INTERNAL MEDICINE JOURNAL

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doi:10.1111/imj.15590

SUPPLEMENT ARTICLE

Consensus guidelines for the diagnosis and management of cryptococcosis and rare yeast infections in the haematology/oncology setting, 2021

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Key words
cryptococcosis, cryptococcal meningitis, *Cryptococcus* spp., immune reconstitution inflammatory syndrome, *C. gattii*.

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Abstract

Cryptococcosis caused by the *Cryptococcus neoformans–Cryptococcus gattii* complex is an important opportunistic infection in people with immunodeficiency, including in the haematology/oncology setting. This may manifest clinically as cryptococcal meningitis or pulmonary cryptococcosis, or be detected incidentally by cryptococcal antigenemia, a positive sputum culture or radiological imaging. Non-*Candida,* non-*Cryptococcus* spp. rare yeast fungaemia are increasingly common in this population. These consensus guidelines aim to provide clinicians working in the Australian and New Zealand haematology/oncology setting with clear guiding principles and practical recommendations for the management of cryptococcosis, while also highlighting important and emerging rare yeast infections and their recommended management.

Introduction

This chapter provides an update of key advances in the management of cryptococcosis and rare yeast infection by building on information presented in the preceding consensus guidelines for the treatment of yeast infections in the haematology and oncology setting by Chen *et al.*[1] We aim to provide clinicians with clear guiding principles and practical recommendations on the management of cryptococcosis, focusing on cryptococcal meningitis (CM), pulmonary cryptococcosis and cryptococcal antigenemia. We also highlight important and emerging rare yeast infections and their recommended management for Australian and New Zealand haematology-oncology settings.

Cryptococcosis caused by the *Cryptococcus neoformans–Cryptococcus gattii* complex is an important opportunistic infection in immunodeficient persons. Other non-*neoformans,* non-*gattii Cryptococcus* species of lower pathogenicity are not covered in these guidelines. Cryptococcosis affects persons living with human immunodeficiency virus (HIV) disproportionately. Persons with haematological and oncological malignancies, those on biological therapies, and solid organ transplant (SOT) and haematological stem cell transplant (HSCT) recipients are also at increased risk. Moreover, a significant proportion of cases of cryptococcosis, especially those due to *C. gattii,* occur in individuals

Funding: None.
Conflict of interest: None.

who are seemingly immunocompetent. Despite its endemicity in Australia, cryptococcosis remains underappreciated, does not feature highly on most clinicians' list of differential diagnoses and is underdiagnosed (particularly in non-HIV settings). Cryptococcosis is mostly due to reactivation but can also occur as an acute infection. Of its many manifestations, those involving the central nervous system (CNS) are best known (CM, encephalitis, cerebral cryptococcomas) and are usually lethal if left untreated. Although infection is predominantly acquired by inhalation, less is known about pulmonary than CNS cryptococcosis, as the former is often subclinical or asymptomatic. Clinical research studies in cryptococcosis focus on CM in high-burden settings, which are generally resource-limited settings (RLS) and associated with HIV infection. There are large research gaps in every other setting and in non-CNS clinical syndromes.

Here, we discuss key management principles for CM (drawn largely from the HIV literature) and pulmonary cryptococcosis. In contrast to the 2014 guidelines,[1] where management was 'split' and considered in relation to infecting species as well as the underlying host's immune status and clinical syndromes, here we will focus predominantly on clinical syndromes while providing some guiding principles for optimising individualised care. The lack of clinical trials in non-HIV settings and non-CM settings makes it difficult to justify dogmatic recommendations on treatment duration and choice when considering different hosts and infecting species. A unifying approach is presented, along with some exceptions in order to cater for individual scenarios. We cross-reference other contemporary guidelines on cryptococcosis,[1–4] highlighting the varying target audience for whom the guidelines are written.

Furthermore, we will discuss two common clinical conundrums to illustrate approaches to diagnosing underlying cryptococcosis: (i) a positive culture of *Cryptococcus* spp. from sputum and (ii) a positive serum cryptococcal antigen (sCrAg). We follow with a discussion on the diagnosis and management of cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS) where an immune flare due to dysfunctional immune recovery leads to severe illness mimicking cryptococcal infection.

The evolving nomenclature of fungi and the rapid expansion of hosts susceptible to opportunistic infections have contributed to an increase in the number and range of rare yeast infections. Emerging (non-*Candida*, non-*Cryptococcus* spp.) yeast infections in haematology-oncology settings are closely linked to in-dwelling devices, mucositis and admission to intensive care units (ICU), and occasionally to healthcare outbreaks. As a result of their rarity, the literature is largely comprised of retrospective case series, reports of outbreaks and case-reports. In discussing these infections, we highlight laboratory features important for microbiological phenotyping, recognising that molecular identification is critical. While acknowledging that robust data for rare infections are limited, we provide recommendations for antifungal therapy and key management steps, cross-referencing other contemporary guidelines where relevant,[5] including a new comprehensive global guideline by Chen *et al*., 2021.[221] Treatment of *Candida* spp. (including several previous *Candida* spp. that have now been reclassified) infections are discussed in the accompanying consensus guidelines for the management of *Candida* by Keighley *et al*. 2021,[223] which can be found elsewhere in this supplement.

Methodology

Questions asked

This update addresses the following questions:

1 Is speciation of *Cryptococcus* species necessary in clinical practice and does it change management?
2 How do we best diagnose, treat and monitor patients with cryptococcosis?
3 How do we manage raised increased intracranial pressure (ICP) in patients with cryptococcal meningoencephalitis?
4 How do we manage a patient with a sputum positive for *Cryptococcus* spp. growth?
5 How do we manage a patient with a positive serum cryptococcal antigen, including incidental/asymptomatic antigenemia?
6 How can we best diagnose and manage C-IRIS?
7 What are the rare but clinically relevant yeasts, and how should they be diagnosed and treated?

Search strategy

A literature review was performed using PubMed, Medline and contemporary conference abstracts to identify relevant publications up until June 2020. Search terms included 'cryptococcosis', 'cryptococcal meningitis', 'pulmonary cryptococcosis', 'serum cryptococcal antigen', 'cryptococcosis-associated immune reconstitution inflammatory syndrome', '*Cryptococcus neoformans*', '*Cryptococcus gattii*' and 'yeast and diagnosis, treatment and management'.

Question 1: Is speciation of *Cryptococcus* species necessary in clinical practice and does it change management?

Recommendations

- Differences in morphology, biology and phylogenetics support the concept of *C. gattii* as a species distinct from *C. neoformans*. We recommend isolates be routinely differentiated into *C. neoformans* complex and *C. gattii* complex in clinical laboratories (Strong recommendation, Level II evidence).
- Further division into molecular clades does not need to be routinely done in clinical practice (Strong recommendation, Level III evidence).

In 2002, based on morphological, biological and phylogenetic (genetic) species concepts, *C. neoformans* was separated taxonomically into two species: (i) *C. neoformans* and (ii) *C. gattii* (reviewed by Chen *et al.*).[6] These species may be divided further into varieties (var.) by serology and into genotypes by molecular testing,[7] but this is usually limited to research settings. The cryptococcal research community continues to debate the utility of a recent proposal[8] to divide *C. neoformans* into two species and *C. gattii* into five species, with an overhaul of the nomenclature.[9,10] Recognising its many species and varieties, a positive culture for *Cryptococcus* spp. is commonly reported in some laboratories as the *C. neoformans–C. gattii* complex. In laboratories where speciation is performed (usually by inoculation onto canavanine-glycine-bromothymol agar where colonies of the *C. gattii* complex appear blue and the *C. neoformans* complex exhibit no colour change),[11–13] reporting of species type is available.

In clinical settings, differentiation of *Cryptococcus* spp. into *C. neoformans* complex and *C. gattii* complex is recommended (*Strong recommendation, Level II evidence*). This allows for a deeper appreciation and understanding of observed differences in ecology, epidemiology and clinical presentation and assists in fungal surveillance generally. In brief, *C. neoformans* occurs worldwide. High concentrations are found in the environment in association with weathered pigeon droppings and its two varieties, *C. neoformans* var. *grubii* and var. *neoformans*, are typically associated with underlying immunodeficiency (particularly in persons living with HIV). In contrast, *C. gattii* is more geographically restricted and its environmental niche comprises a range of tree species such as eucalyptus and mopane trees. *C. gattii* typically (but not exclusively) affects immunocompetent hosts and in Australia, it is more likely to present with mass lesions (cryptococcomas) in both the lung and brain, occasionally requiring surgery.[14] While *C. gattii* is said to occur in patients with normal immune systems, it can also occur in HIV-infected patients, and in those with cancers or on immunosuppressant agents. Detailed studies of select individuals have revealed underlying subtle and unrecognised immunodeficiencies, such as the presence of autoantibodies to granulocyte-macrophage colony-stimulating factor[15] and idiopathic lymphocytopenia (reviewed by Chen *et al.*).[6]

In research settings, a variety of molecular and serological methods are used to distinguish the specific molecular types of the *C. neoformans–C. gattii* complex into *C. neoformans* I–IV and *C. gattii* I–V, with some attendant differences in epidemiology and risk setting. There is no clear association of cryptococcal species and/or molecular type and azole drug susceptibility (reviewed by Datta *et al.*).[16] Serological and molecular typing are not routinely done in clinical practice in Australia and New Zealand.

Differences in morphology, biology and phylogenetics support the concept of *C. gattii* as a species distinct from *C. neoformans*. We recommend that clinical isolates are routinely differentiated into *C. neoformans* complex and *C. gattii* complex in clinical laboratories (*Strong recommendation, Level II evidence*). Further division into molecular clades does not need to be routinely done in clinical practice (*Strong recommendation, Level III evidence*). It is recommended that all cases of cryptococcosis, including those due to the *C. gattii* complex have an assessment of immune function that includes full blood examination and film, HIV screening and measurement of T lymphocyte subsets (CD4+/CD8+ T cells) as a minimum (*Strong recommendation, Level II evidence*). Patients with severe cryptococcosis, without any obvious immunodeficiency, particularly those with a prior history of another opportunistic infection, may benefit from a detailed assessment by a clinical immunologist to explore the possibility of subtle immunodeficiencies (*Moderate recommendation, Level III evidence*).

There are no head-to-head clinical trials comparing the clinical response to antifungal therapy and cryptococcal species or molecular type. Therefore, it is recommended that choice of therapy is rather based primarily on the site of infection with a longer duration of induction and total therapy in patients with CNS involvement or severe lung disease than for patients with an isolated pulmonary focus of infection (*Moderate recommendation, Level II evidence*). Further studies are required to delineate whether treatment should vary according to infecting *Cryptococcus* species.

Question 2: How do we best diagnose, treat and monitor patients with cryptococcosis?

Recommendations

- Diagnosis of cryptococcosis relies on careful history and examination, serum cryptococcal antigen, chest

X-ray ± chest computed tomography (CT), and lumbar puncture with measurement of opening pressure and cerebrospinal fluid (CSF) analysis (Strong recommendation, Level II evidence).

- We recommend liposomal amphotericin 3–4 mg/kg/day and 5-Flucytosine is 25mg/kg four times daily (qid) as induction therapy for CM (Strong recommendation, Level I evidence).
- See in-text commentary and tables provided for detailed treatment recommendations and related evidence grading.

Diagnosis of cryptococcal infection

The presentation of cryptococcosis is protean. Alongside constitutional symptoms of fever, malaise and weight loss, site-specific symptoms can occur. These include CNS-based symptoms such as headache, confusion, nausea, vomiting, visual and hearing impairment; respiratory-based symptoms of cough and shortness of breath; skin lesions; or hoarse voice in the case of laryngeal cryptococcomas. It may even be detected incidentally on imaging (particularly chest and brain). General recommendations for diagnosis are unchanged from the 2014 guidelines[1] with careful history and examination, serum cryptococcal antigen, chest X-ray ± chest CT, lumbar puncture with measurement of opening pressure and CSF analysis (including biochemistry, cell counts, culture and CSF cryptococcal antigen (CrAg)), recommended (*Strong recommendation, Level II evidence*). We continue to advocate for a high degree of clinical suspicion of cryptococcosis and low threshold for diagnostic testing in all immunocompromised hosts (*Strong recommendation, Level II evidence*).

A recent publication reported 145 cases of non-HIV cryptococcosis over 4 years in the United States. Underlying diseases included SOT (33.8%), autoimmune syndromes (15.9%), haematological malignancy (11.7%), decompensated liver disease (9.7%), solid tumour (5.6%), primary immunodeficiency (2.1%) and HSCT (1.3%).[17] Evidence continues to accumulate that non-HIV, non-SOT patients suffer poorer outcomes from cryptococcal infection, especially with regards to long-term neurological sequelae.[17,18] Atypical clinical presentations and low clinical suspicion are likely contributors to its delayed diagnosis.[17] Subclinical disease is common. In a recent study of 31 patients with cryptococcosis and cancers in Victoria, Australia, almost 20% were asymptomatic and discovered as part of staging and treatment for cancer.[19]

There have been advances in screening for cryptococcosis by CrAg amongst HIV-infected patients, and where testing is available, a screen and treat approach is cost-effective and is recommended by the World Health Organisation (WHO).[3] No research into primary surveillance in non-HIV patient groups has been conducted, so there is no evidence on which to base additional recommendations for screening (see Question 5).

Treatment in resource-rich settings such as Australia and New Zealand

To date, all prospective treatment studies in cryptococcosis have been conducted in CM. Over the last 20 years, these trials have been based nearly exclusively in patients co-infected with HIV in RLS, where access to liposomal amphotericin (L-AMB) and 5-flucytosine are constrained along with other healthcare system challenges. The evidence for treatment approaches may thus be biased with regards to both syndrome and setting. Non-HIV associated cryptococcosis is relatively rare and large studies are limited to a descriptive cohort in SOT recipients,[20–24] retrospective studies in *C. gattii*,[14,25] or descriptive reports subsequent to the Vancouver outbreak.[18,26] As such, all treatment recommendations here are extrapolated from the findings of multiple, well-designed therapeutic trials in HIV-associated cryptococcosis in RLS where L-AMB and 5-flucytosine are scarce. Treatment updates since 2014 are outlined in Table 1. Our recommendations assume that clinicians in Australia and New Zealand have access to the full antifungal repertoire including L-AMB and 5-flucytosine, both cornerstones to cryptococcosis, and enhanced clinical staff and laboratory services to facilitate therapeutic lumbar punctures (LP) and their analyses.

Other frequently referenced cryptococcal guidelines include the Infectious Diseases Society of America (IDSA) cryptococcal guidelines by Perfect *et al.*,[4] written for an American infectious disease audience managing any patient with cryptococcosis; the HIV/AIDS-focused guidelines for the prevention and treatment of opportunistic infection by the Centers for Disease Control and Prevention, the National Institutes of Health and the HIV Medicine Association of IDSA last updated in 2016 and reviewed in 2019[2]; and the 2018 WHO management guidelines supplement targeted at HIV-infected individuals in RLS.[3] Under the 'One World – One Guideline' initiative, the International Society of Human and Animal Mycology/European Confederation of Medical Mycology are also currently developing guidelines for cryptococcosis.[28]

Principles of CM antifungal therapy

CM treatment traditionally has been divided into induction, consolidation and maintenance phases. Induction relies on intravenous amphotericin-based regimens and the later phases use varying doses of oral fluconazole.

Table 1 Antifungal therapy recommendations for the treatment of CNS cryptococcosis encompassing CM, cryptococcal meningoencephalitis and cerebral cryptococcomas in Australian/New Zealand settings by induction, consolidation and maintenance phase

Phase	First-line agent	SoR	QoE	Comments re: first-line agent	Alternative agents	Comments re: alternative agents
Induction (usually ~2 weeks)	L-AMB 3–4 mg/kg daily plus 5-flucytosine 25 mg/kg QID	A	I	AMB-D 1 mg/kg daily plus 5-flucytosine 25 mg/kg QID shows mortality benefit compared with AMB-D plus fluconazole and AMB-D 1 mg/kg daily monotherapy[27] Where available, L-AMB is preferred over AMB-D to reduce renal toxicity Consider longer duration in cerebral cryptococcoma	Where liposomal formulations are not available: AMB-D 1 mg/kg daily plus 5-flucytosine 25 mg/kg QID	Conventional AMB-D 1 mg/kg daily plus 5-flucytosine 25mg/kg qid showed mortality benefit compared with AMB-D plus fluconazole and AMB-D 1 mg/kg daily as monotherapy[27]
					Where 5-flucytosine is not available: L-AMB 3–4 mg/kg daily (or AMB-D 1 mg/kg daily) plus fluconazole 800–1200 mg daily	AMB-D 1mg/kg daily plus fluconazole 400 mg twice daily was inferior to AMB-D 1mg/kg daily plus 5-flucytosine 25mg/kg qid but superior to fluconazole alone[27]
					Where neither amphotericin-based nor 5-flucytosine therapy are available: fluconazole 1200 mg daily	In RLS, the use of high-dose fluconazole for induction therapy delivers better outcomes than low-dose fluconazole
Consolidation (usually ~8 weeks)	Fluconazole 400–800 mg daily	A	II	In those with higher disease burden, consider a higher dose of fluconazole	–	–
Maintenance (usually 6–12 months as immunodeficiency improves, e.g. CD4 >100 on ART)	Fluconazole 200 mg daily for 6–12 months	A	III	No clear duration known for non-HIV settings	–	–

AMB-D, amphotericin B deoxycholate (conventional amphotericin); ART, antiretroviral therapy; HIV, human immunodeficiency virus; L-AMB, liposomal amphotericin; QoE, quality of evidence; RLS, resource-limited settings; SoR, strength of recommendation.

Nearly all treatment studies to date focus on the induction phase, and contemporary trials generally compare by antifungal agents rather than by length of induction. The 2-week recommended duration of the induction phase is extrapolated from prior study designs, but in practice, clinicians will vary the length of induction based on clinical response. Consolidation is usually given for about 8 weeks, with some clinicians extending this duration or increasing the dose of consolidation therapy. Maintenance is given largely as secondary prophylaxis, usually until there is measurable immune recovery. This is best demonstrated in HIV where discontinuation in those with CD4 ≥100 cells/μL and an undetectable viral load on antiretroviral therapy (ART) for >3 months, showed no episodes of CM recurrence.[29] A dose of 400–800 mg of fluconazole is recommended in consolidation phase and 200 mg in maintenance phase (*Strong recommendation, Level II evidence*).

First-line induction therapy in CM infection

The best trial evidence for induction therapy for CM infection continues to be the combination of conventional amphotericin B deoxycholate (AMB-D) 1 mg/kg/day and 5-flucytosine 25 mg QID[27,30–32] (Table 1; *Strong recommendation, Level I evidence*). While the clinical trials performed in RLS studied AMB-D, in Australia and New Zealand, we continue to recommend substituting this with liposomal amphotericin (3–4 mg/kg/day) (*Strong recommendation, Level I evidence*). There is no evidence for AMB-D being more effective than the liposomal formulation, and the latter is associated with fewer adverse events, especially in patients with pre-existing renal impairment.[33–35]

Alternative drugs in induction therapy

In RLS, where amphotericin and flucytosine are not commonly available, alternative induction therapies

Internal Medicine Journal (2021) **51**(Suppl. 7) 118–142

using high-dose fluconazole (up to 1200 mg daily) have been studied (Table 1).[36,37] Shorter duration of amphotericin-based induction therapy followed by higher oral fluconazole-based induction have been trialled,[38,39] as have higher but less frequent doses of liposomal amphotericin.[33] A Cochrane systematic review in 2018 explored the best induction therapy in RLS and suggested that 1 week of AMB-D and 5-flucytosine was probably superior to other regimens for treatment of HIV-associated CM. It also found that the all-oral regimen of 2 weeks of fluconazole and 5-flucytosine may be an alternative in settings where amphotericin B is unavailable or intravenous therapy cannot be safely administered.[40] Interim results of the AMBITION-CM trial suggests that a single-dose of L-Amb 10mg/kg and 14 days of 5-flucytosine 25mg/kg qid and fluconazole 1200mg daily to be non-inferior to 7 days of Amb-D 1mg/kg daily plus 5-flucytosine 25mg/kg qid followed by 7 days of 1200mg fluconazole.[222] These findings are not generalisable to Australian and New Zealand settings.

Intensifying induction therapy

Clinicians should utilise clinical judgement when managing individual cases of CM. When faced with patients with severe neurological deficits, large cerebral cryptococcomas, advanced immunodeficiency or an immunodeficient state that cannot be readily reversed, some have attempted to intensify induction therapy. This has been done by extending the duration of amphotericin-based induction therapy (e.g. 4–6 weeks or longer), increasing the dose of antifungal agents (e.g. 5 mg/kg/day L-AMB) and/or increasing the dose of fluconazole consolidation therapy to approximate what is used in alternative induction regimens.

Treatment of *C. gattii* infection

C. gattii has long been known to be endemic in Australia, with early reports from tropical areas of the Northern Territory[41] and also from temperate Australia.[42] Key Australian papers on *C. gattii* infection include a comprehensive review by Chen *et al.*,[6] insights derived from a nationwide retrospective study of culture-confirmed *C. gattii* from 2000 to 2007[14,25] and work emphasising its zoonotic aspects.[43,44]

There has been no prospective treatment study focused on *C. gattii* infection to date and no new data have emerged to guide therapy of *C. gattii* infection since the previous 2014 guidelines. Locally, clinicians typically use a prolonged induction phase with amphotericin B and 5-flucytosine for 4–6 weeks followed by consolidation therapy for 12–18 months, for treatment of CNS cryptococcosis. An Australian series of 86 cases suggested that this approach enabled clinical cure (*Marginal recommendation, Level III evidence*).[25] Based on small case numbers, fluconazole monotherapy is not recommended in *C. gattii* meningitis due to the high risk of failure. Single, large, surgically accessible cryptococcomas may require surgical removal in addition to antifungal therapy to effect cure.[25]

Disease restricted to the lung may be managed with 2 weeks of induction therapy with amphotericin B and 5-flucytosine. Treatment failure has been documented following fluconazole monotherapy,[25] although very mild lung disease with no immunosuppression may be amenable to such therapy (*Marginal recommendation, Level III evidence*). Severe failure to thrive or progression of disease despite adequate antifungal therapy are indications for surgical removal. Expert review is recommended.

Adjunctive therapies

Driven by the paucity of new antifungal agents and the prospect of host immunomodulation, the use of adjuvant therapies in CM has been actively investigated, albeit unsuccessfully, since the 2014 guidelines. Two older randomised trials of exogenous interferon gamma (IFN-γ) as adjuvant therapy for CM are discussed here, beginning with a study of two patients with CM and idiopathic CD4 lymphopenia, in whom defective IFN-γ production was reversed with exogenous IFN-γ 50 μg thrice weekly, with associated improvement in clinical outcome.[45] An early phase 2, double-blind, placebo-controlled study of antifungal therapy combined with IFN-γ 1b (100 or 200 μg thrice weekly for 10 weeks) or placebo in CM-HIV co-infected individuals ($n = 70$) showed a non-significant trend towards improved CSF clearance of cryptococci.[46] Adverse events were significantly increased and included fever, rigours, headache, malaise and fatigue.[46] A later randomised, open-label study compared the addition of two or six doses of 100 μg IFN-γ 1b to antifungal therapy ($n = 88$). Both IFN-γ-containing arms demonstrated faster rates of CSF fungal clearance but no difference in mortality.[47] Since the last guidelines were published in 2014, an open-label study of the role of IFN-γ 1b in invasive fungal infections was reported in a handful of patients with invasive candidiasis and aspergillosis, demonstrating improved pro-inflammatory cytokine production *ex vivo*.[48] Based on current evidence, we do not recommend the routine use of IFN-γ in CM (*Not recommended, Level II evidence*). Use of IFN-γ may be considered in exceptional circumstances with expert consultation (*Marginal recommendation, Level II evidence*). Further studies are needed.

Based on the proven benefit of adjunctive corticosteroid treatment in tuberculous meningitis,[49] adjunctive dexamethasone commenced at diagnosis of HIV-associated CM was investigated in a randomised, double-

blind, placebo-controlled trial ('Crypto-Dex') in a range of RLS. The trial was halted by the data safety and monitoring board after 451 persons (just over half of the number planned) were enrolled,[50] as it conclusively showed that daily high-dose dexamethasone (starting at 0.3 mg/kg/day then weaned weekly over 6 weeks to 1 mg/day) was harmful.[50] Compared with placebo, dexamethasone caused increased rates of disability, slower fungal clearance, more adverse events and a trend towards increased mortality at 10 weeks (47% vs 41%).[50] Because the trial was stopped early, the intended pre-specified subgroup analyses for efficacy in IRIS, space-occupying lesions and acute respiratory distress syndrome could not be performed. It remains unclear whether steroids are beneficial in these specific circumstances.

Although case series have suggested steroids can be of benefit in non-HIV disease, especially those with *C. gattii* infections and cases with CNS mass lesion with significant oedema,[51,52] there is no clinical trial evidence for efficacy or harm of steroids in these patients. Notably, their baseline immune function differs from that of patients with HIV-associated disease. On balance, we recommend against the routine use of high-dose steroids in CM treatment (*Not recommended, Level I evidence*), but a short course may be considered for specific indications such as space-occupying lesions with surrounding mass effect (*Marginal recommendation, Level III evidence*).

Sertraline, a selective serotonin reuptake inhibitor, was investigated as adjunctive therapy in Astro-CM, a phase 3 double-blind, randomised, placebo-controlled study conducted in Uganda in HIV-CM co-infected patients,[53] and in a smaller study in Mexico,[54] and was found to be ineffective. Hence, sertraline is not recommended for the treatment of CM (*Not recommended, Level I evidence*). A randomised open-label trial of adjunctive tamoxifen 300 mg/day was ineffective.[55] Thus, tamoxifen is also not recommended for the treatment of CM (*Not recommended, Level II evidence*).

General principles in CM management

Management of raised ICP is critical in a patient with CM. All patients with CM should have therapeutic LP performed (see Question 3). For all patient populations, a repeat LP to check for cryptococcal sterility before switching from induction to consolidation is prudent (*Moderate recommendation, Level II evidence*). Although there are no studies to guide responses to positive cultures at the end of induction therapy, continuing induction therapy for a further week and repeating LP or utilising a higher dose of consolidation therapy may be advisable (*Moderate recommendation, Level III evidence*). Table 2 provides some guiding principles for the management of cryptococcosis and CM.

Table 2 Guiding principles for cryptococcosis and CM management

1	Always consider cryptococcosis and CM – understand its varied clinical manifestations and have a low threshold for considering this possibility
2	Measure opening pressure when performing all LP – may be a diagnostic clue to CM. Raised ICP is a poor prognostic factor in CM but is also modifiable with good management, including therapeutic LP
3	Administer the best available antifungal therapy and persist. Mild/moderate adverse events may be managed without switching to less-optimal antifungal regimens
4	Investigate for underlying immunosuppression – if history and examination do not reveal an underlying primary or acquired immunodeficiency, consider HIV serology, full blood examination and blood film, $CD4^+$ and $CD8^+$ T cell subsets, and/or discussion with or referral to a clinical immunologist
5	Culture large volumes of CSF – CSF fungal burden vary and larger volumes of CSF allow for increased sensitivity of culture for diagnosis and exclusion of other pathogens
6	Be proactive in performing therapeutic LP in CM – management of raised ICP is key in CM management; good control of raised ICP reduces morbidity
7	Aim for CSF culture negativity – culture negativity reduces future risk of neurological deterioration, C-IRIS and mycological relapse[56]
8	Do not start ART 'too early' – be careful when altering underlying immunosuppression. In HIV, very early ART treatment in patients with very low CD4 counts increases risk of C-IRIS and death. In SOTs, cessation of calcineurin inhibitors is associated with increased risk of C-IRIS[57]
9	Be prepared for symptom recurrence – CM is a complex and protracted condition; signs and symptoms may wax and wane. Patient education and heightened awareness by patients and clinicians is necessary to allow for quick responses, including urgent therapeutic LP. Careful clinical assessment is key. Do not rely on sCrAg levels
10	Forewarn patients of the possibility of C-IRIS – this will alert patients to the importance of monitoring for and reporting symptom recurrence and reduces patient disappointment in clinical care

ART, antiretroviral therapy; C-IRIS, cryptococcosis-associated immune reconstitution inflammatory syndrome; CM, cryptococcal meningitis; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; ICP, intracranial pressure; LP, lumbar puncture; sCrAg, positive serum cryptococcal antigen; SOT, solid organ transplant.

Management of pulmonary cryptococcosis

Please see Table 3 for antifungal recommendations. For detailed commentary, refer to Question 4.

Other non-CNS, non-pulmonary cryptococcosis

Of 146 SOT recipients with cryptococcosis, cutaneous cryptococcosis was the third most common manifestation ($n = 26$, 17.8%) occurring at a median of 27.3 months (interquartile range 9.5–68.4 months) post-transplantation.[24] In eight of these recipients, cryptococcosis was limited to the skin.[24] There are no treatment studies on cutaneous cryptococcosis or other

Table 3 Antifungal therapy recommendations for the treatment of pulmonary cryptococcosis and non-CNS, non-pulmonary cryptococcosis in the Australian/New Zealand setting

Cryptococcosis syndrome and severity	Antifungal therapy	SoR	QoE	Comment
Concurrent pulmonary and CNS cryptococcosis	As per CNS cryptococcosis	A	III	CNS disease manifestations may be subtle. Thorough assessment including LP and CSF analysis is recommended
Severe pulmonary cryptococcosis (e.g. large obstructing lesion)	As per CNS cryptococcosis	A	III	CNS disease manifestations may be subtle. Thorough assessment including LP and CSF analysis is recommended Surgical debulking may be required if vital structures are threatened, there is no reduction in lesion size despite optimal therapy, or the patient fails to thrive after prolonged therapy
Moderate, mild or asymptomatic pulmonary cryptococcosis	Fluconazole 400–800 mg daily for 6–12 months	B	III	In patients who are immunodeficient, clinicians may consider more aggressive treatment (i.e. CNS guidelines) even in mild/moderate disease
Other non-CNS, non-pulmonary cryptococcosis	Fluconazole 400 mg daily for 6–12 months	B	III	No studies to guide choice or duration of therapy Recommend thorough assessment to exclude CNS and pulmonary involvement

CNS, central nervous system; CSF, cerebrospinal fluid; LP, lumbar puncture; QoE, quality of evidence; SoR, strength of recommendation.

non-CNS, non-pulmonary cryptococcosis. Fluconazole 400 mg daily for 6–12 months is recommended (Table 3; *Moderate recommendation, Level III evidence*). Further research is needed. Seek expert advice for bone cryptococcosis and other unique sites.

Antimicrobial susceptibility testing

Our recommendation that routine susceptibility testing is not required remains unchanged from the 2014 guidelines (*Not recommended, Level III evidence*).[1] There are no standardised minimum inhibitory concentrations (MIC) breakpoints; MIC levels do not correspond with outcomes and primary resistance is uncommon in Australia. In rare cases where fluconazole resistance is suspected, therapeutic drug monitoring levels are recommended (*Moderate recommendation, Level III evidence*). Please refer to the accompanying guidelines on optimising antifungal therapy and TDM by Chau *et al*. 2021,[224] which can be found elsewhere in this supplement, for detailed guidance. High-end dosing coupled with TDM is recommended.

Post-cryptococcosis monitoring

Careful clinical evaluation is critical following cryptococcosis. Cryptococcomas and serum antigenemia persist usually beyond the duration of therapy and sCrAg may be positive for years,[18] especially when initial values are high. While clinicians commonly perform sCrAg testing every few months post CM or cryptococcosis therapy, where a reduction in sCrAg titres can be reassuring, persistently high titres or slight increases in titres are of little consequence and should not be used in isolation to alter management. There is little utility in regular or long-term secondary surveillance with sCrAg (*Not recommended, Level II evidence*). Clinical assessment is key to interpreting any sCrAg result. Suspicion of cryptococcal relapse should trigger thorough clinical assessment, including LP with opening pressure assessment, CSF cultures and imaging; C-IRIS must be considered in the differential (*Strong recommendation, Level II evidence*).

Paediatrics and pregnancy

There is a lack of studies addressing CM treatment in children. Our recommendations are extrapolated from adult studies and represent expert opinion. A recent 10-year audit from the Australia paediatric network, described 22 rare paediatric cases of CM; CNS manifestations predominated, and mortality and long-term morbidity were both high.[58] In contrast, CM is the dominant aetiology in paediatric meningitis in Botswana,[59] mirroring adult CM epidemiology in settings with a high burden of HIV.

L-AMB has been used safely in immunocompromised children at mg/kg doses comparable to those used in adults.[60] There are limited data (small retrospective studies only) on the use of L-AMB in neonates at doses of 1–7 mg/kg/day.[61] Recommended doses are 3 mg/kg/day for neonates and 3–5 mg/kg/day for infants and children.[62] Treatment doses of fluconazole in infants and

children range from 6 to 12 mg/kg/day.[62] Pharmacokinetic studies in neonates have demonstrated that for invasive fungal infection, a fluconazole loading dose of 25 mg/kg followed by daily dosing of 12 mg/kg is required to achieve desired pharmacokinetic/pharmacodynamic parameters.[63] In infants and children, 5-flucytosine is dosed at 100–150 mg/kg/day in divided doses. Given the limited pharmacokinetic, safety and efficacy data, clinicians should use 5-flucytosine with caution and maintain a high level of vigilance for adverse events. The use of 5-flucytosine in neonates is complicated by reduced renal clearance, which results in high drug concentrations and toxicity. Thus, it is not recommended for use in neonates.[64] Neonatal antifungal dosing is complex and dependant on both gestational and postnatal age of the patient. It is recommended that clinicians consult a neonatal medication dosing reference document, such as the Australasian Neonatal Medicines Formulary,[65] for specific dosing (*Strong recommendation, Level III evidence*).

Treatment of cryptococcosis in pregnancy is difficult, particularly with limited options for consolidation and maintenance therapy. In a review of 50 cases of cryptococcosis in pregnancy, out of those with known outcomes, 27.7% of women and 19.0% of babies died.[66] L-AMB (Category B2 in pregnancy), AMB-D (Category B3 in pregnancy) and 5-flucytosine (Category B3 drug in pregnancy) may be considered in pregnancy if the possible benefits outweigh the potential risks. Where possible, fluconazole (Category D drug in pregnancy) should be avoided until after delivery, but especially in the first 22 weeks of pregnancy due to an increased risk of musculoskeletal malformations,[67] tetralogy of Fallot[68] and spontaneous abortions[69] (*Not recommended, Level II evidence*). Intermittent dosing of L-AMB as consolidation and maintenance therapy may be an alternative. Of note, several cases of transplacental transmission of cryptococcosis have been described,[70,71] suggesting that careful assessment of newborns of infected mothers is necessary.

Question 3: How do we manage raised ICP in patients with cryptococcal meningoencephalitis?

Recommendations

- Therapeutic LP are necessary in patients with symptoms and signs of raised ICP and in those with known raised ICP regardless of symptoms (Strong recommendation, Level II evidence).
- Key management recommendations are provided in Table 4.

Table 4 Recommendations for management of raised ICP

Recommendation	SoR	QoE
If there is persistent pressure elevation is ≥25 cm H_2O and/or there are symptoms of increased ICP during induction therapy, relieve by CSF drainage (by LP, reduce the opening pressure by 50% if it is extremely high, or to a normal pressure of 20 cm H_2O)[3,4,72]	A	II
If there is persistent pressure elevation ≥25 cm H_2O and symptoms, repeat LP daily until the CSF pressure and symptoms stabilise[2,3,72,73]	A	II
External ventricular drains (EVD), lumbar drains, lumbo-peritoneal shunts or ventriculo-peritoneal shunts should be considered[3,4,74–77] if more conservative measures to control raised ICP pressure have failed and the patient is receiving or has received appropriate antifungal therapy	B	III
Drains and shunts may be placed during active infection and without complete sterilisation of CNS, if clinically necessary[74–77]	B	III

CNS, central nervous system; CSF, cerebrospinal fluid; EVD, external ventricular drains; H_2O, water; ICP, intracranial pressure; LP, lumbar puncture; QoE, quality of evidence; SoR, strength of recommendation.

Overall, 50–70% of patients with CM, both in *C. neoformans* and *C. gattii* infections, have raised ICP, defined as CSF opening pressures >25 cm of water (H_2O)[14,25,72] (reviewed in World Health Organization,[3] Perfect *et al.*[4] and Chang and Perfect[73]). Early detection and reduction of raised ICP is critical, as increased ICP has been associated with increased mortality and neurological sequelae.[3,4,14,25,72,73] Performance of regular therapeutic LP mitigate against rapidly progressive cerebral oedema, is associated with 69% relative survival protection and minimises morbidity of acute CM.[3,4,72,73] Patients with raised ICP who are symptomatic require more urgent management than those who are asymptomatic. Nonetheless, LP should be undertaken at daily intervals until the CSF pressure is ≤20 cm H_2O or <50% of the initial opening pressure[3,4,14,25,72,73] (Table 4; *Strong recommendation, Level II evidence*).

If repeated LP fail to control CSF pressure, CSF shunts or drains are recommended (*Moderate recommendation, level III evidence*), although the optimal timing and the efficacy of these procedures have not been examined systematically.[74–77] Shunts have also been used successfully in children.[78] Pharmacological interventions are not recommended. When trialled, acetazolamide was both harmful and ineffective[79] and dexamethasone reduced pressure but worsened clinical outcome.[50]

Notably, neurapheresis therapy and extracorporeal filtration of yeasts from CSF was tested in a rabbit model of CM and a human trial is being planned.[80]

Question 4: How do we manage a patient with a sputum positive for *Cryptococcus* spp. growth?

Recommendations

- All patients with sputa positive for *C. neoformans* or *C. gattii* species should be investigated for pulmonary cryptococcosis and disseminated disease, particularly for CNS cryptococcosis (Strong recommendation, Level III evidence).
- Patients with concurrent pulmonary and CNS involvement should be managed as per CNS management guidelines (Tables 1 and 3; Strong recommendation, Level III evidence).
- Patients with isolated pulmonary disease may be treated with oral fluconazole, although those with immunosuppression and those with severe lung disease should be considered for L-AMB and 5-flucytosine (Moderate recommendation, Level III evidence).

Pulmonary cryptococcosis is a well-established clinical syndrome. Indeed, cryptococcosis is mainly acquired through inhalation, so the lung is often the first site of infection, although this is often asymptomatic or minimally symptomatic and therefore goes unrecognised. In the haematology-oncology setting, patients with pulmonary cryptococcosis may be recognised by the presence of incidental pulmonary nodules on chest imaging, including PET scans for tumour staging; a sputum positive for *Cryptococcus* species; mild symptoms of cough, chest pains and fever, not infrequently in conjunction with central nervous symptoms of headache, fevers and confusion; or the presence of yeasts in a lung biopsy specimen.

To date, there are no prospective epidemiological or treatment studies in pulmonary cryptococcosis. We recommend that all patients with sputa positive for *Cryptococcus* spp. be investigated for pulmonary involvement and disseminated disease, particularly for CNS cryptococcosis (*Strong recommendation, Level III evidence*). Respiratory culture with *Cryptococcus* growth should not be ignored or deemed a contaminant regardless of symptoms (*Strong recommendation, Level III evidence*). We acknowledge that this may potentially lead to over-investigation, but stratifying the clinical syndrome is critical in guiding therapy and missing the diagnosis of CNS cryptococcosis, which may be asymptomatic, has major repercussions. Whether cryptococci may be a benign coloniser of the respiratory tract remains controversial.

Expert recommendations for diagnosis and management include sCrAg, chest X-ray and chest CT (looking for pulmonary nodules in particular and for extent of disease), LP for CNS involvement (for CSF examination, cell count, biochemistry, CSF cryptococcal antigen and India ink) and clinical examination, including skin and other organ involvement. Immunocompetent persons should be investigated for previously undiagnosed immunodeficiency (*Moderate recommendation, Level III evidence*). Bronchoscopy has not provided additional benefit in this scenario and is not indicated unless required for other clinical indications. Serum CrAg is usually low in isolated pulmonary cryptococcosis compared with CNS disease.

Apart from pulmonary nodules, which can be solitary or multiple, less common imaging findings include consolidation, infiltrates and rarely, pleural effusions. *C. gattii* has a predilection for the lung and can be associated with large pulmonary cryptococcomas, which are sometimes mistaken for cancer. The differential diagnoses for incidental pulmonary nodules found on imaging in asymptomatic individuals should include pulmonary cryptococcosis and sterile respiratory specimens may be collected through a bronchoscopy or lung biopsy.

Patients with concurrent pulmonary and CNS involvement should be managed as per CNS guidelines (Tables 1 and 3; *Strong recommendation, Level III evidence*). Patients with isolated pulmonary disease may be treated with oral fluconazole, although those with immunosuppression and those with severe lung disease should receive L-AMB and 5-flucytosine (*Strong recommendation, Level III evidence*). Recommendations for duration of therapy range from 6 months in immunocompetent persons with mild disease to 6–12 months or longer in immunocompromised persons with severe disease (Table 3; *Strong recommendation, Level III evidence*). Large pulmonary cryptococcomas may require surgical excision particularly if there is risk of airway obstruction or other vital structures are threatened (*Marginal recommendation, Level III evidence*). Pulmonary cryptococcomas and serum antigenemia often persist beyond the duration of therapy. Two helpful recent reviews on pulmonary cryptococcosis include Chang *et al*.[81] and Setianingrum *et al*.[82]

Question 5: How do we manage a patient with a positive serum cryptococcal antigen including incidental/asymptomatic antigenemia?

Recommendations

- Any patient with a positive serum CrAg should have a thorough clinical assessment, including screening for symptoms of meningoencephalitis, raised ICP,

neurological deficit, pulmonary and skin manifestations, in addition to LP, chest XR (±CT chest) and cultures of CSF, sputum and blood (Strong recommendation, Level III evidence).

- Routine sCrAg screening in haematology and oncology patients is not currently recommended (Not recommended, Level III evidence).
- Individuals with increased risk exposure, undifferentiated infectious symptomatology and/or disease localised to the lung, CNS or skin, or in unique situations (e.g. organ donor screening), may be selected for individualised screening (Strong recommendation, level III evidence).

A positive CrAg test in serum in a person without a known history of cryptococcosis implies active cryptococcal disease that requires assessment and appropriate investigation.[4,83] Cryptococcal disease has been described in the haematology population, affecting a wide spectrum of malignant conditions.[84–88]

Any patient with a positive serum CrAg should have a thorough clinical assessment, including screening for symptoms of meningoencephalitis, raised ICP, neurological deficit, pulmonary and skin manifestations, in addition to LP, chest XR (±CT chest) and cultures of CSF, sputum and blood[4,89] (*Strong recommendation, Level III evidence*). Cultures of other tissues such as urine and skin should be performed as clinically indicated. If imaging of sites for which *Cryptococcus* spp. has a known predilection for has not been performed, we recommend a chest X-ray followed by a CT chest to identify and further characterise any pulmonary disease, and CT or magnetic resonance imaging (MRI) to check for and assess CNS involvement (MRI brains are more sensitive than CT generally[21,90,91]) (*Moderate recommendation, Level III evidence*). Abnormal brain imaging has been associated with a poorer prognosis in both HIV-infected and HIV-uninfected patients with cryptococcal CNS disease.[91,92] While this has not been specifically studied in the haematology population, it may be assumed given the critical site of infection. Treatment is dependent on the extent of cryptococcal disease after clinical assessment. Please refer to earlier discussion: Question 4 'pulmonary' and Question 2 'CNS and/or disseminated cryptococcosis' for specific management of these conditions.

Cryptococcal antigen – lateral flow assay (LFA)

Most laboratories now prefer to use a rapid cryptococcal LFA over the latex agglutination test.[83,93] This is an immunochromatographic dipstick assay that offers point-of-care testing for the qualitative or semi-quantitative detection of the capsular polysaccharide antigens of *Cryptococcus* species complex, with very high sensitivity and specificity in both serum and CSF for the diagnosis of cryptococcal infection.[58,83,93–95] Cryptococcal antibody testing is not used in the diagnostic pathway due to lack of sensitivity and possibility of cross-reactivity with other fungi (e.g. in histoplasmosis, blastomycosis).[96] Data on the performance of the LFA test is limited in children.[83]

Higher CrAg titres have been shown to correlate with an increased likelihood of disseminated disease, CM and death in HIV-infected cohorts.[20,91,92,97] However, in a study of SOT recipients, high serum or CSF antigen titres did not correlate with mortality at 90 days or CSF sterilisation at 2 weeks.[23] Of note, in non-HIV infected hosts, serum and CSF antigen titres are usually lower than in HIV-infected patients with CNS cryptococcosis.[98] In the SOT population, higher antigen titres have been noted in those with more extensive pulmonary involvement, concomitant extra-pulmonary disease and/or fungaemia.[21] The value of semi-quantitative serum CrAg titres and its clinical relevance have not been studied in the haematology population.

False-positive LFA tests, false-negative tests and CrAg persistence

The rate of false-positive LFA results appears rare; previous reports include two patients with disseminated *Trichosporon asahii* fungemia.[99,100] A retrospective study of 38 positive CrAg LFA tests performed on CSF or serum from 3969 patients and revealed 13 (0.34%) to be false positives.[99] All had a low titre of 1:2 except one patient with a titre of 1:5 in CSF.[99] None of the 13 patients had positive cultures or histopathology for *Cryptococcus* spp. and all were found to have an alternate diagnosis.[99] Due to the high sensitivity of the test, especially in low incidence settings, we recommend that CrAg LFA testing should be based on pre-test probability and reserved for patients who are at risk for and/or who present with symptoms consistent with cryptococcal infection[99] (*Strong recommendation, Level III evidence*). Patients with a positive sCrAg LFA, even with a low titre, should be carefully evaluated for cryptococcosis[89,99] (*Strong recommendation, Level II evidence*).

A false-negative LFA test may be due to low fungal burden, clinical samples transported in inappropriate vials, infection due to acapsular strains of *Cryptococcus* spp., immunocomplexes preventing the release of antigen, or due to a prozone effect, the latter occurring in the presence of very high antigen levels limiting the antigen–antibody reaction.[22,89,94,101,102] Most reports of the prozone effect relate to CSF samples.[22,88,102,103] To increase the sensitivity of the LFA test when CSF samples are suspected of having high cryptococcal burden, it is suggested that the specimen be diluted before the

assay is performed.[89,94,101,102,104] A negative serum cryptococcal antigen result does not exclude the diagnosis of cryptococcal disease and the patient should be evaluated for cryptococcosis depending on index of clinical suspicion[4,89] (*Strong recommendation, Level III evidence*).

The sCrAg has been found to persist for long periods of time in patients despite clinical improvement and appropriate treatment, possibly related to continuous release of capsular polysaccharide antigens from dead cryptococci, which are slowly eliminated from infected sites.[4,105,106] Therefore, serial evaluations of CSF or serum cryptococcal antigen titres have not been found to be useful in the acute management of transplant or HIV-infected patients on treatment, nor has its use as a precise indicator for relapse or persistent disease been established.[4,22,91,105,107,108] In the HIV-infected population, most cases of relapse are due to inadequate primary therapy (dose and/or duration) or lack of compliance with consolidation or maintenance fluconazole.[4] Therefore, we recommend close patient follow-up for relapse and other complications by clinical assessment at regular intervals (*Strong recommendation, Level III evidence*). Serum CrAg should not be repeated at timed/pre-determined intervals as secondary monitoring (*Not recommended, Level III evidence*), but performed only as clinically indicated. Serum CrAg measurement (when performed) needs to be interpreted within the clinical context (*Strong recommendation, Level III evidence*).

Primary surveillance with sCrAg in non-HIV settings

To date, there is no evidence that screening non-HIV populations for sCrAg is of value.[4,83,89] This is in contrast to people with advanced HIV (CD4 T cell count <100 cells/μL) where sCrAg screening is strongly recommended, based on a well-described clinical phenomenon of asymptomatic antigenemia, which may herald CNS disease and is associated with increased mortality.[4,83,104,109–115]

Given that cost-effectiveness is determined by disease incidence, routine sCrAg screening in haematology and oncology patients where the incidence of cryptococcosis is low is not currently recommended (*Not recommended, Level III evidence*). Individuals with increased risk exposure (e.g. epidemiological factors such as occupational, environmental risk), those with undifferentiated infectious symptomatology and/or disease localised to the pulmonary, CNS or cutaneous systems, or in unique situations (e.g. organ donor screening particularly in those dying with an undiagnosed CNS syndrome), may be selected for individualised screening (*Strong recommendation, Level III evidence*).

Question 6: How can we best diagnose and manage C-IRIS?

Recommendations

- A short course of steroids may be considered in severe C-IRIS not amenable to simple symptomatic treatment and therapeutic LP (Moderate recommendation, Level III evidence).
- Withdrawal of immunosuppressants solely for IRIS is not recommended (Not recommended, Level III evidence).
- Refractory C-IRIS, particularly steroid-refractory C-IRIS, should be discussed with experts in the field and where possible, managed in the setting of detailed immunological follow-up (Strong recommendation, Level III evidence).

IRIS is best described in the setting of ART commencement in HIV-infected individuals co-infected with opportunistic infections, including tuberculosis, cryptococcosis and other endemic mycoses. IRIS is classically divided into paradoxical IRIS or unmasking IRIS. Paradoxical C-IRIS may be diagnosed in a person with HIV-associated CM who improves with antifungal therapy and therapeutic LP, but then has a recurrence of symptoms post-ART commencement, with no evidence of recurrent infection. Unmasking C-IRIS may be diagnosed in an HIV-infected patient with no symptoms of cryptococcosis, who develops a new headache or seizures post-ART commencement and is diagnosed with CM.

C-IRIS can occur in any immunosuppressed individual, including patients with haematological malignancies who are receiving chemotherapy, are post-transplant or on biologic agents. For example, patients on biologic agents who develop cryptococcosis, often have their biologic agent stopped, which may lead to paradoxical C-IRIS. Similarly, patients with acute leukaemia with invasive fungal disease who undergo a stem cell transplant may paradoxically experience worsening of their previously treated infection. Currently, understanding of C-IRIS immunopathogenesis is largely based on CNS-paradoxical C-IRIS in HIV-infected individuals.[56,116–120] C-IRIS has also been reported in paediatric patients.[121,122] In a study of cryptococcosis in SOT recipients followed for a year after cryptococcosis diagnosis, 13 out of 89 (14%) developed C-IRIS occurring at a median of 45 days (interquartile range 15–76 days).[57] CNS disease and discontinuation of calcineurin inhibitor were independently associated with C-IRIS.[57]

There have been no advances on a biomarker for C-IRIS suitable for use in routine clinical practice. The diagnosis of C-IRIS remains a clinical diagnosis, where

there is a temporal relationship with a change in immunosuppression and alternative explanations (e.g. cryptococcal relapse, other infective and non-infective causes) have been excluded. Recognising risk factors for C-IRIS is key to prevention and early recognition. Risk factors include patients with advanced immunosuppression (e.g. very low CD4), patients who do not or are slow to improve their immunosuppressive state (e.g. poor CD4 recovery), patients with an acellular CSF profile (e.g. low or absent CSF white cell count) and patients with high CSF protein at time of initial CM presentation.[56,123]

At the time of C-IRIS, C-reactive protein may be high, but this is non-specific. Typically, LP at the time of C-IRIS presentation will show a high white cell count in the CSF consistent with an inflammatory state, will often be culture-negative (but need not be) and may have a high opening pressure. Radiological manifestations may include T2 enhancement and cerebral oedema in brain imaging and worsening pneumonia or pulmonary infiltrates on chest imaging. MRI brain lesions occur mostly in supratentorial regions.[124] Skin cryptococcomas may paradoxically worsen as cutaneous C-IRIS and may be mistaken as skin graft-versus-host disease.

There have been no clinical trials to determine the best treatment for C-IRIS. Treatment of C-IRIS should include therapeutic LP, symptomatic therapy such as analgesia, antiemetics and antiepileptics where relevant. In severe C-IRIS, clinicians have resorted to steroids to dampen inflammation,[125,126] as is commonly done when managing IRIS involving other infective agents. There have been no clinical trials of steroid use in C-IRIS treatment. Notably, the use of high-dose dexamethasone as adjunctive CM treatment (therefore potentially as prevention) did not show a reduction in C-IRIS,[50] although case recognition of C-IRIS in this trial may not have been optimal. In contrast, moderate-dose prednisolone as prevention has been shown to reduce tuberculosis (TB)-IRIS incidence in TB-HIV coinfection.[127] An older, small trial of steroid treatment in TB-IRIS showed moderate effect using a composite endpoint.[128] A short course of steroids may be considered in severe C-IRIS not amenable to simple symptomatic treatment and therapeutic LP (*Moderate recommendation, Level III evidence*). Just as ART should not be withdrawn in HIV-associated C-IRIS, we do not recommend withdrawal of immunosuppressants solely for IRIS (*Not recommended, Level III evidence*).

In steroid-refractory C-IRIS, there are case reports on the use of tumour necrosis factor alpha (TNF-α) blockers such as adalimumab with mixed response in renal transplant recipients[129,130] and in HIV-infected patients.[131,132] Thalidomide has been used in HIV-infected patients[133,134] and in an immunocompetent patient experiencing C-IRIS.[135]

Innovative, though unproven therapies in other forms of IRIS have been reported, including interleukin 6 (IL-6) inhibitors such as tocilizumab, best known for its role in chimeric antigen receptor T-cell therapy-associated neurological immune response, anakinra (human recombinant IL-1 receptor antagonist),[136] maraviroc (a C-C chemokine receptor 5 (CCR5) inhibitor)[137,138] and other TNF-blockers such as infliximab.[139] CCR2/CCR5 inhibitors such as cenicriviroc (also called CVC) is currently being trialled in COVID-19 treatment studies[140] and may have potential in C-IRIS.[116] Other hypothetical therapies may include emapalumab, a monoclonal antibody that binds and neutralises IFN-γ, which is approved for adult and paediatric primary haemophagocytic lymphohistiocytosis (HLH) refractory to conventional HLH therapy,[141] or Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) inhibitors such as ruxolitinib.[142] We recommend that refractory C-IRIS, particularly steroid-refractory C-IRIS, be discussed with experts in the field and where possible be managed in the setting of detailed immunological follow-up (*Strong recommendation, Level III evidence*).

Question 7: What are the rare but clinically relevant yeasts, and how should they be diagnosed and treated?

Recommendations

- Refer to Table 5 for detailed recommendations.

Clinically relevant, rare (non-*Candida* spp., non-*Cryptococcus* spp.) yeast genera include *Malassezia*, *Rhodotorula*, *Trichosporon*, *Geotrichum*, *Kodamaea*, *Pseudozyma* (now *Dirkmeia* spp. or *Moesziomyces* spp. dependant on species), *Saprochaete*, *Sporobolomyces* and *Saccharomyces*. Notably, recent taxonomic revisions have led to several previously well-known *Candida* spp. being reclassified into non-*Candida* species such as *Meyerozyma guilliermondii* (previously *Candida guilliermondii*), *Yarrowia lipolytica* (previously *Candida lipolytica*), *Diutina rugosa* (previously *Candida rugosa*), *Diutina catenula* (previously *Candida catenula*) and *Clavispora lusitaniae* (previously *Candida lusitaniae*). For historical reasons, these will be discussed in the accompanying guidelines for the management of *Candida* by Keighley *et al.* 2021,[223] which can be found elsewhere in this supplement. Importantly, rare yeasts discussed here are limited to human pathogens. A detailed discussion on taxonomical changes is beyond the scope of this paper; we encourage readers to refer to other articles for further information.[203–205]

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Table 5 Rare yeast infections: Epidemiology, key laboratory features and recommended antifungal therapy

Organism(s)	Epidemiology	Key laboratory features†	Laboratory comments‡,§,¶,††	Preferred antifungal agents	SoR	QoE	Treatment comments‡‡,§§,¶¶
Geotrichum spp.†††	Immunocompromised host, breakthrough infections, bloodstream infections (BSI)[143–146]	Empty cells that fragment (disjunctor cells) releasing arthroconidia[146]; arthroconidia seen on microscopy of *G. candidum*[146]	Easily mistaken for *Coccidioides immitis*[146] and occasionally for *Nannizziopsis* spp. complex.[147] Rarely linked to CVAD-associated infections[143,146]	Amphotericin B‡‡‡ ± 5-flucytosine	C	III	Fluconazole resistant (based on high MIC values); third and fourth generation triazoles (low MIC values), but limited human data[35,143–146,148]
Kodamaea ohmeri†††	Immunocompromised host[149]; premature neonate sepsis[150,151]; BSI[150,152–154]; cellulitis; breakthrough infections	CHROMagar™ characteristic change from pink to blue colonies[150]	Commonly reported from China; CVAD line removal recommended[150]	Amphotericin B‡‡‡ or echinocandins (EC)[5,150–153]	C	III	Limited data; suggest treat like *Candida glabrata* infections; mixed success with fluconazole[5,149,152]
Saccharomyces cerevisiae†††	Immunocompromised host; breakthrough infections; BSI[155,156]; post intra-abdominal surgery (including after liver transplant); other complex hepatobiliary surgery[157]	Produce large oval to elongated blastospores, sometimes arranged as poorly formed pseudohyphae[155] *Saccharomyces boulardii* is conspecific (i.e. same clade) with *S. cerevisiae*, and is no longer a valid species name	Translocation from GI lumen or breach in skin barriers (e.g. vascular access devices) Linked to exogenous probiotics[158–163] Nosocomial clusters have been linked to probiotic use[158,159] Fungaemia linked to CVAD lines, ICU stay, and immunosuppression[5,164]	Amphotericin B‡‡‡ ± 5-flucytosine	B	III	*In vitro* susceptibility to all azoles (including fluconazole) and EC[155,156,158,165]
Saprochaete spp.†††	Immunocompromised host/ neutropenic sepsis[166,167]; case clusters[168]; BSI[143,167–169]; vascular access devices[166]; breakthrough infection[166]	Produce true hyphae, pseudohyphae, and annelloconidia resembling arthroconidia[167]	Nosocomial clusters are reported[167,170] Teleomorph is Magnusiomyces capitatus[167] Fungaemia with neutropenia in ~75% of cases; is associated with a crude mortality of 60% in neutropenic patients[167]	Amphotericin B‡‡‡ or third/ fourth generation triazoles	C	III	Preferred therapy but scarce data[166–168]; fluconazole resistance; EC resistant[143,168]
Malassezia spp.§§§	Immunocompromised host[171]; breakthrough infections; fungaemia linked to CVAD lines, TPN, ICU stay, with immune suppression[171]	Requires lipophilic (e.g. Dixon's sterile olive oil) agar for culture[171] Bottle-shaped budding yeasts with annelloconidia and collarettes[171]	CVAD line removal recommendation (Strong recommendation, Level II evidence)[171,172]; CHROMagar™ *M. furfur* large, pale pink, wrinkled colonies; *M. globosa* pink-purple colonies[171] Case clusters[173,174] and neonatal sepsis[171,173,174] reported	Amphotericin B‡‡‡ ± 5-flucytosine[171,175]	C	III	Preferred therapy but scarce data; *in vitro* resistance to fluconazole, 5-flucytosine and amphotericin B‡‡‡ reported[171,175] Most (though limited clinical experience with amphotericin B‡‡‡); elevated azole MIC for some isolates[171,175]
Pseudozyma (*Moesziomyces*) spp.§§§	Immunocompromised host; breakthrough infections; BSI[176]	Produce fusiform ballistoconida and hyphae[176]	~80% of infections associated with fungaemia[176] Recently renamed *Moesziomyces* species	Amphotericin B‡‡‡ or third/ fourth generation triazoles	C	III	Preferred therapy but scarce data; fluconazole resistance; EC resistant; *in vitro* resistance to 5-flucytosine and amphotericin B‡‡‡ reported[176–182]

Table 5 *Continued*

Organism(s)	Epidemiology	Key laboratory features†	Laboratory comments‡,§,¶,††	Preferred antifungal agents	SoR	QoE	Treatment comments‡‡,§§,¶¶
Rhodotorula spp.§§§	Immunocompromised host; BSI[183,184]; CNS infection[184]; CVAD-related[183,185,186]; breakthrough infection[185]; renal dialysis catheter-associated peritonitis[184]	Salmon coloured colonies *R. mucilaginosa* on SDA[184]	Cross-reactivity with *Cryptococcus* antigens (LCAT, LFA); remove CVAD and/or renal dialysis catheter if present (Strong recommendation, Level III evidence)[184]	Amphotericin B‡‡‡[119,124,125,131,138]	B	II	The use of azoles and ECs is strongly discouraged; (Not recommended, Level 3 evidence).[119] Limited clinical experience with combination therapy: Amphotericin B‡‡‡ + 5-flucytosine
Sporobolomyces spp.§§§	Immunocompromised host; case clusters, CVAD-related[187] Deep-seated infections/ fungaemia in immunocompromised host[5]	Budding yeasts, pseudohyphae and ballistoconida on large sterigmata[5]	Environmental yeasts that are opportunistic human pathogens[5]	Amphotericin B‡‡‡ or third/ fourth generation triazoles[188–192]	C	III	Preferred therapy but scarce data; *in vitro* resistance to fluconazole, 5-flucytosine; EC resistant[188–192]
Trichosporon spp.§§§	Immunocompromised host; breakthrough infections[177,193]; BSI[177,194]; premature neonatal sepsis[195]; pancreatitis[196]; burns patient[194]	Fungal hyphae not seen with *Trichosporon* spp. (Moderate recommendation, Level II evidence)[197]	Cross-reactivity with *Cryptococcus* antigens (LCAT, LFA); more commonly reported from South America, particularly Brazil[194]; fungaemia associated with 40–90% mortality rates[172,197]; can be mistaken for *Nannizziopsis* spp. complex[147]	Voriconazole	C	III	Preferred therapy but scarce data; *in vitro* resistance to fluconazole[198]; Amphotericin B‡‡‡ resistant (Marginal recommendation, Level III evidence)[177,178,194]; EC resistant; fluconazole and/or triazoles susceptibility (low MIC) are reported[193,196,197] CVAD-line removal is recommended[199]

†Strong support (Strong recommendation, Level III evidence) for undertaking histopathology on fresh tissue and formalin-fixed, paraffin-embedded (FFPE) (ante-mortem or post-mortem) where invasive fungal disease (IFD) is in the differential. Histopathology includes fluorescent brighteners (Calcofluor) and fungal stains (Grocott's methenamine silver (GMS), Periodic acid-Schiff (PAS), other). ‡Shared themes: fungaemia is common; therefore, blood cultures remain the mainstay of diagnosis. §Molecular identification methods targeting the internal transcribed spacer (ITS) (generally ITS-1 and ITS-2) regions of the fungal ribosomal ribonucleic acid (RNA) genes are the most reliable methods to establish a specific fungal identification for most isolates of rare yeasts.[200] MALDI-TOF MS is promising for the speciation of many rare yeast species. Using the Bruker Biotyper MALDI-TOF MS platform (Bruker Daltoniks, GmbH, Bremen, Germany), scores of ≥2.0 generally indicates reliable species-level identification.[201] ¶Strong support for antifungal susceptibility testing (AFST) for epidemiological studies (Strong recommendation, Level II evidence). AFST: Tested by reference broth colorimetric microdilution method with the Sensititre™ YeastOne™ (SYO) YO10 (TREK Diagnostics, Cleveland, OH, USA). Has utility for future epidemiological studies on rare yeasts.[202] ††Moderate to modest support for AFST to guide treatment and resistance detected by AFST associated with treatment failure (B-III/C-II). ‡‡For neonates and children: amphotericin B when susceptible is preferred with relative preference for liposomal formulations based on more favourable pharmacokinetics/pharmacodynamics, but amphotericin B deoxycholate is well tolerated in neonates. §§Susceptibility variable hence perform AFST on all clinically significant isolates by reference broth microdilution method. ¶¶Antifungal of choice is generally genus specific. Amphotericin B formulations are preferred. Remove infected devices. †††Ascomycetes include: *Geotrichum* spp., *Kodameae ohmeri*, *Saccharomyces cerevisiae* and *Saprochaete* spp. ‡‡‡Refers to amphotericin B deoxycholate and its lipid formulations. §§§Basidiomycetes include: *Malassezia* spp., *Pseudozyma* (*Moesziomyces*) spp., *Rhodotorula* spp., *Sporobolomyces* spp. and *Trichosporon* spp. AFST, antifungal susceptibility testing; BSI, bloodstream infections; CNS, central nervous system; CVAD, central venous access device; EC, echinocandins; GI, gastrointestinal; ICU, intensive care unit; IFD; invasive fungal disease; LCAT, latex cryptococcal antigen agglutination test; LFA, lateral flow assay; MALDI-TOF MS, Matrix-assisted laser desorption/ionisation-time of flight mass spectrometry; MIC, minimum inhibitory concentration; QoE, level of evidence; SDA, Sabouraud dextrose agar; SoR, strength of recommendation; TPN, total parenteral nutrition.

Rare yeasts are considered emerging fungal pathogens and now collectively cause 1.1–1.7% of fungaemia cases,[5,164,197] with some well-known and others recently described and/or re-classified. Generally, they colonise the skin and mucosal surfaces. However, in severely immunocompromised patients, or in association with indwelling devices, especially central venous access devices (CVAD), rare yeasts can cause systemic or invasive infections.[5,143,149,166,171,175,177,183–185,206–209] Patients at particularly high risk include those with haematological malignancies, post-haemopoietic stem cell transplantation, prolonged neutropenia, complex intra-abdominal pathology, SOT recipients and pre-term infants in neonatal ICU.[5,143,149,150,166,171,173,175,177,183–187,193,195,206–210] Rare yeast fungaemia can result in endovascular infections, chiefly infective endocarditis, in addition to the seeding of virtually any organ, particularly the skin, liver, spleen, brain and lungs.[5,143,149,166,171,175,177,183–185,206–209] The epidemiology and key clinical features of these organisms, including the routine laboratory methods utilised for phenotypic identifications, are summarised in Table 5.

Matrix-assisted laser desorption/ionisation-time of flight mass spectrometry (MALDI-TOF MS) is now frequently used for rapid preliminary identification of the rare yeasts, limited by the reference database employed.[211] Currently, fungal DNA sequencing is considered the gold standard for reliable identification of most rare yeasts.[5,152,169,212,213] Genus-specific antifungal drug profiles can be observed but species-level susceptibility profiles are often variable.[5,172,197] Local antifungal prophylactic strategies may increase the risk of nosocomial rare yeast infections by exerting excessive selective pressure.[5,155,165,166,177,183–187,193,214]

Several small, though important, nosocomial outbreaks are reported in the literature. A recent outbreak of *Dirkmeia churashimaensis* (previously *Pseudozyma churashimaensis*) in 12 premature neonates in a subspecialty hospital in Delhi, India, over 6 months, resulted in 5 deaths (42%), without an environmental source identified.[210] Three recent nosocomial outbreaks in unrelated haematology populations due to *Saprochaete clavata* (formerly *Geotrichum clavatum* and now *Magnusiomyces capitatus*) have been reported.[168–170,215] Zoonotic spread involving *Malassezia pachydermatis* in an intensive care nursery has been linked to health care worker colonisation from pet dogs at home.[173] An outbreak investigation triggered by the occurrence of two cases of *M. pachydermatis* fungaemia over a period of 6 months in a French neonatal ICU, revealed high numbers of colonised (93.8% of 64) neonates.[174]

Key management principles for invasive, systemic rare yeast infections are derived from poor-quality data, but include surgical source control, removal of infected foreign material, and investigation for disseminated disease and other occult sites of clinical disease.[5,164,172] Common sites of dissemination include the liver, spleen, brain, eyes, skin, heart valves and lungs. Moreover, rare yeast species in general (except *Saccharomyces* and *Kodamaea ohmeri*) are considered intrinsically resistant to the echinocandins.[5,143,156] Consequently, if empirical echinocandins are prescribed for severely ill hospitalised patients with yeast fungaemia, careful patient selection is required when treating unstable fungaemic patients.[172]

Optimal directed antifungal treatment should be individualised to the patient, taking into consideration their clinical status, the likely source of infection and comorbidities such as renal and hepatic function, which may influence choice of antifungal therapy[5,172,216] (*Strong recommendation, Level III evidence*). Table 5 provides recommendations for antifungal therapy, acknowledging the lack of generally agreed break-points and clinical efficacy trials.[5,172,202] Accordingly, invasive rare yeast infections are challenging to manage due to limited clinical experience, severely immunocompromised hosts, lack of validated susceptibility data, unpredictable susceptibility profiles, and are associated with high crude morbidity and mortality rates.[5,164]

Outbreak investigation

Clinicians and microbiologists need to be vigilant to the possibility of nosocomial outbreaks, particularly when fungaemia of rare yeasts are seen. A thorough history should be taken from the patient, including food and environmental exposures, and a detailed review of ward infection control practices should be conducted. While there is no specific threshold for a formal outbreak investigation, a cluster of infections in high-risk settings is concerning. Notably, rates of rare yeast colonisation frequently outnumber that of clinically recognised infections. Thus, two clinical cases of the same rare organism separated by time may still be linked. Key steps include collection of clinical and environmental isolates for genotypic analysis, detailed patient and healthcare worker movement charts and revisiting infection prevention strategies including CVAD management bundles and hand hygiene practices (please refer to the accompanying antifungal stewardship, surveillance and infection prevention guidelines by Khanina *et al*. 2021,[225] which can be found elsewhere in this supplement).

Implications for future research

We await the full publication of results from the AMBITION-CM trial[33,217,222] exploring the use of shorter courses of L-AMB. Several new studies in CM are being planned. A phase 1, ascending dose study of an orally administered,

encochleated formulation of amphotericin B (MAT2203) administered in 4–6 divided daily doses was found to be generally safe and tolerated in in Ugandan HIV-CM survivors at doses of up to 2 g/day.[218] This lipid-crystal encochleated drug formulation of nanosized particles is thought to be resistant to digestive enzymes and is engulfed by macrophages where the lowered intracellular calcium levels trigger the cochleate to open, limiting toxicities. A phase 2 study will follow with MAT2203 2 g/day and flucytosine for CM therapy, followed by MATT2203 1.5 g/day with fluconazole for 4 weeks of consolidation therapy.[218] A trial of Fosmanogepix (APX001), a broad spectrum first-in-class small-molecule antifungal agent, is being planned. This prodrug is metabolised to its active moiety, manogepix (MGX, formerly known as APX001A), which targets a highly conserved fungal enzyme Gwt1 important in fungal cell wall synthesis (reviewed by Lima *et al*. and Rauseo *et al*.[219,220]).

Our understanding of cryptococcosis in non-HIV related settings, non-CNS cryptococcosis and C-IRIS remains poor. There is a clear need to encourage collaborative networks to prospectively describe cryptococcosis in these understudied settings and clinical syndromes. A major unanswered question is whether treatment strategies should differ between cryptococcosis caused by *C. neoformans* and *C. gattii*. We need to investigate novel antifungal therapies and drug interactions in all affected populations, including the haematology-oncology setting, paediatric/neonatal populations and pregnant women. There is a need for quicker translation of research knowledge into clinical practice with broader access to immunogenomics and greater utilisation of basic science in describing immunopathogenic pathways. Greater utilisation of molecular techniques and improved infection prevention, including early global outbreak alerts, will aid our ability to combat rare yeast infections.

Conclusion

Cryptococcosis remains underappreciated in haematological-oncological and other non-HIV settings. Increased awareness and an understanding of the key principles in its management is necessary. Antifungal therapy and management of raised ICP are both key to optimising CM outcomes. Rare yeast infections require prompt assessment and a heightened alertness for the development of potential nosocomial outbreaks.

Acknowledgements

The authors would like to thank members of the Australasian Leukaemia & Lymphoma Group (ALLG), the Australasian Society for Infectious Diseases (ASID), the Australian & New Zealand Children's Haematology/Oncology Group (ANZCHOG), the Medical Oncology Group of Australia (MOGA) and the Haematology Society of Australia and New Zealand (HSANZ) for their review of the draft manuscript, and Dr. Candice O'Sullivan and Angelica Papanicolaou from Wellmark Pty Ltd. for their assistance in preparing the manuscript for submission.

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