Delivery Note

Hannover Medical School -Library-
Carl-Neuberg-Str. 1
D-30625 Hannover

Fon: ++49-511-532-3342
Fax: ++49-511-532-16-3342
E-mail: fernleihe.bibliothek@mh-hannover.de

Delivery address

Academic Research Information Division / ILL
KERIS\50Korea Education Research & Information Service\51
KERIS BD 8F, 64 Dongnae-ro,Donggu
KR-41061 Daegu

Data concerning order:

Order date:	2025-10-20 10:15:39
Order number:	SUBITO:LE25102000224 /
Customer name:	KERIS\50Korea Education Research & Information Service\51
User account:	SLI12X00004W
Delivery date:	2025-10-20 10:35:02
Delivery priority:	NORMAL
Delivery way:	Email
E-mail address:	edds@riss.kr

Remarks concerning delivery:

Data concerning document:

Signature:	[ONL] ND:2039749-5
Author:	
Title:	Seminars in respiratory and critical care medicine
Year:	2015
Volume / Issue:	36 / 05
Pages:	681-691
Author of article:	Chang, C.; Sorrell, T.; Chen, S.;
Title of article:	Pulmonary Cryptococcosis
ISSN:	1098-9048
ISBN:	
CODEN:	

Your comment concerning the order:
S2025102026745

subito copyright notice

Ordering and use of copies of articles supplied via subito are subject to copyright regulations. By registering with subito, you commit to these copyright regulations.

Copies from subito are intended for your personal use only and may not be passed on to third parties unless they have been ordered by an auxiliary person. However, for commercial users of copies supplied by subito, the joint use of supplied copies within a company or organization is permitted.

The copies are provided with a watermark containing a copyright notice. The watermark placed by subito e.V. must not be removed.

Copies supplied by German libraries may be reused within Germany in compliance with the copyright law. For example, they may be used for teaching and instruction at educational institutions, i.e. for semester apparatus and in schools, in compliance with § 60a UrhG. This applies not only to analog, but also to digital platforms for teaching and educational materials. Subject to section § 45 UrhG, analog and digital copies may also be used in proceedings before a court, an arbitration board or a public authority.

For copy deliveries outside of Germany, all relevant copyright laws of the country in which the user is located must be complied with.

In case of doubt, please contact the legal department of your company or a lawyer.

Bestell-Nr: SUBITO-LE25102000224
lok. Nr: S2025102026745
PPN: 2039749
Bestelldatum: 2025-10-20 10:15:39

Medizinische Hochschule Hannover

--- Bibliothek---

SUBITO-BESTELLUNG

NORMAL

MHH - Bibliothek/Fernleihe - OE 8900 - 30625 Hannover

KERIS(Korea Education Research & Information Service)
Academic Research Information Division / ILL

KERIS BD 8F, 64 Dongnae-ro,Donggu
41061 Daegu

Herr/Frau
KERIS(Korea Education Research & Information Service)
SLI12X00004W

Tel: +82 53 714-0416
Mail: docdel@subito-doc.de
Fax: +82 2 2261-0163
Ben.-Gruppe: USER-GROUP-8

Benutzer-Ausweisnummer

Lieferschein

Lieferbibliothek: <354>
Medizinische Hochschule Hannover
Bibliothek OE 8900
Subito/Fernleihe
Carl-Neuberg-Str. 1
D-30625 Hannover

Telefon: +49 (0511) 532 - 9839
Fax: +49 (0511) 532 - 3346
E-Mail: fernleihe.bibliothek@mh-hannover.de

Bearbeitungsvermerke:

() Leihfrist für Bücher 4 Wochen () Kurzausleihe 8 Tage
() Verlängerung nicht möglich () Kopierverbot
() Lesesaal
() nicht am Standort (6) () bibligr. unrichtig (9)
() noch nicht vorhanden (4) () nicht ausleihbar (8)
() Buchbinder (0) () ausgeliehen (7)
() nicht vorhanden (5)

Unter Anerkennung der Benutzungsbedingungen wird bestellt:

Verfasser: Chang, C.; Sorrell, T.; Chen, S.;
(Aufsatz)

Titel: Pulmonary Cryptococcosis
(Aufsatz)

Seiten: 681-691

Titel (Monographie/ Zeitschrift)

Seminars in respiratory and critical care medicine
Thieme
Stuttgart u.a.

1098-9048

Lieferung erwünscht bis:
2025-10-23 10:20:01

Standort:
[ONL] ND:2039749-5

Band/Heft: 36 / 05
Jahr: 2015

Lieferform: KOPIE
Lieferart: FTP

SUBITO-LE25102000224

Bemerkung:
Zusatzinfo: S2025102026745
Bemerkung vom Kunden:

Pulmonary Cryptococcosis

C. C. Chang, MBBS, FRACP, PhD[1,2,3] T. C. Sorrell, MBBS, MD, AM, FRACP[4,5]
S. C.-A. Chen, MBBS, FRACP, FRCPA, PhD[4,6]

[1] Lewin-Cameron Laboratory, The Doherty Institute, University of Melbourne, Melbourne, Australia
[2] Department of Infectious Diseases, Alfred Hospital, Melbourne, Australia
[3] HIV Pathogenesis Programme, University of KwaZulu Natal, Durban, South Africa
[4] Marie Bashir Institute for Infectious Diseases and Biosecurity, University of Sydney, Sydney, NSW, Australia
[5] Centre for Infectious Diseases and Microbiology, Westmead Millennium Institute, Westmead, NSW, Australia
[6] Centre for Infectious Diseases and Microbiology Laboratory Services, ICPMR – Pathology West, Westmead Hospital, Sydney, NSW, Australia

Address for correspondence S. C.-A. Chen, MBBS, FRACP, FRCPA, PhD, Centre for Infectious Diseases and Microbiology Laboratory Services, 3rd Level, ICPMR Building, Westmead Hospital, Darcy Road, Westmead, NSW 2145, Australia (e-mail: Sharon.chen@health.nsw.gov.au).

Semin Respir Crit Care Med 2015;36:681–691.

Abstract

Inhalation of *Cryptococcus* into the respiratory system is the main route of acquisition of human infection, yet pulmonary cryptococcosis goes mostly unrecognized by many clinicians. This delay in diagnosis, or misdiagnosis, of lung infections is due in part to frequently subtle clinical manifestations such as a subacute or chronic cough, a broad differential of diagnostic possibilities for associated pulmonary masses (cryptococcomas) and, on occasion, negative respiratory tract cultures. Hematogenous dissemination from the lung can result in protean manifestations, the most severe of which is meningoencephalitis. There are few clinical studies of pulmonary cryptococcosis and its pathogenesis is poorly understood. The main purpose of this review is to describe the epidemiology, clinical presentation, diagnosis, and treatment of pulmonary cryptococcosis to increase clinician's awareness of this diagnostic possibility and to enhance clinical management. Useful pointers to the approach and management of pulmonary cryptococcosis and the implications of disseminated disease are included, together with recommendations for future research.

Keywords
- pulmonary cryptococcosis
- *C. neoformans*
- *C. gattii*
- cryptococcomas
- invasive fungal disease

Cryptococcosis

Cryptococcal disease (cryptococcosis) is caused by *Cryptococcus* spp., a ubiquitous budding yeast-like basidiomycete that is endemic in many countries. Cryptococcosis is most often associated with human immunodeficiency virus (HIV) infection, and a million new cases a year are thought to occur globally[1] with a mortality rate of 20 to 70%.[2] Although patients with other immunodeficiency states including organ transplantation, and the use of corticosteroid and other immunosuppressive therapies, are at increased risk, cryptococcosis is also well described in apparently healthy hosts.

The clinical manifestations of cryptococcosis are protean. Cryptococcal meningoencephalitis (CM) is the most frequent and most severe form in both HIV-infected and HIV-negative patients, and is the best studied. Pulmonary disease is the next most common presentation and is manifest as lung infiltrates and/or cryptococcomas. Skin/subcutaneous, ophthalmic, bone, and prostatic disease also occur.[3] Even though the most common route of acquisition follows inhalation, ironically, pulmonary cryptococcosis is often not recognized. The purpose of this review is to describe the epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment of pulmonary cryptococcosis. We also briefly discuss aspects of cryptococcosis in resource-limited settings.

Issue Theme Pulmonary and Invasive Fungal Infections; Guest Editor: Carol A. Kauffman, MD

DOI http://dx.doi.org/10.1055/s-0035-1562895.
ISSN 1069-3424.

The Genus *Cryptococcus*—Update on Taxonomy

Modern molecular techniques have identified that the polyphyletic genus, *Cryptococcus*, comprises more than 70 species; for the majority of these, only the anamorph (nonsexual) state has been described.[4] The nomenclature of the teleomorph state is *Filobasidiella*. This nomenclature is being revised as part of the "One fungus–One name" project, in common with reclassification of all botanical names.[5–7] Based on expert consensus, closely related sibling species, causing disease with similar clinical management, are considered to be members of a complex[7]—hence the assignment of "*Cryptococcus neoformans–Cryptococcus gattii* complex"—to the two main pathogenic species, *C. neoformans* and *C. gattii*. Both *C. neoformans* and *C. gattii* are environmental, noncontagious pathogens, but differ in genetic, ecological, physiological, and pathobiological properties.[8]

There are two varieties within *C. neoformans*—*C. neoformans* var. *grubii* (serotype A) and *C. neoformans* var. *neoformans* (serotype D), which generally cause disease in immunocompromised patients. More than 90% of infections worldwide are caused by *C. neoformans* var. *grubii*. *C. gattii* (serotypes B and C) has a propensity to cause disease in immunocompetent patients,[4,9–11] and also infects immunosuppressed individuals; this species gained particular notoriety following outbreaks in North America.[12] In addition, infections may be caused by hybrid strains of either species (serotypes AB, AD, and BC).[13,14]

Many molecular typing techniques have been applied to delineate strains of the *C. neoformans–C. gattii complex* more precisely (reviewed by Meyer et al[9] and Chen et al[15]). The International Society of Human and Animal Mycology (ISHAM) has endorsed genotyping by multilocus sequence typing (MLST) as the gold standard method of strain classification with eight molecular types described—genotypes VNI to VNIV for *C. neoformans* and genotypes VGI to VGIV for *C. gattii*.[9] This typing classification is based on seven unlinked genetic loci, including six housekeeping genes, three of which —*CAP 59* (polysaccharide capsule), *LAC1* (melanin synthesis), and *PLB1* (cell invasion)—encode virulence factors.[9] Generally, *C. neoformans* molecular types are aligned with the serotypes (►**Table 1**).

Ecology and Epidemiology

In the environment, *C. neoformans* var. *grubii* has been recovered from decaying wood, soil, and pigeon excreta. The endemic tree species, *Colophospermum mopane*, has been reported as an important natural reservoir in Southern Africa,[16] with implications for the resurgence of cryptococcosis in this region. The likelihood of environmental acquisition is further supported by the isolation of *Cryptococcus* from soil, bird droppings, and dust samples in home environments of patients with cryptococcosis in Burundi.[17] In Australia, *C. gattii* infection has been associated with exposure to several tree species, in particular, two species of eucalypt, *Eucalyptus camaldulensis* and *Eucalyptus tereticornis*.[15] Trees such as Douglas fir and coastal western hemlock, native to Vancouver Island in British Columbia, Canada, have also been implicated as an environmental niche of *C. gattii*.[18]

In the 1980s, *C. neoformans* was the predominant species in North and South America, accounting for 85% of human cases, but with a higher prevalence of *C. gattii* in southern California (41%) and Brazil (35.5%).[19] In this same study, *C. gattii* was over-represented (41.2%) in Australia and South East Asia, suggesting that this species was more likely to occur in tropical and subtropical climates.[19] However, recently, *C. gattii* infection has spread into new geographical regions. Since the Vancouver Island outbreak in the 1990s,[12] more than 200 cases of *C. gattii* infection have been reported in British Columbia[20] with extension into the Pacific Northwest of the United States[21,22] and to eastern states.[23] Phylogenetic and recombination analyses indicate that these outbreaks originated from a highly recombining *C. gattii* population in northern Brazil, with climatic change playing a possible role in dispersal.[24] There is also increasing interest in *C. gattii* infection of domestic animals, sheep, cows, and koalas (reviewed by Chen et al[15]). A recent U.S. study found a predominance of the VGIII genotype in cats and genotype VNI strains in dogs; both genotypes are similar to those infecting humans.[25]

Host Risk Factors

HIV infection is the major risk factor for cryptococcosis. Other populations at risk include solid-organ and hematological stem cell transplant recipients; patients with malignancies[26,27]; those receiving immunomodulating and biologic agents, including patients treated for systemic lupus erythematosus (SLE),[28,29] sarcoidosis,[30] and rheumatoid arthritis[31]; and individuals with CD4 lymphopaenia.[32,33] These risk factors have been described in both *C. neoformans* and *C. gattii* infections. Donor-derived cryptococcosis has also been previously reported in liver and kidney recipients.[34,35] In an older study, approximately 20% of HIV-negative patients with cryptococcosis lacked any predisposing factors.[36] Further, 44% of 151 HIV-negative patients with pulmonary cryptococcosis had no underlying illness; comorbid conditions included diabetes (32.1%), hematologic diseases (22.6%), connective tissue disease (22.6%), renal failure 16.7%, solid-organ malignancy (13.1%), chronic lung disease (13.1%), liver disease (9.5%), and renal transplantation (2.4%).[37]

The prevalence of cryptococcosis in HIV-negative patients is less well defined than in HIV-infected individuals, but is probably low. An earlier North American study reported an incidence of 0.9 cases per 100,000.[38] Cryptococcosis is uncommon in children despite potential predisposing conditions similar to those in adults and occurs at a median age of 7 to 11 years (reviewed by Lizarazo et al[39]).

Virulence, Pathogenesis, and Latency

While cases of cryptococcosis are most often encountered as acute infection, most are caused by reactivation of latent infection. Evidence for this stems from high prevalence of cryptococcal antibodies in healthy individuals[40,41] and the

Table 1 Serotypes and molecular types of the *Cryptococcus neoformans–Cryptococcus gattii* complex

	Varieties	Serotypes	MLST
C. neoformans	var. *grubii*	A	VNI
	var. *grubii*	A	VNII
	var. *grubii*	A	VNB
	var. *neoformans*	D (2 lineages)	VNIV
	Hybrids	AD hybrid (3 lineages)	VNIII
C. gattii	–	B or C	VGI
	–	B or C	VGII
	–	B or C	VGIII
	–	B or C	VGIV
Other Tremalleles species		12 other species	

ability of cryptococci to infect macrophages and remain latent.[42] Factors that trigger reactivation of infection are unknown.

Both *C. neoformans* and *C. gattii* have a similar suite of virulence determinants. The three best-characterized virulence factors are an ability to grow at 37°C, produce melanin (via laccase activity), and the polysaccharide capsule.[10] The capsule, which is composed predominantly of glucuronoxylomannan (88%) and galactoxylomannan (10%), interferes with macrophage phagocytosis, depletes complement, and impairs leucocytosis[10] and its size can increase substantially in response to environmental stress.[43] The ability of cryptococci to grow at human body temperature enables it to withstand the dramatic change in temperature from environment to host,[44] while melanin is protective against toxic-free radicals and affects endothelial porosity.[10] Melanized cryptococci are less susceptible to amphotericin B than non-melanized cryptococci.[45] Other virulence factors include the production of invasins (e.g., phospholipase B [Plb1] and urease) and antioxidants (e.g., superoxide dismutase [SOD1]). In murine models of *C. neoformans* infection, Plb1 and laccase are essential for egress of cryptococci from the lung and dissemination to the central nervous system (CNS), whereas Plb1 and urease are required for cryptococci to cross the blood–brain barrier.[46]

Cryptococcal strain variance influences virulence capacity and clinical outcomes.[47,48] Clinical studies suggest that lung involvement occurs only in 20 to 35% of patients with *C. neoformans* infection[49,50] but in 60 to 76% of those with *C. gattii* infection.[20,50,51] In support of this, murine studies show that mice infected by intrapharyngeal aspiration of *C. gattii* strain R265 (VGII) die from pulmonary causes, while those infected with *C. neoformans* VNI H99 strain die from CM.[52] Growth rate in blood was slower for strain R265 compared with H99 and intravenous infection of either demonstrated similar capacity to cross the blood–brain barrier, though at low levels of inocula, more H99 crossed the blood–brain barrier.[52] Furthermore, infection in mice with strain R265 was associated with alveolar expansion due to yeast proliferation and a much reduced macrophage response, whereas infection with H99 showed numerous nodules in the alveolar space consisting of macrophages and multinucleated giant cells.[53] This suggests diminished control of *C. gattii* in the pulmonary compartment contributes to its propensity for lung manifestations.

Immunopathogenesis of Cryptococcosis

Innate and adaptive responses are critical for the control of all forms of cryptococcal infection including pulmonary disease. Cell-mediated immunity (CMI) is the key as evidenced by the preponderance of cryptococcosis in HIV/AIDS patients with impaired T-cell immunity and granuloma formation that is characteristic of CMI (reviewed by Chang et al[54]). Protective CMI is based primarily on Cryptococcus-specific Th1-type CD4+ T cells which produce interleukin (IL)-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α.[55] CMI-mediated responses include direct cytotoxic effects and regulation of cytokine production, a Th1–Th17 cytokine profile is associated with increased phagocytic activity and inhibition of cryptococcal growth, while a Th2 response is nonprotective.[56]

Immunological responses to *Cryptococcus* spp. are characteristically Th1 driven—with CXCR3 and CCR5 as homing receptors for effector T cells and natural killer (NK) cells and IFN-γ as the common effector molecule (reviewed by Chang et al[54]). The latter plays a critical role in the control of pulmonary disease in murine models and in human cryptococcosis (reviewed by Chang et al[54]). The impact of HIV on the immune response to cryptococcosis is also reviewed by Chang et al.[54] Complement and mannose-binding lectin deficiency, impaired chemotaxis and phagocytosis of macrophages and polymorphonuclear cells, and abnormal T-cell-mediated cytotoxicity associated with SLE and glucocorticoid use contribute to the pathogenesis of cryptococcosis.[29]

Clinical Presentation

Diagnosing pulmonary cryptococcosis may be problematic owing to lack of specificity of symptoms, often a low index of suspicion and limited diagnostics in resource-limited settings. Indeed, patients diagnosed with isolated pulmonary

cryptococcosis are often asymptomatic, presenting instead with an "incidental" radiological abnormality, mimicking lung malignancy. All patients with CNS cryptococcosis should be assessed radiologically for pulmonary involvement.

Severe pneumonia with acute respiratory failure was not uncommon in older studies of pulmonary cryptococcosis in the early era of HIV, where advanced immunodeficiency was the norm.[57] Recently, a majority of patients with pulmonary cryptococcosis are asymptomatic or simply report cough, scant sputum production, fever, dyspnea, and chest pain,[37,58–60] indistinguishable from other causes of pneumonia.

There are no direct comparative studies between HIV-infected and noninfected patients. It is likely that the range of symptoms is similar, although severe presentations are more likely in immunosuppressed hosts. In a large Japanese study of HIV-uninfected patients with pulmonary cryptococcosis, asymptomatic, incidental illness was seen in 46.4% of those with underlying conditions and 64.2% without any underlying disease.[37] Those with symptoms presented with cough (17.6 and 22.3%), chest pain (3.6 and 10.4%), sputum production (17.6 and 6%), and fevers (3 and 23%) in patients with and without underlying disease, respectively.[37] In a small series of 23 patients from Korea, 57% had no symptoms or signs, and 26% had a cough, 17% had chest pain, and 9% experienced fever.[60] Importantly, only one patient was diagnosed with pulmonary cryptococcosis prior to culture confirmation.[60] In a retrospective Chinese study of cryptococcal lung infection in immunocompetent individuals, 24% were asymptomatic; symptoms included cough (62%), expectoration (38%), dyspnea (22%), fever (21%), chest pain (20%), and emaciation (13%).[59] Studies of *C. gattii* infection in Australia revealed pulmonary involvement in 63% of cases, mostly occurring concurrently with CNS disease (81% of cases).[51] In contrast, in the North American outbreaks, many patients presented with respiratory symptoms (87% of British Columbian cases and 59% of U.S. cases),[61] often without CNS involvement.

Radiology

Chest X-rays and a complementary chest computed tomographic (CT) scan are important components of the diagnostic algorithm in patients suspected of pulmonary cryptococcosis. Overall, peripherally distributed lung nodules and masses are most common[37,58] with the right lower lobe being the most common location[37] (►**Fig. 1**). More than 60% of patients had multiple nodules.[37] In one study, patients with lung consolidation had higher serum cryptococcal antigen titers compared with those with solitary or multiple nodules and were also at increased risk of death.[37] Immunocompromised hosts have a greater propensity for cavitating lesions.[62] Very large lesions (more than 5–10 cm) are typical of *C. gattii* lung infection[63,64] and have been associated with Pancoast syndrome with respiratory stridor.[65]

Laboratory Diagnosis

The laboratory diagnosis is typically based on the isolation of *Cryptococcus*. Ideally, this should be supported by histopathological evidence of tissue invasion. Diagnosis by molecular, including polymerase chain reaction (PCR)-based, methods is not usually required and is not further discussed here.

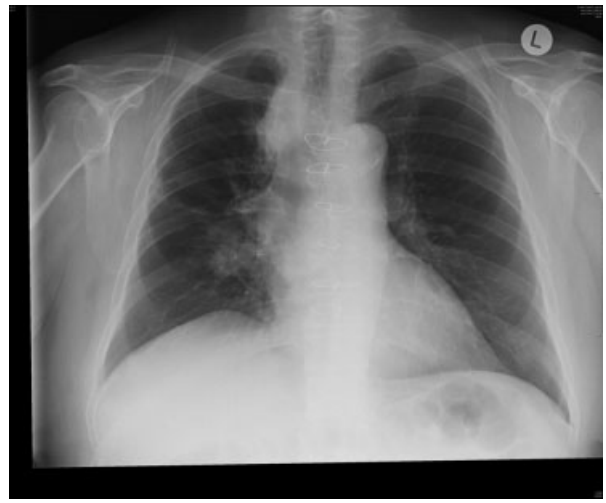

Fig. 1 Chest X-ray depicting right hilar mass and right upper lobe consolidation in a patient with isolated pulmonary cryptococcosis.

Culture of Clinical Specimens

Culture of *Cryptococcus* from lung biopsies provides a definitive diagnosis but requires an invasive procedure. More often, sputum and bronchoalveolar lavage (BAL) fluid are collected for culture. Budding encapsulated yeasts may be seen on microscopy. Cultures held at 30°C are typically positive within 7 days and should be examined daily; uncommonly they require incubation for up to 14 days. Hematoxylin and eosin stains will detect Cryptococci, but specific stains for the fungal cell wall, melanin, or polysaccharide capsule may be more helpful.

Laboratory processing of sputum is not standardized; different culture media and culture conditions are used and many laboratories do not routinely report yeast or fungal growth from sputum. Isolation of the *C. neoformans–C. gattii complex* should not be dismissed as contamination, and all source patients deserve clinical evaluation. Culture of BAL fluid has a higher diagnostic yield than that of sputum. With the emergence of *C. gattii* in temperate climates and its ability to cause outbreaks, it is advisable that laboratories routinely distinguish between *C. gattii* and *C. neoformans*. A simple test to distinguish them is by inoculation onto Canavanine-glycine-bromothymol blue (CGB) agar when colonies of *C. gattii* appear blue while *C. neoformans* colonies exhibit no color change.

Histology—Tissue Sampling by VATS, Percutaneous or Open Lung Biopsy

As microbiological isolation of *Cryptococcus* in sputum and bronchoscopy specimens may be unsuccessful, lung biopsies may be needed for diagnosis. The choice of invasive procedure is based on the location of the lesion and the availability of skilled operators. Transbronchial lung biopsy, video-assisted

thoracoscopic (VAT) biopsy, percutaneous, and open lung biopsy may be considered.

Serum Cryptococcal Antigen

In contrast to CNS cryptococcosis, serum cryptococcal antigen titers in isolated pulmonary cryptococcosis are relatively low (median 1:16 in those without underlying disease, 1:32 in those with underlying disease) but remain a helpful test.[37] While the serum antigen titer typically falls with antifungal treatment, it can rise transiently after initiation of antifungal therapy and remain elevated for a prolonged period. In a retrospective case series, the titer became negative at a median on 13 and 10.7 months in those with and without underlying disease, respectively.[37] In a prospective study of pulmonary cryptococcosis in 48 transplant recipients, 83% tested positive for serum cryptococcal antigen, primarily in patients with extrapulmonary disease and fungemia.[27]

The new lateral flow assay (LFA) for measuring cryptococcal antigen has performed well (>95% sensitivity and 100% specificity when used on serum and cerebrospinal fluid [CSF] in predominantly HIV-infected patients with CM).[66,67] Its simplicity and suitability as a point-of-care test make it attractive for routine use, especially in resource-limited settings. However, its performance in other patient populations including those with isolated pulmonary cryptococcal disease remains to be evaluated.

Antifungal Susceptibility

Clinical and environmental isolates of *C. neoformans* and *C. gattii* from multiple countries demonstrate low rates of resistance and overall susceptibility to agents such as fluconazole, amphotericin,[68–70] and the newer azoles, voriconazole and posaconazole. The echinocandins have poor activity in intro against *Cryptococcus* and should not be used for therapy.[71]

Antifungal susceptibility testing of *C. neoformans* and *C. gattii* is not performed routinely in many clinical laboratories. The gold standard for antifungal susceptibility testing is the broth microdilution method, though recent studies suggest that testing by the Vitek-2 and E-test may be comparable.[68] The absence of a clinical breakpoint makes interpretation of drug minimum inhibitory concentrations difficult. However, susceptibility testing is helpful in patients failing antifungal therapy.

Molecular Diagnosis and Typing

While MLST of *Cryptococcus* is widely used in research studies, at present, molecular methods are not required in routine clinical practice. Molecular typing is particularly useful in tracking outbreaks and health care associated transmission.[72] Should molecular data be available, clinicians should be aware that antifungal susceptibility profile may vary with molecular type,[73] with host immune responses[47] and hence potentially result in different clinical outcomes.

Principles of Management

Any patient with a diagnosis of pulmonary cryptococcosis should be investigated for disseminated disease and for underlying immunodeficiency (►**Table 2**). Blood culture, serum cryptococcal antigen test, and a lumbar puncture for CSF examination including measurement of the CSF opening pressure are routinely recommended, with additional investigations depending on the clinical presentation. Approximately 9.3% of 122 non-HIV infected patients with pulmonary cryptococcosis who underwent a lumbar puncture were diagnosed with CM.[37] Concurrent lung and neurological manifestations occurred in 85% of patients in a study of *C. gattii* in Australia.[32]

The presence of a positive blood culture is indicative of disseminated disease and attendant increased risk of CNS involvement. In turn, the presence of CM or CNS cryptococcomas significantly alters patient management, including the need for longer duration and escalation of antifungal therapy. International guidelines for the management of CNS cryptococcosis[74–77] are published.

Antifungal Therapy for Pulmonary Cryptococcosis

Definitive treatment recommendations for pulmonary cryptococcosis are hampered by the absence of prospective, randomized controlled trials or prospective cohort studies of patient outcomes. Thus, treatment guidelines are based on retrospective case series, expert opinion, and are inferred from studies of CNS cryptococcosis, especially those of CM in HIV-infected patients. Treatment guidelines from the Infectious Diseases Society of America (IDSA),[76] the American Thoracic Society (ATS),[78] the Australia and New Zealand Mycoses Interest Group (ANZMIG),[75] World Health Organization (WHO),[74] and other professional societies are summarized in ►**Table 3**.

Table 2 Helpful hints for managing pulmonary cryptococcosis

• Pulmonary tissue sampling is critical as culture techniques for respiratory samples may be nondiagnostic
• Ascertain dissemination to the central nervous system—Perform blood culture, serum cryptococcal antigen, and a lumbar puncture (including opening pressure, cell count, biochemistry, culture, and CSF cryptococcal antigen)
• Examine for other clinical manifestation including skin cryptococcoma
• Look for immunodeficiency states including HIV and underlying malignancy, but it is not surprising if none are identified
• Reduce immunosuppression where possible in transplant recipients
• Cryptococcal disease can occur in any patient including those without host risk factors

Table 3 Summary of available guidelines on the treatment of pulmonary cryptococcosis

Guideline	Mild to moderate symptoms and focal pulmonary infiltrates	Diffuse pulmonary disease (to treat as per CNS cryptococcosis)	Comments
General cryptococcosis guidelines			
Infectious Diseases Society of America (IDSA) CID 2010[76]	400 mg fluconazole daily 6–12 mo	**HIV:** *Induction:* Conventional amphotericin 0.7–1.0 mg/kg/d plus Flucytosine 100 mg/kg/d for 2 wk *Consolidation:* Fluconazole 400 mg daily for 8 wk *Maintenance:* Fluconazole 200 mg daily for 12 mo **Transplant:** *Induction:* [Liposomal amphotericin 3–4 mg/kg/d or ABLC 5 mg/kg/d] plus flucytosine (100 mg/kg/d) for 2 wk *Consolidation:* Fluconazole 400–800 mg daily for 8 wk *Maintenance:* Fluconazole 200–400 mg daily for 12 mo **Non-HIV, nontransplant:** *Induction:* Conventional amphotericin 0.7–1.0 mg/kg/d plus flucytosine 100 mg/kg/d for 4 wk *Consolidation:* Fluconazole 400–800 mg daily for 8 wk *Maintenance:* Fluconazole 200 mg daily for 12 mo	Multiple recommendations—graded Does not alter management based on *C. neoformans* vs. *C. gattii* Host-based guidelines and suggests 12 mo treatment for severe pulmonary cryptococcosis using CNS-like strategy
American Thoracic Society AJRCCM 2011[102]	400 mg fluconazole daily (then taper to 200 mg for 6 mo) Or Itraconazole for 6 mo	Amphotericin B 0.7–1.0 mg/kg/d plus flucytosine 100 mg/kg/d for 2 wk, then fluconazole or itraconazole 400 mg/d for 10 wk or Amphotericin B 0.7–1.0 mg/kg/d plus flucytosine 100 mg/kg/d for 6–10 wk	Controversially recommends no therapy in "colonized" immunocompetent Recommends extension if *C. gattii* Also extend to 12 mo if mild disease in immunocompromised
Australian guidelines IMJ 2014[75]	400–800 mg fluconazole for 6–12 mo	Liposomal amphotericin 3 mg/kg/d (or conventional amphotericin 0.7–1.0 mg/kg/d) plus flucytosine (100 mg/kg/d) for 2 wk then Fluconazole 400 mg daily for 6–12 mo	Recommends more intensive treatment in any immunocompromised patient and also those with large cryptococcomas
HIV-specific guidelines			
AIDSinfo guidelines 2013[77]	Fluconazole 400 mg daily for 12 mo	*Induction*: Liposomal amphotericin B 3–4 mg/kg/d plus flucytosine 100 mg/kg/d in 4 divided doses for $\geq$ 2 wk *Consolidation*: Fluconazole 400 mg daily for $\geq$ 8 wk *Maintenance*: Fluconazole 200 mg daily for $\geq$ 1 y and CD4 $\geq$ 100 cells/μL	Does not alter management based on *C. neoformans* vs. *C. gattii*
WHO 2012[74]	*No details available*	*No details available*	*No specific discussion on the treatment of pulmonary cryptococcosis*

Table 3 (*Continued*)

Guideline	Mild to moderate symptoms and focal pulmonary infiltrates	Diffuse pulmonary disease (to treat as per CNS cryptococcosis)	Comments
MMWR 2009[103]	*No details available*	*No details available*	*No specific discussion on the treatment of pulmonary cryptococcosis*

Many expert panels have developed broad treatment recommendations subclassified by host immune status (e.g., IDSA guidelines[76]). Other guidelines are targeted at specific patient groups, such as the AIDSinfo guidelines[77] for HIV-infected patients and the ATS guidelines[78] (for transplant recipients). The WHO guidelines[74] focus on CM treatment and care in resource-limited settings with no comment on pulmonary cryptococcosis.

Overall, similar treatment regimens are recommended for *C. neoformans* and *C. gattii* pulmonary disease. Asymptomatic or mild to moderate pulmonary cryptococcosis may be treated with 400 to 800 mg fluconazole daily for 6 to 12 months, while those with severe symptoms, diffuse infiltrates on imaging, or with concomitant CNS disease should be treated as CNS disease. The latter includes induction therapy with a combination of an amphotericin B formulation and 5-flucytosine,[79] followed by a period of consolidation and maintenance with oral fluconazole. Patients intolerant of fluconazole may be given itraconazole 200 to 400 mg/day, though there is growing experience with the use of posaconazole[80] and voriconazole.[81]

Adjunctive Therapy for Pulmonary Cryptococcosis

Surgical resection should be considered in those with persistent symptoms despite therapy and those with very large pulmonary cryptococcomas (> 5 cm), particularly in the presence of a mass effect.

There have been two randomized studies[82,83] of exogenous IFN-γ as adjuvant therapy in the setting of CM but none in pulmonary cryptococcosis. Exogenous IFN-γ showed no impact on mortality but was associated with faster rate of CSF fungal clearance.[83] So far, this is not yet widely recommended as an adjuvant in CM. There is no evidence to support its use in isolated pulmonary cryptococcosis.

Specific Conditions

HIV Infection

Access to 5-flucytosine and amphotericin remains a major obstacle to providing the best CM management internationally. Research in many resource-limited settings has focused on high-dose induction therapy with fluconazole as an alternative treatment strategy.[84,85]

The timing of antiretroviral therapy (ART) commencement in the setting of any newly diagnosed opportunistic infection must balance the risk of immune reconstitution inflammatory syndrome (IRIS) with early ART commencement against the ongoing risk of CM and other coinfections with late commencement. Early ART commencement (within 10 days of CM diagnosis) has been associated with increased mortality in randomized controlled studies.[86–88] Equally, delay of ART prolongs the duration of immunodeficiency and may result in losses in follow-up, particularly in resource-limited settings. These considerations mean that clinical judgment and individualized care are necessary.[89] While the timing of ART commencement has not been specifically studied in isolated lung cryptococcosis, delay in its commencement is unlikely to be necessary.

Transplant Recipients

The American Transplant Society guidelines emphasizes that all *Cryptococcus* spp. may be pathogenic in transplant recipients.[78] Donor-derived cryptococcosis should be considered in any of the following scenarios: (1) *Cryptococcus* is demonstrated histologically or cultured at the surgical or graft site; (2) cryptococcosis is documented at any body site within 30 days after transplant, particularly outside the lung and CNS; or (3) cryptococcal disease is diagnosed in more than one recipient from a single donor.[78] While reduction in immunosuppressive therapy is important, rapid reduction should be avoided particularly with regard to corticosteroids to minimize risk of IRIS.[78]

Pregnancy

Clinical judgment is especially important in the management of pregnant patients, as safe therapeutic options are limited. It may be reasonable to withhold antifungals till postpregnancy in those with very mild pulmonary cryptococcal disease, while monitoring progress and/or attempt to delay fluconazole therapy until at least after the first trimester.[76]

Children

There are no prospective clinical trials in children with cryptococcosis. The IDSA guidelines[76] recommend fluconazole 6 to 12 mg/kg/day orally for 6 to 12 months in children with cryptococcal pneumonia.

Methamphetamine

Recent murine studies demonstrate that methamphetamine administration in experimental murine infection accelerates time to death, promotes *C. neoformans* dissemination from the respiratory tract to the brain, and stimulates cryptococcal adhesion, GXM release, and biofilm formation in the lungs. While this has not been studied in humans, this suggests

patients using methamphetamine may be at increased risk of pulmonary cryptococcosis and disseminated disease.[90]

Patient Suitability as Organ Donor

Transmission of cryptococcosis via organ transplantation has been reported.[34] Potential donors with untreated cryptococcal disease are not recommended for organ donation because of the high risk of transmission to the recipient.[78] The suitability of potential donors currently receiving antifungal treatment for cryptococcal disease should be evaluated on an individual basis—evidence of mycological eradication is preferred.[78] Potential donors with unexplained neurological symptoms should be evaluated for cryptococcosis.

Suitability of Patients with Cryptococcosis for Organ Transplantation

Patients treated for cryptococcal disease have undergone successful autologous and allogeneic stem cell transplantation 1 to 10 months after diagnosis of cryptococcosis[91] and should not be excluded for consideration for solid-organ or stem cell transplantation.

Preventing Cryptococcosis

Preventing exposure to cryptococcosis is impractical in endemic regions. There is good randomized controlled trial evidence for the use of fluconazole,[92,93] or as second line, itraconazole[94] 200 mg daily, as primary prophylaxis in HIV-infected patients with low CD4 T cell counts; however, uptake of this practice has been poor globally. There have been no studies on the use of fluconazole as primary prevention in other high-risk groups such as transplant recipients or in the setting of a health-care-associated outbreak.

Cryptococcosis-Associated Immune Reconstitution Inflammatory Syndrome

Cryptococcosis-associated immune reconstitution inflammatory syndrome (C-IRIS) presents as clinical worsening or new presentation of cryptococcal disease due to a dysfunctional immune response. It typically occurs soon after ART (antiretroviral therapy) commencement, but has been reported after reduction of immunosuppressive therapy in transplant recipients.[95,96] While the manifestations of C-IRIS vary with the organs involved, these are most severe when they occur in the CNS. The strongest predictors of risk for IRIS include a lower CD4+ T-cell count and active or subclinical opportunistic infection or antigens,[97–99] but other host, pathogen, and immune factors have been recognized. There are two forms of C-IRIS: "Unmasking C-IRIS," where a patient not previously known to have cryptococcal disease experiences a new episode of cryptococcal infection after ART commencement, and "paradoxical C-IRIS," where a patient has been adequately treated for cryptococcosis and re-presents with a flare of cryptococcal-like symptoms after commencement of ART.[100] The proposed case definitions for paradoxical C-IRIS, cART-associated cryptococcosis, and unmasking C-IRIS have been published by Haddow et al.[100] The immunopathogenesis and recent advances in understanding C-IRIS are reviewed by Chang et al.[101]

Research Gaps

Little clinical research has been undertaken in patients with isolated pulmonary cryptococcosis, although earlier recognition and management of this entity should reduce risk of dissemination. Performance of large seroprevalence studies in endemic areas, development of improved staining procedures and molecular methods for cryptococcal detection in respiratory specimens, genome sequencing of cryptococcal isolates, and longitudinal studies on optimal antifungal duration and time to radiological resolution are all avenues to pursue. There is no current test of cure for cryptococcosis. To improve outcomes, detailed human immunopathological studies of the lung compartment should include not only antigen-specific T-cell immunity and interferon-γ production but also innate immunity, including the role of macrophages and an understanding of the constituents, process, and role of granuloma formation. Recognition that the at-risk group for cryptococcosis is increasingly broad should stimulate studies identifying environmental "hotspots" and risk activities to inform preventative strategies.

Conclusion

Pulmonary cryptococcosis is under-recognized in both resource-limited and resource-rich settings, particularly in apparently immunocompetent hosts. An eminently treatable disease, early diagnosis of pulmonary cryptococcosis should prevent further dissemination to its more lethal forms of CNS involvement. Imaging and tissue sampling for histological examination are important diagnostic adjuncts. More researches focusing on the pathogenesis, epidemiology, and clinical manifestations and treatment of pulmonary cryptococcosis are needed.

Acknowledgments

The authors thank the patient for allowing access to and publication of the chest X-ray (►**Fig. 1**). C. C. C. is an Australian National Health and Medical Research Council (NHMRC) Early Career Fellow. T. C. S. is a Sydney Medical Foundation fellow.

References

1 Park BJ, Wannemuehler KA, Marston BJ, Govender N, Pappas PG, Chiller TM. Estimation of the current global burden of cryptococcal meningitis among persons living with HIV/AIDS. AIDS 2009; 23(4):525–530
2 Brown GD, Denning DW, Gow NA, Levitz SM, Netea MG, White TC. Hidden killers: human fungal infections. Sci Transl Med 2012; 4(165):165rv13
3 Chayakulkeeree M, Perfect JR. Cryptococcosis. Infect Dis Clin North Am 2006;20(3):507–544, v–vi
4 Kwon-Chung KJ, Boekhout T, Wickes BL, Fell JW. Systematics of the genus Cryptococcus and its type species *C. neoformans*. In: Heitman J, Kozel TR, Kwon-Chung KJ, Perfect JR, Casadevall A, eds. Cryptococcus—From Human Pathogen to Model Yeast. Washington, DC: ASM Press; 2011:3–15

5 Braun U. The impacts of the discontinuation of dual nomenclature of pleomorphic fungi: the trivial facts, problems, and strategies. IMA Fungus 2012;3(1):81–86
6 Hawksworth DL. Managing and coping with names of pleomorphic fungi in a period of transition. IMA Fungus 2012;3(1): 15–24
7 De Hoog GS, Chaturvedi V, Denning DW, et al. ISHAM Working Group on Nomenclature of Medical Fungi. Name changes in medically important fungi and their implications for clinical practice. J Clin Microbiol 2015;53(4):1056–1062
8 Kwon-Chung KJ, Varma A. Do major species concepts support one, two or more species within Cryptococcus neoformans? FEMS Yeast Res 2006;6(4):574–587
9 Meyer W, Aanensen DM, Boekhout T, et al. Consensus multi-locus sequence typing scheme for *Cryptococcus neoformans* and *Cryptococcus gattii*. Med Mycol 2009;47(6):561–570
10 Idnurm A, Bahn YS, Nielsen K, Lin X, Fraser JA, Heitman J. Deciphering the model pathogenic fungus *Cryptococcus neoformans*. Nat Rev Microbiol 2005;3(10):753–764
11 D'Souza CA, Kronstad JW, Taylor G, et al. Genome variation in *Cryptococcus gattii*, an emerging pathogen of immunocompetent hosts. MBio 2011;2(1):e00342–e10
12 Kidd SE, Hagen F, Tscharke RL, et al. A rare genotype of *Cryptococcus gattii* caused the cryptococcosis outbreak on Vancouver Island (British Columbia, Canada). Proc Natl Acad Sci U S A 2004; 101(49):17258–17263
13 Lin X, Litvintseva AP, Nielsen K, et al. alpha AD alpha hybrids of *Cryptococcus neoformans*: evidence of same-sex mating in nature and hybrid fitness. PLoS Genet 2007;3(10):1975–1990
14 Bovers M, Hagen F, Kuramae EE, et al. AIDS patient death caused by novel *Cryptococcus neoformans* x *C. gattii* hybrid. Emerg Infect Dis 2008;14(7):1105–1108
15 Chen SC, Meyer W, Sorrell TC. *Cryptococcus gattii* infections. Clin Microbiol Rev 2014;27(4):980–1024
16 Litvintseva AP, Carbone I, Rossouw J, Thakur R, Govender NP, Mitchell TG. Evidence that the human pathogenic fungus *Cryptococcus neoformans* var. grubii may have evolved in Africa. PLoS ONE 2011;6(5):e19688
17 Swinne D, Deppner M, Laroche R, Floch JJ, Kadende P. Isolation of *Cryptococcus neoformans* from houses of AIDS-associated cryptococcosis patients in Bujumbura (Burundi). AIDS 1989;3(6): 389–390
18 Harris J, Lockhart S, Chiller T. *Cryptococcus gattii*: where do we go from here? Med Mycol 2012;50(2):113–129
19 Kwon-Chung KJ, Bennett JE. Epidemiologic differences between the two varieties of Cryptococcus neoformans. Am J Epidemiol 1984;120(1):123–130
20 Galanis E, Macdougall L, Kidd S, Morshed M; British Columbia Cryptococcus gattii Working Group. Epidemiology of *Cryptococcus gattii*, British Columbia, Canada, 1999-2007. Emerg Infect Dis 2010;16(2):251–257 [erratum in: Emerg Infect Dis. 2010 Apr;16 (4):750]
21 Marr KA. *Cryptococcus gattii*: the tip of the iceberg. Clin Infect Dis 2011;53(12):1196–1198
22 Engelthaler DM, Hicks ND, Gillece JD, et al. *Cryptococcus gattii* in North American Pacific Northwest: whole-population genome analysis provides insights into species evolution and dispersal. MBio 2014;5(4):e01464–e14
23 Harris JR, Lockhart SR, Sondermeyer G, et al. *Cryptococcus gattii* infections in multiple states outside the US Pacific Northwest. Emerg Infect Dis 2013;19(10):1620–1626
24 Hagen F, Ceresini PC, Polacheck I, et al. Ancient dispersal of the human fungal pathogen *Cryptococcus gattii* from the Amazon rainforest. PLoS ONE 2013;8(8):e71148
25 Singer LM, Meyer W, Firacative C, Thompson GR III, Samitz E, Sykes JE. Antifungal drug susceptibility and phylogenetic diversity among Cryptococcus isolates from dogs and cats in North America. J Clin Microbiol 2014;52(6):2061–2070
26 Sun HY, Wagener MM, Singh N. Cryptococcosis in solid-organ, hematopoietic stem cell, and tissue transplant recipients: evidence-based evolving trends. Clin Infect Dis 2009;48(11): 1566–1576
27 Singh N, Alexander BD, Lortholary O, et al. Pulmonary cryptococcosis in solid organ transplant recipients: clinical relevance of serum cryptococcal antigen. Clin Infect Dis 2008;46(2):e12–e18
28 Wang LR, Barber CE, Johnson AS, Barnabe C. Invasive fungal disease in systemic lupus erythematosus: a systematic review of disease characteristics, risk factors, and prognosis. Semin Arthritis Rheum 2014;44(3):325–330
29 González LA, Vásquez G, Restrepo JP, Velásquez M, Ramírez LA. Cryptococcosis in systemic lupus erythematosus: a series of six cases. Lupus 2010;19(5):639–645
30 Bernard C, Maucort-Boulch D, Varron L, et al; French Cryptococcosis Study Group. Cryptococcosis in sarcoidosis: cryptOsarc, a comparative study of 18 cases. QJM 2013;106(6):523–539
31 Yanagawa N, Sakai F, Takemura T, et al. Pulmonary cryptococcosis in rheumatoid arthritis (RA) patients: comparison of imaging characteristics among RA, acquired immunodeficiency syndrome, and immunocompetent patients. Eur J Radiol 2013; 82(11):2035–2042
32 Chen SC, Slavin MA, Heath CH, et al; Australia and New Zealand Mycoses Interest Group (ANZMIG)-Cryptococcus Study. Clinical manifestations of *Cryptococcus gattii* infection: determinants of neurological sequelae and death. Clin Infect Dis 2012;55(6): 789–798
33 Zonios DI, Falloon J, Huang CY, Chaitt D, Bennett JE. Cryptococcosis and idiopathic CD4 lymphocytopenia. Medicine (Baltimore) 2007;86(2):78–92
34 Baddley JW, Schain DC, Gupte AA, et al. Transmission of Cryptococcus neoformans by organ transplantation. Clin Infect Dis 2011;52(4):e94–e98
35 Sun HY, Alexander BD, Lortholary O, et al; Cryptococcal Collaborative Transplant Study Group. Unrecognized pretransplant and donor-derived cryptococcal disease in organ transplant recipients. Clin Infect Dis 2010;51(9):1062–1069
36 Dromer F, Mathoulin S, Dupont B, Laporte A; French Cryptococcosis Study Group. Epidemiology of cryptococcosis in France: a 9-year survey (1985-1993). Clin Infect Dis 1996; 23(1):82–90
37 Kohno S, Kakeya H, Izumikawa K, et al. Clinical features of pulmonary cryptococcosis in non-HIV patients in Japan. J Infect Chemother 2015;21(1):23–30
38 Hajjeh RA, Conn LA, Stephens DS, et al; Cryptococcal Active Surveillance Group. Cryptococcosis: population-based multistate active surveillance and risk factors in human immunodeficiency virus-infected persons. J Infect Dis 1999;179(2):449–454
39 Lizarazo J, Escandón P, Agudelo CI, Castañeda E. Cryptococcosis in Colombian children and literature review. Mem Inst Oswaldo Cruz 2014;109(6):797–804
40 Chai HC, Tay ST. Detection of IgM and IgG antibodies to *Cryptococcus neoformans* proteins in blood donors and HIV patients with active cryptococcosis. Mycoses 2009;52(2):166–170
41 Goldman DL, Khine H, Abadi J, et al. Serologic evidence for *Cryptococcus neoformans* infection in early childhood. Pediatrics 2001;107(5):E66
42 Goldman DL, Lee SC, Mednick AJ, Montella L, Casadevall A. Persistent *Cryptococcus neoformans* pulmonary infection in the rat is associated with intracellular parasitism, decreased inducible nitric oxide synthase expression, and altered antibody responsiveness to cryptococcal polysaccharide. Infect Immun 2000;68(2):832–838
43 Rodrigues ML, Casadevall A, Zaragoza O. The architecture and antigenic composition of the polysaccharide capsule. In: Heitman J, Kozel TR, Kwon-Chung KJ, Perfect JR, Casadevall A, eds. Cryptococcus: From Human Pathogen to Model Yeast. Washington, DC: ASM Press; 2011:43–54

44 Rodrigues ML, Alviano CS, Travassos LR. Pathogenicity of *Cryptococcus neoformans*: virulence factors and immunological mechanisms. Microbes Infect 1999;1(4):293–301

45 Jacobson ES, Ikeda R. Effect of melanization upon porosity of the cryptococcal cell wall. Med Mycol 2005;43(4):327–333

46 Santangelo R, Zoellner H, Sorrell T, et al. Role of extracellular phospholipases and mononuclear phagocytes in dissemination of cryptococcosis in a murine model. Infect Immun 2004;72(4): 2229–2239

47 Wiesner DL, Moskalenko O, Corcoran JM, et al. Cryptococcal genotype influences immunologic response and human clinical outcome after meningitis. MBio 2012;3(5):

48 Alanio A, Desnos-Ollivier M, Dromer F. Dynamics of *Cryptococcus neoformans*-macrophage interactions reveal that fungal background influences outcome during cryptococcal meningoencephalitis in humans. MBio 2011;2(4):

49 Tseng HK, Liu CP, Ho MW, et al; Taiwan Infectious Diseases Study Network for Cryptococcosis. Microbiological, epidemiological, and clinical characteristics and outcomes of patients with cryptococcosis in Taiwan, 1997-2010. PLoS ONE 2013; 8(4):e61921

50 Chen S, Sorrell T, Nimmo G, et al; Australasian Cryptococcal Study Group. Epidemiology and host- and variety-dependent characteristics of infection due to *Cryptococcus neoformans* in Australia and New Zealand. Clin Infect Dis 2000;31(2):499–508

51 Chen SC, Korman TM, Slavin MA, et al; Australia and New Zealand Mycoses Interest Group (ANZMIG) Cryptococcus Study. Antifungal therapy and management of complications of cryptococcosis due to *Cryptococcus gattii*. Clin Infect Dis 2013;57(4):543–551

52 Ngamskulrungroj P, Chang Y, Sionov E, Kwon-Chung KJ. The primary target organ of *Cryptococcus gattii* is different from that of *Cryptococcus neoformans* in a murine model. MBio 2012;3(3):

53 Okubo Y, Wakayama M, Ohno H, et al. Histopathological study of murine pulmonary cryptococcosis induced by *Cryptococcus gattii* and *Cryptococcus neoformans*. Jpn J Infect Dis 2013;66(3): 216–221

54 Chang CC, Crane M, Zhou J, et al. HIV and co-infections. Immunol Rev 2013;254(1):114–142

55 Hole CR, Wormley FL Jr. Vaccine and immunotherapeutic approaches for the prevention of cryptococcosis: lessons learned from animal models. Front Microbiol 2012;3:291

56 Antachopoulos C, Walsh TJ. Immunotherapy of Cryptococcus infections. Clin Microbiol Infect 2012;18(2):126–133

57 Visnegarwala F, Graviss EA, Lacke CE, et al. Acute respiratory failure associated with cryptococcosis in patients with AIDS: analysis of predictive factors. Clin Infect Dis 1998;27(5): 1231–1237

58 Zhang Y, Li N, Zhang Y, et al. Clinical analysis of 76 patients pathologically diagnosed with pulmonary cryptococcosis. Eur Respir J 2012;40(5):1191–1200

59 Ye F, Xie JX, Zeng QS, Chen GQ, Zhong SQ, Zhong NS. Retrospective analysis of 76 immunocompetent patients with primary pulmonary cryptococcosis. Lung 2012;190(3):339–346

60 Song KD, Lee KS, Chung MP, et al. Pulmonary cryptococcosis: imaging findings in 23 non-AIDS patients. Korean J Radiol 2010; 11(4):407–416

61 Franco-Paredes C, Womack T, Bohlmeyer T, et al. Management of *Cryptococcus gattii* meningoencephalitis. Lancet Infect Dis 2015; 15(3):348–355

62 Kishi K, Homma S, Kurosaki A, Kohno T, Motoi N, Yoshimura K. Clinical features and high-resolution CT findings of pulmonary cryptococcosis in non-AIDS patients. Respir Med 2006;100(5): 807–812

63 Jenney A, Pandithage K, Fisher DA, Currie BJ. Cryptococcus infection in tropical Australia. J Clin Microbiol 2004;42(8): 3865–3868

64 Garrett L, Marr K, West S, Allada G. 74-year-old man from the pacific northwest with fever and a lung mass. Chest 2011;140(3): 814–817

65 Mitchell DH, Sorrell TC. Pancoast's syndrome due to pulmonary infection with *Cryptococcus neoformans* variety gattii. Clin Infect Dis 1992;14(5):1142–1144

66 Kabanda T, Siedner MJ, Klausner JD, Muzoora C, Boulware DR. Point-of-care diagnosis and prognostication of cryptococcal meningitis with the cryptococcal antigen lateral flow assay on cerebrospinal fluid. Clin Infect Dis 2014;58(1):113–116

67 Rajasingham R, Rolfes MA, Birkenkamp KE, Meya DB, Boulware DR. Cryptococcal meningitis treatment strategies in resource-limited settings: a cost-effectiveness analysis. PLoS Med 2012; 9(9):e1001316

68 Mahabeer Y, Chang CC, Naidu D, et al. Comparison of Etests and Vitek 2 ® to broth microdilution for the susceptibility testing of Cryptococcus neoformans. Diagn Microbiol Infect Dis 2014; 80(4):294–298

69 Andrade-Silva L, Ferreira-Paim K, Mora DJ, et al. Susceptibility profile of clinical and environmental isolates of *Cryptococcus neoformans* and *Cryptococcus gattii* in Uberaba, Minas Gerais, Brazil. Med Mycol 2013;51(6):635–640

70 Bejar V, Tello M, García R, et al. Molecular characterization and antifungal susceptibility of *Cryptococcus neoformans* strains collected from a single institution in Lima, Peru. Rev Iberoam Micol 2015;32(2):88–92

71 Pfaller MA, Messer SA, Woosley LN, Jones RN, Castanheira M. Echinocandin and triazole antifungal susceptibility profiles for clinical opportunistic yeast and mold isolates collected from 2010 to 2011: application of new CLSI clinical breakpoints and epidemiological cutoff values for characterization of geographic and temporal trends of antifungal resistance. J Clin Microbiol 2013;51(8):2571–2581

72 Chang CC, Ananda-Rajah M, Belcastro A, et al. Consensus guidelines for implementation of quality processes to prevent invasive fungal disease and enhanced surveillance measures during hospital building works, 2014. Intern Med J 2014;44 (12b):1389–1397

73 Espinel-Ingroff A, Aller AI, Canton E, et al. *Cryptococcus neoformans-Cryptococcus gattii* species complex: an international study of wild-type susceptibility endpoint distributions and epidemiological cutoff values for fluconazole, itraconazole, posaconazole, and voriconazole. Antimicrob Agents Chemother 2012;56(11): 5898–5906

74 Rapid advice: Diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. WHO Library Cataloguing-in-Publication Data, 2011. Available at http://www.who.int/hiv/pub/cryptococcal_disease2011/en/

75 Chen SC, Sorrell TC, Chang CC, Paige EK, Bryant PA, Slavin MA. Consensus guidelines for the treatment of yeast infections in the haematology, oncology and intensive care setting, 2014. Intern Med J 2014;44(12b):1315–1332

76 Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2010;50(3):291–322

77 Panel on Opportunistic Infections in HIV-Infected Adults and Adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. 2013 Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adult_oi.pdf. Accessed October 31, 2011

78 Singh N, Huprikar S, Burdette SD, Morris MI, Blair JE, Wheat LJ; American Society of Transplantation, Infectious Diseases Community of Practice, Donor-Derived Fungal Infection Working Group. Donor-derived fungal infections in organ transplant

recipients: guidelines of the American Society of Transplantation, infectious diseases community of practice. Am J Transplant 2012; 12(9):2414–2428
79 Day JN, Chau TT, Wolbers M, et al. Combination antifungal therapy for cryptococcal meningitis. N Engl J Med 2013; 368(14):1291–1302
80 Flores VG, Tovar RM, Zaldivar PG, Martinez EA. Meningitis due to Cryptococcus neoformans: treatment with posaconazole. Curr HIV Res 2012;10(7):620–623
81 Gamaletsou MN, Sipsas NV, Kontoyiannis DP, et al. Successful salvage therapy of refractory HIV-related cryptococcal meningitis with the combination of liposomal amphotericin B, voriconazole, and recombinant interferon-γ. Diagn Microbiol Infect Dis 2012; 74(4):409–411
82 Pappas PG, Bustamante B, Ticona E, et al. Recombinant interferon- gamma 1b as adjunctive therapy for AIDS-related acute cryptococcal meningitis. J Infect Dis 2004;189(12): 2185–2191
83 Jarvis JN, Meintjes G, Rebe K, et al. Adjunctive interferon-γ immunotherapy for the treatment of HIV-associated cryptococcal meningitis: a randomized controlled trial. AIDS 2012;26(9): 1105–1113
84 Longley N, Muzoora C, Taseera K, et al. Dose response effect of high-dose fluconazole for HIV-associated cryptococcal meningitis in southwestern Uganda. Clin Infect Dis 2008;47(12):1556–1561
85 Loyse A, Wilson D, Meintjes G, et al. Comparison of the early fungicidal activity of high-dose fluconazole, voriconazole, and flucytosine as second-line drugs given in combination with amphotericin B for the treatment of HIV-associated cryptococcal meningitis. Clin Infect Dis 2012;54(1):121–128
86 Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-Saharan Africa. Clin Infect Dis 2010;50(11):1532–1538
87 Bisson GP, Molefi M, Bellamy S, et al. Early versus delayed antiretroviral therapy and cerebrospinal fluid fungal clearance in adults with HIV and cryptococcal meningitis. Clin Infect Dis 2013;56(8):1165–1173
88 Boulware DR, Meya DB, Muzoora C, et al; COAT Trial Team. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. N Engl J Med 2014;370(26):2487–2498
89 Günthard HF, Aberg JA, Eron JJ, et al; International Antiviral Society-USA Panel. Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel. JAMA 2014;312(4):410–425
90 Patel D, Desai GM, Frases S, et al. Methamphetamine enhances Cryptococcus neoformans pulmonary infection and dissemination to the brain. MBio 2013;4(4):
91 Cahuayme-Zuniga L, Kontoyiannis DP. Is it safe to proceed with stem cell transplant in cancer patients treated for cryptococcal infection? A focus on recent IDSA cryptococcal guidelines. Clin Infect Dis 2010;50(12):1687–1689
92 Powderly WG, Finkelstein D, Feinberg J, et al; NIAID AIDS Clinical Trials Group. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. N Engl J Med 1995;332(11):700–705
93 Parkes-Ratanshi R, Wakeham K, Levin J, et al; Cryptococcal Trial Team. Primary prophylaxis of cryptococcal disease with fluconazole in HIV-positive Ugandan adults: a double-blind, randomised, placebo-controlled trial. Lancet Infect Dis 2011;11(12): 933–941
94 McKinsey DS, Wheat LJ, Cloud GA, et al; National Institute of Allergy and Infectious Diseases Mycoses Study Group. Itraconazole prophylaxis for fungal infections in patients with advanced human immunodeficiency virus infection: randomized, placebo-controlled, double-blind study. Clin Infect Dis 1999;28(5): 1049–1056
95 Sun HY, Singh N. Opportunistic infection-associated immune reconstitution syndrome in transplant recipients. Clin Infect Dis 2011;53(2):168–176
96 Singh N, Perfect JR. Immune reconstitution syndrome associated with opportunistic mycoses. Lancet Infect Dis 2007;7(6): 395–401
97 French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS 2004;18(12):1615–1627
98 French MA. HIV/AIDS: immune reconstitution inflammatory syndrome: a reappraisal. Clin Infect Dis 2009;48(1):101–107
99 French MA. Immune reconstitution inflammatory syndrome: immune restoration disease 20 years on. Med J Aust 2012; 196(5):318–321
100 Haddow LJ, Colebunders R, Meintjes G, et al; International Network for the Study of HIV-associated IRIS (INSHI). Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. Lancet Infect Dis 2010;10(11):791–802
101 Chang CC, Sheikh V, Sereti I, French MA. Immune reconstitution disorders in patients with HIV infection: from pathogenesis to prevention and treatment. Curr HIV/AIDS Rep 2014;11(3): 223–232
102 Limper AH, Knox KS, Sarosi GA, et al; American Thoracic Society Fungal Working Group. An official American Thoracic Society statement: treatment of fungal infections in adult pulmonary and critical care patients. Am J Respir Crit Care Med 2011;183(1): 96–128
103 Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58(RR-4):1–207, quiz CE1–CE4