating treatment efficacy in cryptococcosis

Category	Evaluation Indicator	Favorable Response	Improvement	Treatment non-response or progression
PC	Clinical Symptoms	Complete resolution	Significant improvement	No improvement or worsening
	Serum CrAg Titer ^[28]	Significant decrease to a low level or negative conversion (combined with imaging findings for comprehensive evaluation)	Significant downward trend	No downward trend, or even elevation
	Imaging ^[107,108]	Obvious absorption of lesions, or residual fibrous strands / calcifications	Significant reduction in lesion size/extent compared to baseline; no new lesions	No reduction in lesion size, or enlargement
CM	Clinical Symptoms	Complete resolution	Significant improvement	No improvement or worsening
	CSF Examination ^[44]	Normalization of pressure, cell count, protein, and glucose; negative culture	Improvement in pressure and biochemical indicators; negative culture	No improvement or worsening of indicators; persistently positive culture
	Imaging	Disappearance or near-disappearance of meningeal/ependymal enhancement; disappearance of cryptococcomas or tree-in-bud lesions, or only residual glial scarring; resolution of hydrocephalus and ventriculitis-related signs; no new lesions	Reduction in lesion size compared to baseline, significant reduction in perilesional edema; no new lesions	No reduction in lesion size, or enlargement, or new lesions; persistent obvious meningeal/ependymal enhancement; no improvement or progression of hydrocephalus and ventriculitis signs
	Serum / CSF CrAg Titer	Significant decrease to a low level or negative conversion ^[28,29] (requires comprehensive evaluation combined with the above indicators)	Significant downward trend	No downward trend, or even elevation

Note. CrAg, Cryptococcal Antigen; CSF, cerebrospinal fluid.

Recommendation 18 For treatment nonresponsive cryptococcosis, a comprehensive evaluation integrating diagnostic accuracy, host immune status, fungal drug resistance, and drug-related factors should be performed, and diagnostic and therapeutic measures should be adjusted under the guidance of an MDT. [GPS]

CENTRAL NERVOUS SYSTEM CRYPTOCOCCOSIS

CNS cryptococcosis includes CM, meningoencephalitis, and cryptococcal brain lesions. Because delayed diagnosis is associated with severe neurological sequelae and mortality, suspected cases require prompt CSF testing and early antifungal therapy.

Clinical Manifestations

Typical manifestations of CNS cryptococcosis include fever, headache, altered mental status, meningeal irritation, cranial nerve involvement, seizures, focal neurological deficits, and signs of raised intracranial pressure. Absence of classic meningeal signs does not exclude CM.

Diagnostic Techniques for CNS Cryptococcosis

Imaging Diagnosis: Brain MRI with contrast is

recommended for suspected CNS cryptococcosis to evaluate meningeal, parenchymal, ependymal, choroid plexus, hydrocephalus, infarction, or mass-effect complications. If MRI is unavailable or contraindicated, contrast-enhanced computed tomography (CT) may be used as an alternative^[44]. Imaging features that support the diagnosis of CNS cryptococcosis include leptomeningeal or cisternal enhancement, gelatinous pseudocysts along perivascular spaces, thin-walled ring or nodular parenchymal lesions, ventriculitis, choroid pleinitis, hydrocephalus, and infarcts in perforator territories^[69-71].

Differential diagnosis should include tuberculous meningitis or tuberculoma, other fungal CNS infections, toxoplasmosis, pyogenic brain abscess, primary or secondary CNS lymphoma, metastases, and carcinomatous meningitis. Final diagnosis requires integration of imaging with serum or CSF CrAg, CSF findings, culture, molecular testing, or histopathology^[69].

Recommendation 19 For imaging diagnosis of CNS cryptococcosis, plain and contrast-enhanced brain MRI is recommended; CT with contrast can be used as an alternative. [GPS]

Recommendation 20 Characteristic MRI findings of CNS cryptococcosis include the following: changes

Table 7. Drug treatment regimens for central nervous system cryptococcosis

Phase	Preferred Regimen	Alternative Regimens	Duration
Induction	L-AmB [3–4 mg/(kg·d)] + 5-FC (25 mg/kg qid) [total 100 mg/(kg·d), same below]	Non-HIV patients: 1. AmB-D [0.7–1.0 mg/(kg·d)] + 5-FC for 2 weeks; 2. AmB-D [0.5–0.7 mg/(kg·d)] + 5-FC, extended beyond 2 weeks; 3. ABLC [5 mg/(kg·d)] or ABCD [3–4 mg/(kg·d)] + 5-FC for 2 weeks; 4. Fluconazole (800–1,200 mg/d) + 5-FC for 2 weeks.	At least 2 weeks; For <i>C. gattii</i> infection or cryptococcoma, induction therapy should be extended to 4–6 weeks.
		HIV patients: 1. If L-AmB is unavailable, ABLC/ABCD + 5-FC can be used; if none of the above AmB formulations are available, one of the following: 1) AmB-D [0.7–1.0 mg/(kg·d)] + 5-FC; 2) AmB-D [1.0 mg/(kg·d)] + 5-FC for 1 week, then fluconazole (1,200 mg/d) for 1 week; 2. If 5-FC is unavailable, any of the following combinations: 1) L-AmB + fluconazole (800–1,200 mg/d); 2) ABLC + fluconazole (800–1,200 mg/d); 3) AmB-D [0.7–1.0 mg/(kg·d)] + fluconazole (800–1,200 mg/d); 3. If no AmB-based formulation is available, 5-FC + fluconazole (800–1,200 mg/d) may be considered; 4. If no fluconazole is available, use fluconazole monotherapy at (800–1,200 mg/d).	
Consolidation	Fluconazole (400–800 mg/d)	Voriconazole, isavuconazole (limited by blood-brain barrier issues), posaconazole	At least 8 weeks
Maintenance	Fluconazole 200 mg/d	Voriconazole, isavuconazole, posaconazole (insufficient evidence for substitution)	At least 12 months or until immune recovery

Note. If L-AmB is unavailable, other AmB formulations (e.g., AmB-D, ABLC, ABCD) combined with 5-FC can be used as alternatives^[44,128].

related to perivascular spaces (gelatinous pseudocysts or colloid pseudotumors), abnormal meningeal or cisternal enhancement, cryptococcomas or abscess-like lesions, ependymal or choroid plexus involvement,

signs of ventriculitis, and secondary hydrocephalus. [Moderate-certainty evidence, conditional recommendation]

Recommendation 21 In cases with imaging findings suspicious for CM, lumbar puncture should be performed promptly to obtain CSF for CrAg testing and to actively pursue etiological evidence. [Moderate-certainty evidence, strong recommendation]

Diagnostic Principles for CNS Cryptococcosis

When CNS cryptococcosis is suspected, the diagnostic steps of "rapid screening - accurate diagnosis - supplementary verification" should be followed.

Rapid Screening for Cryptococcal Infection: For high-risk populations (e.g., immunocompromised individuals) or suspected CNS cryptococcosis cases presenting with fever, headache, and CNS symptoms/signs, initiate serum CrAg rapid screening^[26].

Imaging Evaluation: For suspected cases with positive serum CrAg or who present with

neuropsychiatric symptoms/signs, perform plain and contrast-enhanced brain MRI to evaluate the imaging characteristics, extent, severity, and complications.

Lumbar Puncture and CSF Testing: For patients with HIV/AIDS ($CD4^+$ T cell count < 200 cells/ μ L) and positive studies have confirmed that a CrAg titer of 1:160 is closely associated with the development of CM, given the high risk of mortality from CM, it is recommended that lumbar puncture be performed immediately for CSF testing regardless of whether CNS symptoms are present. For non-HIV/AIDS patients, especially immunocompromised individuals, prompt lumbar puncture is recommended once neurological symptoms develop. For asymptomatic CrAg-positive patients with immunodeficiency, clinical evidence regarding the correlation between CrAg titer and risk of CM is lacking; lumbar puncture and CSF testing are recommended after assessing the risk of CM and performing systematic evaluation.

A positive CSF CrAg result can serve as a basis for early clinical intervention^[26,30]. Positive CSF India ink staining^[33] can provide rapid confirmatory evidence to guide precise treatment. At the same time, routine CSF biochemical tests, CrAg, and cryptococcal etiological testing should be completed. Routine CSF tests lack specificity and are often used

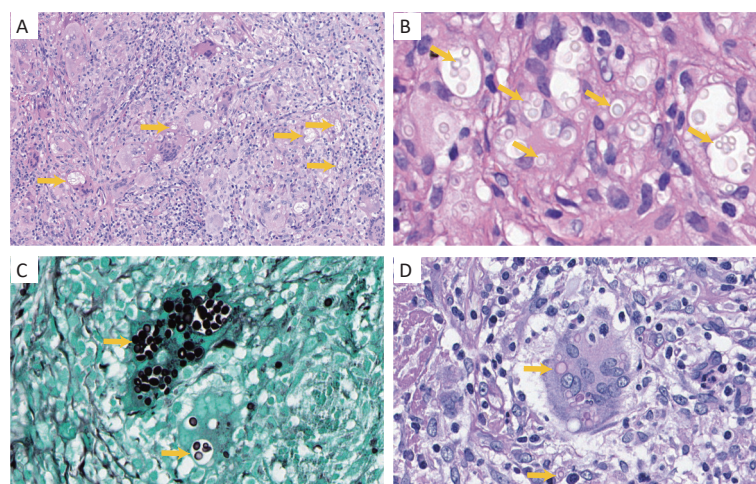


Figure 1. Histopathological features and histochemical staining of cryptococcal infection. (A) Non-necrotizing granulomatous inflammation accompanied by interstitial fibrosis and chronic inflammatory cell infiltration (H&E, $\times 100$); (B) Round or oval *Cryptococcus* organisms with clear pericellular halos corresponding to the capsules are visible within multinucleated giant cells (H&E, $\times 600$); (C) GMS staining shows the cell walls of *Cryptococcus* as black ring-like structures (GMS, $\times 600$); (D) PAS staining shows the cell walls of *Cryptococcus* in magenta and the fungal bodies in pale red (PAS, $\times 600$). Yellow arrows indicate *Cryptococcus* organisms. GMS, Grocott's methenamine silver; H&E, hematoxylin and eosin; PAS, Periodic acid–Schiff.

to assess treatment response in CM

Establishing a phased response mechanism for clinical and etiological diagnosis: CSF positive for CrAg can serve as the basis for initiating antifungal therapy for clinical diagnosis^[25,72,73]. Etiological diagnosis has significant value in the diagnosis and assessment of treatment response in CM. CSF cryptococcal culture is the "gold standard" for diagnosing CM^[33,73]. For suspected cases with persistently negative cultures, molecular biological testing is an important supplementary method when traditional etiological tests are negative^[40]. Serial cryptococcal cultures not only help confirm the diagnosis but also provide gold-standard support for subsequent treatment optimization and efficacy evaluation. If the cause of brain parenchymal lesions remains undetermined after conventional diagnostic methods, brain biopsy may be considered.

Treatment of CNS Cryptococcosis

Principles of Treatment for CNS Cryptococcosis:

Treatment of CNS cryptococcosis should follow a three-phase antifungal strategy: induction, consolidation, and maintenance. Induction therapy aims to rapidly reduce the fungal burden using fungicidal combination therapy. Consolidation therapy further clears residual infection and reduces relapse risk. Maintenance therapy uses a lower-dose

oral regimen for a prolonged period to prevent recurrence or reactivation, particularly before immune recovery is achieved.

Treatment of CNS Cryptococcosis in HIV/AIDS: For HIV-associated CM, induction therapy should prioritize amphotericin B plus flucytosine when available. Evidence from randomized trials supports amphotericin B-based combination induction regimens, followed by fluconazole consolidation and maintenance therapy^[44,74,75].

Principles of Treatment for CNS Cryptococcosis in Non-HIV/AIDS Patients: For non-HIV-associated CNS cryptococcosis, L-AmB plus 5-FC is preferred for induction therapy when feasible. High-dose fluconazole may be considered only when standard induction therapy is unavailable or unsuitable; supporting evidence is mainly observational^[76-78].

Principles of Treatment for Intracranial Hypertension in CM: Raised intracranial pressure is a major preventable cause of death and neurological disability in CM. Management should be guided by symptoms, opening pressure, serial examination, and timely CSF drainage^[44,79-83].

Timing of ART and Antifungal Therapy Initiation in HIV-Infected Patients with CM: In HIV-associated CM, ART should be timed according to disease severity, fungal burden, CSF culture status, and the risk of immune reconstitution inflammatory

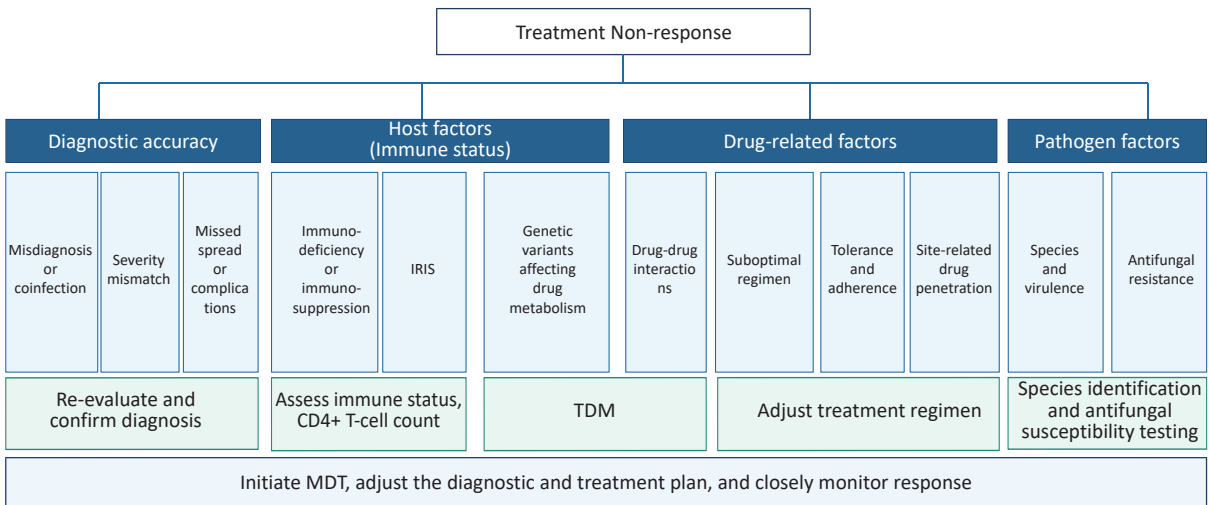


Figure 2. Management algorithm for treatment-refractory cryptococcosis. Treatment-refractory cryptococcosis should undergo a structured reassessment from four perspectives: diagnostic accuracy, host factors (including immune status), drug-related factors, and pathogen-related factors. Management should focus on identifying and correcting potentially reversible causes of treatment failure, including confirmation of the diagnosis, assessment of immune status, TDM, optimization of antifungal therapy, management of associated complications, and, when necessary, *Cryptococcus* species identification and antifungal susceptibility testing. IRIS, immune reconstitution inflammatory syndrome; TDM, therapeutic drug monitoring.

syndrome^[84-88].

A prospective longitudinal cohort study from South Africa showed that patients with negative CSF cultures before ART initiation had a lower risk of C-IRIS than those with persistent culture positivity (HR: 0.33, $P = 0.0042$)^[89]. The timing of ART should generally be 4–6 weeks after initiation of antifungal therapy, with individualization according to clinical stability, fungal burden, intracranial pressure, CSF culture results, and the risk of IRIS. Documented CSF culture conversion should not be required in every patient before ART initiation^[87]. Therefore, negative conversion of CSF cryptococcal culture is recommended as an important reference indicator for initiating ART.

Recognition and Management of IRIS in HIV/AIDS:

IRIS should be suspected when clinical or radiological worsening occurs during immune recovery after ART initiation or immunosuppression reduction^[90,91]. Diagnosis requires exclusion of persistent infection,

relapse, drug resistance, inadequate drug exposure, and alternative diagnoses^[89,92,93].

For IRIS, continue effective antifungal therapy and ART unless a compelling contraindication exists. Manage raised intracranial pressure and other complications promptly. Corticosteroids may be considered for severe inflammatory manifestations, but routine prophylactic glucocorticoids are not recommended^[44,94,95].

Recommendation 22 For CNS cryptococcosis, a three-phase treatment principle of induction, consolidation, and maintenance is recommended: Induction: L-AmB + 5-FC for 2 weeks; Consolidation: fluconazole 400–800 mg/day for at least 8 weeks; Maintenance: fluconazole 200 mg/day for at least 12 months. For HIV/AIDS patients, the maintenance phase continues until immune recovery. [High-quality evidence, strong recommendation]

Recommendation 23 Serum CrAg screening is recommended for newly diagnosed or ART-naïve

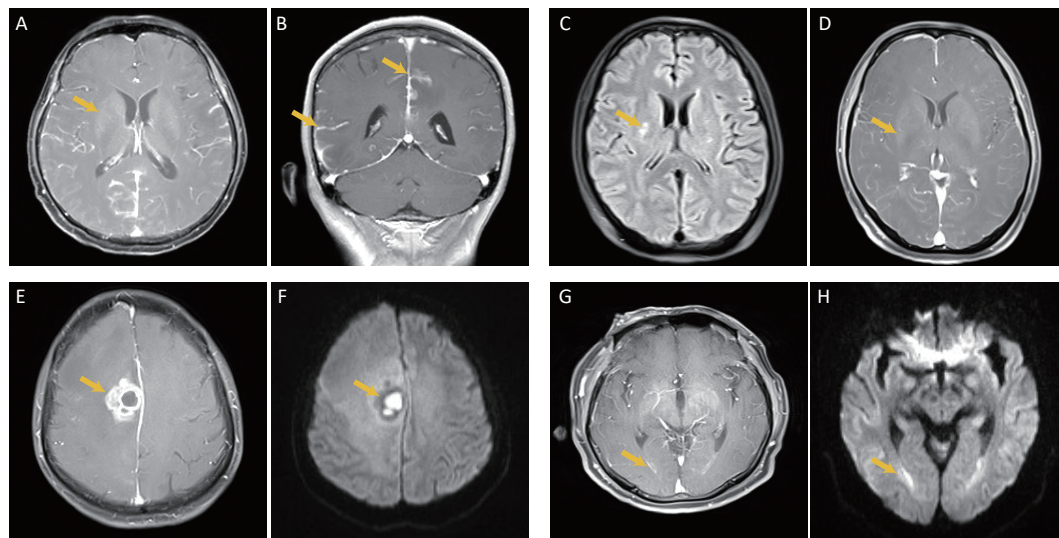


Figure 3. Typical MRI findings of central nervous system cryptococcosis. (A, B) Meningeal involvement. A: Axial contrast-enhanced T1WI shows linear leptomeningeal enhancement along several cerebral sulci with focal nodular enhancement (arrow). B: Coronal contrast-enhanced T1WI shows leptomeningeal enhancement distributed along the cerebral sulci. (C, D) Gelatinous pseudocysts in the perivascular spaces. C: FLAIR imaging shows beaded or clustered hyperintense lesions in the basal ganglia, distributed along the perivascular spaces. D: Contrast-enhanced T1WI shows no obvious enhancement. (E, F) Cryptococcal encephalitis or cryptococcoma-like lesion. The lesion is located in the right parasagittal frontal lobe adjacent to the falx cerebri (arrow). E: Contrast-enhanced T1WI shows thin-walled ring enhancement or focal nodular enhancement with central hypointensity. F: DWI shows focal hyperintensity within the lesion, indicating restricted diffusion. (G, H) Ependymal involvement and ventriculitis, involving the occipital horns of both lateral ventricles (arrows). G: Contrast-enhanced T1WI shows linear ependymal enhancement along the lateral ventricles. H: DWI shows dependent, layering hyperintensity within the ventricles, suggesting deposition of highly viscous or purulent intraventricular contents and supporting the diagnosis of ventriculitis. MRI, magneti resonance imaging; T1WI, T1-weighted imaging.

adults with HIV infection and CD4⁺ T-cell counts < 100 cells/ μ L. Screening may be considered for those with CD4⁺ counts between 100 and 200 cells/ μ L according to local prevalence, clinical risk, and resource availability. [High-quality evidence, strong recommendation]

Recommendation 24 For asymptomatic *Cryptococcus*-infected patients with SID (non-HIV/AIDS), lumbar puncture and CSF CrAg testing should be performed whenever possible. If CSF CrAg is negative, preemptive therapy with fluconazole is recommended; the duration of the maintenance phase depends on the treatment status of the underlying disease. [Moderate-quality evidence, weak recommendation]

Recommendation 25 For CM with elevated intracranial pressure, repeated therapeutic lumbar punctures for CSF drainage are recommended to lower intracranial pressure. [High-quality evidence, strong recommendation]

Recommendation 26 For refractory intracranial hypertension, continuous lumbar drainage, external drainage, Ommaya reservoir placement, long-term subcutaneous tunnel external ventricular drainage, or ventriculoperitoneal shunt may be used^[44,96-98]. [Low-quality evidence, strong recommendation]

Recommendation 27 For HIV/AIDS patients with CM initiating antifungal therapy, it is recommended

to defer the start of ART until 4–6 weeks after the start of antifungal therapy. [High-quality evidence, strong recommendation]

Recommendation 28 The diagnosis of IRIS requires exclusion of cryptococcal disease progression or relapse, and other infectious or non-infectious causes of clinical deterioration.

[Low-quality evidence, strong recommendation]

Recommendation 29 For clinically severe IRIS, glucocorticoids are recommended to suppress the inflammatory response. [Moderate-quality evidence, weak recommendation]

PULMONARY CRYPTOCOCCOSIS

PC is the most common clinical form of cryptococcosis in China. Management should be guided by immune status, symptom burden, imaging severity, microbiological evidence, and risk of CNS or disseminated disease^[10,99-101].

Clinical Manifestations of PC

PC may be asymptomatic or present with cough, sputum production, chest pain, dyspnea, fever, or fatigue. SID patients require particular attention because extrapulmonary dissemination is substantially more frequent than in MID or IC patients^[4,6,10,102].

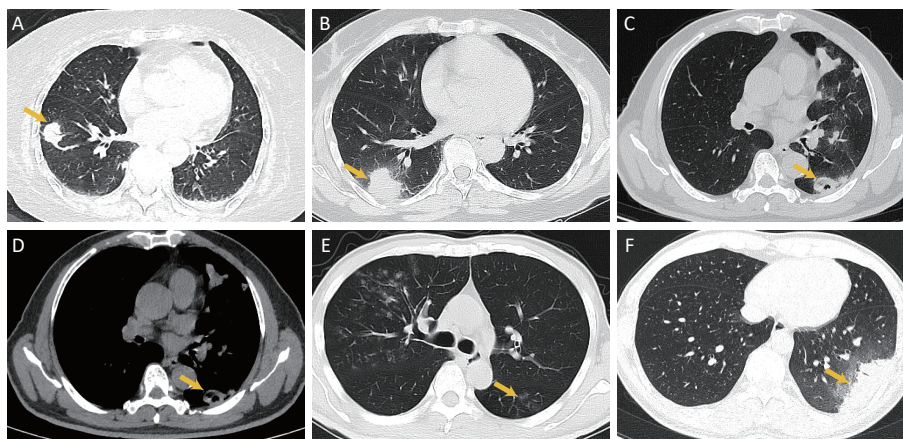


Figure 4. Typical CT findings of pulmonary cryptococcosis. (A) Nodular/mass-like pattern. Thin-section CT on the lung window shows a solitary subpleural nodule in the right lower lobe (arrow), distributed along the bronchovascular bundle, with a relatively well-defined margin. (B) Halo sign pattern. Thin-section CT on the lung window shows a subpleural nodule in the right lower lobe (arrow) surrounded by a rim of ground-glass opacity. (C, D) Cavitory pattern. A subpleural cavitory lesion is seen in the left lower lobe (arrow). C: Lung window; D: Mediastinal window, demonstrating the cavity wall and intracavitary gas. (E) Tree-in-bud pattern with centrilobular nodules. Thin-section CT on the lung window shows centrilobular nodules and branching opacities (arrow), producing a tree-in-bud appearance. (F) Consolidation pattern. Thin-section CT on the lung window shows a peripheral patchy area of consolidation in the left lower lobe (arrow), with an internal air bronchogram. CT, computed tomography.

Asymptomatic PC is common, particularly in IC patients; management should include assessment for dissemination when immune risk or clinical features warrant it^[4,10].

In SID patients with PC, systemic evaluation for extrapulmonary dissemination and CNS involvement is recommended even when respiratory symptoms are mild^[10].

Recommendation 30 Patients with PC and SID are at high risk of disseminated disease; clinicians should closely monitor for CNS involvement. [Moderate-quality evidence, strong recommendation]

Diagnostic Techniques

Imaging Diagnostic Technologies: Chest CT is recommended for initial assessment and follow-up of PC. Findings may include solitary or multiple nodules or masses, consolidation, halo sign, cavitation, tree-in-bud pattern, multilobar disease, or rarely diffuse miliary disease. Imaging severity should be interpreted with symptoms, immune

status, and CrAg results^[103,104].

According to the 2024 global guideline for cryptococcosis^[44], PC is classified into mild and severe. Mild disease is defined by absent or mild symptoms, or by a solitary small pulmonary nodule with a maximum diameter < 2 cm. Severe disease is defined by any of the following: multiple lesions, a single lesion with a maximum diameter ≥2 cm, lobar consolidation, cavitation, multilobar involvement, or hypoxemia. Transient radiological worsening may occur early during treatment; therefore, treatment response should be assessed together with clinical symptoms and CrAg titers. Radiological resolution is often behind clinical improvement, and residual fibrotic streaks, focal fibrosis, or pleural thickening may persist after treatment.

The imaging features of PC overlap with those of other pulmonary diseases. Differential diagnosis should include pulmonary tuberculosis, non-tuberculous mycobacterial infections, invasive fungal infections, peripheral lung cancer and metastases, as well as organizing pneumonia.

Recommendation 31 Chest CT, including contrast-enhanced CT when clinically indicated, is recommended for the imaging diagnosis of PC. [GPS]

Recommendation 32 PC should be classified as mild or severe based on a combination of imaging findings and clinical manifestations. Mild disease is defined as asymptomatic or mildly symptomatic disease, or the presence of a solitary small nodule (< 2 cm). Severe disease is defined by any of the following: multiple lesions, lesion size ≥2 cm, consolidation, cavitation, involvement of multiple lobes, or hypoxemia. [Moderate-quality evidence, strong recommendation]

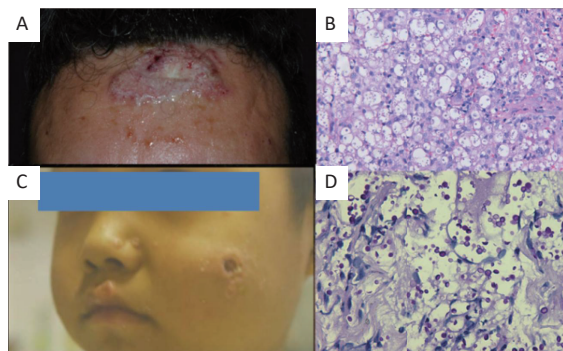


Figure 5. Representative clinical and histopathological findings of cutaneous cryptococcosis. Cutaneous cryptococcosis may present as erythematous plaques, nodules, ulcerative lesions, or molluscum contagiosum-like eruptions. The upper left panel shows forehead erythema, nodules, and ulcerative lesions in an HIV-positive patient reported by Yu et al.^[124] The lower left panel shows typical molluscum contagiosum-like facial lesions in a non-HIV, immunocompetent child reported by Yao et al.^[123] Histopathological examination shows numerous round-to-oval encapsulated yeasts within dermal inflammatory infiltrates; special staining further highlights cryptococcal organisms and supports the diagnosis. Reproduced with permission from references^[123,124].

Bronchoscopy and Percutaneous Lung Biopsy

Bronchoscopic Examination: Bronchoscopy with BALF testing is useful when noninvasive tests are insufficient, lesions are difficult to classify, or microbiological confirmation is needed. BALF may be submitted for CrAg, fungal culture, and molecular testing^[36,105].

Bronchoscopic tissue sampling, including TBLB and other guided bronchoscopic biopsy techniques, may be considered for peripheral or difficult-to-access lesions when noninvasive tests are insufficient. Tissue should be allocated for histopathology, culture, and molecular testing according to specimen volume and diagnostic priority^[36,44,105].

Percutaneous Transthoracic Needle Biopsy: Percutaneous transthoracic needle biopsy (PTNB)

should be considered for peripheral or subpleural lesions when tissue confirmation is needed and procedural risk is acceptable. Samples should be submitted for histopathology, fungal culture, and molecular testing whenever possible^[36,44].

Recommendation 33 Transbronchial lung biopsy (TBLB), transbronchial cryobiopsy (TBCB), and CT-guided PTNB are recommended as minimally invasive techniques for the diagnosis of pulmonary cryptococcosis. [Low-quality evidence, Conditional recommendation]

Principles of PC Diagnosis

For IC patients with mild and stable disease, clinical diagnosis may be sufficient to initiate treatment and follow-up. In patients with immunosuppression, uncertain diagnosis, progressive disease, or risk of dissemination, pathogen-based confirmation-including histopathology, culture, and antigen testing-should be obtained whenever possible to guide targeted therapy and improve prognosis. Comprehensive assessment of underlying host conditions, close monitoring of systemic and neuropsychiatric symptoms, and exclusion of disseminated cryptococcosis and CM are also recommended.

The diagnostic workflow should include: (1) Risk assessment and serum CrAg testing: Evaluate the risk of pulmonary cryptococcal infection based on host factors, environmental exposure, and clinical manifestations. In IC individuals, the positive rate of serum CrAg testing for PC is 56.4%, whereas in MID and SID patients, positivity exceeds 80%^[106]. (2) Chest CT examination and preliminary evaluation: If imaging findings are consistent with cryptococcal patterns, lesions are localized and stable, and CrAg testing is positive, antifungal therapy and follow-up monitoring may be initiated. (3) Indeterminate or progressive cases: If the diagnosis remains unclear, disease progresses, or dissemination is suspected, bronchoscopic examination, percutaneous lung biopsy, or thoracoscopic procedures should be performed to obtain histopathological evidence. Simultaneously, evaluation for EPC should be conducted in the clinical context.

Treatment of PC

Principles of Treatment: Before initiating therapy for PC, disease severity, immune status, and risk of dissemination should be assessed. Fluconazole monotherapy is recommended for mild disease. For severe PC, induction therapy with amphotericin B plus flucytosine is recommended, followed by

consolidation and maintenance therapy according to CM treatment principles. For infection caused by *C. gattii*, induction therapy should be extended to 4–6 weeks. Imaging follow-up should be monitored during treatment. Patients whose disease progresses despite fluconazole therapy should be evaluated for immunodeficiency, inadequate drug exposure, drug interactions, or antifungal resistance, and induction therapy with amphotericin B plus flucytosine should be initiated promptly. In cryptococemia or disseminated disease, including CM, systemic antifungal therapy should follow CM treatment principles regardless of pulmonary lesion severity.

Surgical Management: Most patients with PC achieve clinical cure with standard antifungal therapy, and surgery is not the first-line treatment.

Indications for Surgery: Surgical indications^[107–109] include: (1) persistent or refractory localized lesions that fail to resolve or enlarge after 6–12 months of standard antifungal therapy, or recurrent symptoms that affect quality of life despite adequate pharmacologic control; (2) special lesion types, including lesions ≥ 5 cm in diameter, large cavitory lesions with high hemoptysis risk, or multiple clustered nodular lesions that do not improve or continue to progress despite therapy; (3) diagnostic uncertainty, including lesions suspected to be PC but with repeatedly negative laboratory tests or biopsy, lesions requiring surgical biopsy for definitive diagnosis, or lesions whose imaging features cannot exclude lung cancer and are unsuitable for minimally invasive biopsy; and (4) coexisting early-stage lung cancer. Surgical intervention should prioritize diagnostic purpose and a minimally invasive approach. Video-assisted thoracoscopic surgery with wedge resection or segmentectomy is the standard procedure for typical peripheral localized lesions.

Perioperative Management of PC: Postoperative patients should continue antifungal therapy to ensure complete eradication of *Cryptococcus* and prevent relapse^[107]. Immunocompromised patients (e.g., diabetes, organ transplant, immunosuppressive therapy) should receive 2–4 weeks of preoperative antifungal therapy. During surgery, lesion isolation techniques should be used to prevent rupture, and complete resection of the lesion is recommended^[110]. Antifungal therapy should be resumed within 24–48 hours postoperatively to complete the treatment course. Resected specimens should be submitted for histopathology (PAS/GMS staining) and fungal culture. If *Cryptococcus* is detected at the lesion margins, postoperative therapy should be intensified^[6,110–112].

Recommendation 34 For mild PC, fluconazole is recommended at a dose of 400–800 mg/day for 6–12 months. [Moderate-quality evidence, strong recommendation]

Recommendation 35 For severe PC, induction therapy with liposomal amphotericin B (L-AmB) plus flucytosine (5-FC) for 2 weeks is recommended, followed by consolidation with fluconazole 400–800 mg/day for at least 8 weeks and maintenance with fluconazole 200 mg/day, consistent with the treatment principles for CM. [Moderate-quality evidence, strong recommendation]

Recommendation 36 Indications for induction therapy include: (1) severe PC; (2) mild PC with disease progression despite fluconazole therapy; and (3) pulmonary cryptococcosis with concomitant CM or extrapulmonary dissemination. [Moderate-quality evidence, strong recommendation]

Recommendation 37 Indications for surgical intervention include localized lesions refractory to antifungal therapy, lesions with diagnostic uncertainty requiring differentiation from lung cancer, and severe complications requiring surgical management. Multidisciplinary team (MDT) consultation is recommended to reassess surgical indications. [GPS]

Recommendation 38 After surgical resection of pulmonary cryptococcal lesions, the full antifungal treatment course should be completed to ensure cryptococcal clearance and prevent relapse. [Moderate-quality evidence, strong recommendation]

DISSEMINATED CRYPTOCOCCOSIS

Disseminated cryptococcosis is a systemic infection in which *Cryptococcus* spreads from the primary site, usually the lung, to multiple organs or systems^[113,114]. It is generally defined as involvement of two or more noncontiguous organs or tissues^[44]. CNS cryptococcosis or cryptococcemia should prompt management as disseminated disease unless an alternative explanation is established^[44,109].

Risk Factors of Disseminated Cryptococcosis

Disseminated cryptococcosis occurs predominantly in SID patients but may also occur in MID or IC patients. A positive serum CrAg result, especially at a high titer, should prompt systemic evaluation, including blood culture and molecular testing when appropriate^[10,44,109,113,115-117].

Diagnosis of Disseminated Cryptococcosis

Cryptococcemia: Cryptococcemia is a life-threatening invasive fungal infection and is usually considered part of disseminated cryptococcosis^[115]. Fever is the most common manifestation, occurring in 88% of immunocompromised patients and 75% of IC patients. Septic shock may occur in immunocompromised hosts. Multi-organ involvement may include the CNS, lungs, abdominal cavity, skin, bones, endometrium, or lymph nodes. Cryptococcemia screening is recommended when any of the following is present: (1) single-organ cryptococcosis accompanied by prolonged fever or abnormalities in other organs or systems; (2) rapidly progressive disease or poor control despite antifungal therapy; or (3) SID or MID with progressive immune impairment, including CD4⁺ T-lymphocyte count < 200 cells/μL.

The diagnosis of cryptococcemia should begin with serum CrAg testing to confirm antigenemia. In high-risk populations, this should be followed by blood culture for *Cryptococcus* and/or molecular diagnostic testing. Given the limited sensitivity of blood-based pathogen detection methods, negative results do not exclude the diagnosis. Clinical judgment remains essential, and in highly suspected cases of dissemination, prompt escalation of antifungal therapy is warranted^[115].

Evaluation of Organ Involvement: Disseminated cryptococcosis presents with heterogeneous and nonspecific clinical manifestations. Identification of organ involvement relies on detailed medical history and thorough physical examination. MDT approaches are recommended to establish an optimal diagnostic and therapeutic strategy and to confirm the diagnosis of disseminated disease^[115].

Treatment of Disseminated Cryptococcus

Delayed treatment of disseminated cryptococcosis is associated with poor outcomes. Untreated CM carries a mortality rate approaching 100%^[118]. Therefore, antifungal therapy should be initiated as early as possible. The treatment regimen for disseminated cryptococcosis is consistent with that for CNS cryptococcosis^[44].

Recommendation 39 Disseminated cryptococcosis is defined as involvement of two or more noncontiguous organs or tissues. In cases with single-organ involvement but confirmed cryptococcemia, management as disseminated cryptococcosis is recommended. [High-quality evidence, strong recommendation]

Recommendation 40 SID is a major risk factor for disseminated cryptococcosis. [High-quality evidence,

strong recommendation]

Recommendation 41 CrAg testing combined with blood culture for *Cryptococcus* and/or molecular diagnostic methods constitutes key evidence for the diagnosis of cryptococcemia. [Moderate-quality evidence, strong recommendation]

Recommendation 42 Treatment of disseminated cryptococcosis should follow the therapeutic regimen recommended for CM. [High-quality evidence, strong recommendation]

CRYPTOCOCCOSIS AT OTHER SITES

Cryptococcosis at sites other than the CNS and lungs is uncommon in adults and should generally trigger assessment for disseminated disease. This guideline focuses on cutaneous and genitourinary involvement.

Cutaneous Cryptococcosis

Cutaneous and genitourinary cryptococcosis are uncommon and should prompt evaluation for disseminated disease. Diagnosis requires sampling of suspicious lesions for histopathology, culture, antigen testing, or molecular testing as appropriate.

Cutaneous cryptococcosis requires prompt sampling of suspicious lesions or exudates for histopathology, India ink staining, culture, and molecular testing. Primary cutaneous disease may be treated with local debridement or resection plus fluconazole 400 mg/day for 6–12 months. Secondary cutaneous disease, cryptococcemia, CM, or involvement of multiple organs should be treated according to disseminated-disease or CM principles^[44,119-124].

Genitourinary Cryptococcosis

Genitourinary cryptococcosis, especially prostatic involvement, is rare and occurs mainly in immunocompromised patients. When detected, clinicians should evaluate for disseminated disease and consider whether the prostate may serve as a persistent focus contributing to relapse^[125-127].

Recommendation 43 When cryptococcosis is diagnosed at an extrapulmonary site, disseminated disease should be routinely excluded. [High-quality evidence, strong recommendation]

Recommendation 44 For confirmed primary cutaneous cryptococcosis after adequate evaluation has excluded dissemination, systemic fluconazole may be considered. Local debridement or excision should be reserved for diagnostic purposes, necrotic tissue, symptomatic lesions, or failure of medical

therapy. [Low-quality evidence, conditional recommendation]

IMPLEMENTATION, LIMITATIONS, AND RESEARCH PRIORITIES

This guideline provides a risk-stratified framework for adult cryptococcosis. Important limitations include limited randomized evidence in non-HIV populations, heterogeneous observational data, and uncertainty regarding optimal duration of therapy in selected subgroups. Future updates should incorporate prospective multicenter validation and implementation research.

Future research should focus on multicenter prospective clinical validation and integration of multimodal data, facilitating the incorporation of the artificial intelligence tools into clinical workflows. Ultimate goal is to establish a full-cycle clinical management system that integrates intelligent screening, precise risk stratification, and individualized therapy to address the global challenge of cryptococcal infections.

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