Cryptococcosis

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KEYWORDS

- Cryptococcosis • Opportunistic mycoses • HIV/AIDS
- Solid organ transplantation (SOT) • Central nervous system (CNS) infection
- Immune reconstitution inflammatory syndrome (IRIS)

KEY POINTS

- Cryptococcosis is a major invasive fungal infection that is capable of widespread disease outbreaks in both immunocompromised and apparently immunocompetent hosts.
- Molecular advances continue to enhance our understanding of *Cryptococcus* and provide insight into its evolution into a pathogen of global importance.
- Diagnosis has improved with the introduction of point-of-care diagnostic assays.
- Screening and preemptive antifungal therapy offer great promise in making a significant impact in this highly deadly opportunistic mycosis.

INTRODUCTION

Cryptococcosis is an infectious disease with worldwide distribution and wide array of clinical presentations caused by pathogenic encapsulated yeasts in the genus *Cryptococcus*. Currently, there are 2 species of *Cryptococcus* that commonly cause disease in humans: *Cryptococcus neoformans* and *Cryptococcus gattii*. *C neoformans* was first identified as a human pathogen in the late 19th century, but was not recognized as a common cause of human disease until the late 1970s.[1,2] Over the last several decades, as vulnerable populations have expanded, cryptococcal meningitis became an infection of global importance, with up to 1 million new infections annually and significant attributable morbidity and mortality, especially among patients with human immunodeficiency virus (HIV) infection and AIDS.[3] Although *C neoformans and C gattii* share many features of a highly evolved, environmentally savvy yeast, there are important species- and strain-specific differences with respect to geographic distribution, environmental niches, host predilection, and clinical manifestations that

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should be emphasized. As molecular techniques of identification have evolved, we have gained further insight into the pathobiology of these encapsulated yeasts, and their capacity to adapt to environmental pressures, exploit new geographic environments, and cause disease in both immunocompromised and apparently immunocompetent hosts.[4] Despite increased availability of and success with antiretroviral therapy (ART), the worldwide burden of and mortality associated cryptococcal disease remains unacceptably high, and novel strategies of screening and preemptive therapy offer great promise at making a sustained and much needed impact on this sugar-coated opportunistic mycosis.

THE PATHOGENS: *CRYPTOCOCCUS NEOFORMANS* AND *CRYPTOCOCCUS GATTII*

Cryptococcus is a genus of basidiomycetous fungi with more than 30 species ubiquitously distributed in the environment. There are only 2 species commonly known to cause human disease, *C neoformans* and *C gattii*. The epidemiology of *C neoformans* is well-characterized and this organism causes disease in both immunocompromised and apparently immunocompetent hosts. *C gattii*, conversely, has historically been regarded as a pathogen of apparently immunocompetent patients. However, preexisting conditions and immunocompromised states, including subclinical immune defects, are also reported as risk factors for infection with this species.[5–8] These species differences in clinical presentation may be primarily determined by variable host predilections, but may also be better characterized as we further our understanding of molecular subtypes.[9–12]

Historically, the genus was further classified into 3 varieties, 5 serotypes (based on structural differences in the polysaccharide capsule), and 8 molecular subtypes (**Table 1**). Molecular methods of identification have enhanced our appreciation for the significant genetic diversity among the *C gattii–C neoformans* complex and have called into question the current 2 species classification system. Recent proposed taxonomy changes based on the understanding of molecular studies have divided the pathogenic cryptococcal species from their classic divisions into better-defined molecular and genetic divisions. At present, the following divisions have been proposed: *C neoformans* var. *grubii* (serotype A) with 3 genotypes (VNI, VNII, VNB); *C neoformans* var. *neoformans* (serotype D or VNIV); and 5 other cryptic species, *C gattii*, *C bacillisporus*, *C deuterogattii*, *C tetragattii*, and *C decagattii* (serotypes B/C or VGI-IV).[13] Phylogenetic analyses, combined with recognized heterogeneity with respect to virulence, host preference, and antifungal susceptibility do provide evidence to support

Table 1
Current classification of pathogenic *Cryptococcus* species

Serotype	Species and Varieties	Molecular Types
A	*C neoformans* var. *grubii*[a]	VN I, VN II
B	*C gattii*	VG I, VG II, VG III, VG IV
C	*C gattii*	VG I, VG II, VG III, VG IV
D	*C neoformans* var. *neoformans*	VN IV
AD	*C neoformans*	VN III

[a] Responsible for the vast majority of disease owing to C neoformans worldwide.

Adapted from Hagen F, Khayhan K, Theelen B, et al. Recognition of seven species in the *Cryptococcus gattii/Cryptococcus neoformans* species complex. Fungal Genet Biol 2015;78:17.