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Cryptococcus Speciation: Why Is It Important?

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In the past, cryptococcosis was known as a fungal infection associated with medical conditions causing immunodeficiency. One cryptococcal species now has been identified as a human pathogen also affecting persons who are immunocompetent. Risk factors, medical presentation and treatment differ for this organism, necessitating accurate laboratory diagnostics.

Cryptococcus gattii
[krip" to-kok'ðs ga-te-i]

This yeast genus takes its name from the Greek *kryptos*, hidden, and *kokkos*, berry. The pathogen has been recently recognized as a distinct species that causes infection (with cutaneous, pulmonary, and neurologic manifestations) in both humans and animals. The species was named for Italian mycologist Franco Gatti who, with Roger Eeckels, described an atypical strain of *C. neoformans* in the cerebrospinal fluid of a Congolese Bantu boy with cryptococcosis in 1970.

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Cryptococcal Infections

In humans most cryptococcal infections are caused by either *Cryptococcus neoformans* or *C. gattii* (formerly *C. neoformans* var. *gattii*). For both species the transmission appears to be by inhalation of fungal spores causing infection ranging from asymptomatic or mild disease to severe organ involvement such as pneumonia or meningitis. Although closely related to *C. neoformans*, *C. gattii* causes infections having clinical differences which might warrant differential treatment.

C. neoformans is considered an opportunistic organism, primarily infecting HIV-positive persons. Although *C. gattii* can cause illness in both immunocompetent and immunocompromised persons, most of those infected with *C. gattii* have been HIV-negative. The epidemiology of the two species also differs. *C. neoformans* occurs worldwide and is associated with pigeon guano or soil contaminated by birds. *C. gattii* is associated with trees and soil. The species was previously found only in

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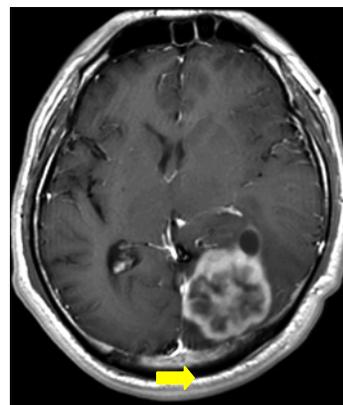
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tropical and subtropical climates, but recently emerged as a pathogen in the Pacific Northwest. Symptoms due to *C. gattii* infection can appear 2 to 13 months after exposure to the fungus, so defining an individual's exposure is challenging; risk factors appear to involve activities causing soil disturbance.

An outbreak of both human and animal cryptococcosis cases due to *C. gattii* was initially identified in 1999 in British Columbia (BC), Canada. Subsequently cases have been identified in Washington and Oregon. Since 2006, 21 human cases have been reported in Washington, including four deaths. Cases in Washington occur mainly but not exclusively near Puget Sound. Throughout the region case reports appear to be increasing over time, which may reflect both increasing disease incidence and increased awareness by diagnosticians. Additionally, a diverse range of animal species has been affected including 38 animal cases in Washington among dogs, cats, porpoises, an elk, a horse, a sheep, and a bird. Other animals such as goats and alpaca have been affected elsewhere.



Cerebral cryptococcoma
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Various reviews of cryptococcosis cases found cerebral and meningeal involvement, major neurologic sequelae or death, need for neurosurgical intervention such as ventricular shunting, and clinical resistance to therapy requiring longer antifungal treatment duration were all more frequent with *C. gattii* as compared with needed *C. neoformans* infections. Duration of treatment to reduce the size of brain cryptococcomas could be up to three times longer.

In parallel, studies suggested a reduced susceptibility of *C. gattii* isolates as compared with *C. neoformans* isolates to multiple antifungal medications, including amphotericin B and fluconazole. This is of particular concern for healthcare providers because these medications are first-line therapies for meningeal and non-meningeal cryptococcosis, respectively. The Centers for Disease Control and Prevention (CDC) have performed limited evaluation of antifungal resistance among *C. gattii* isolates and preliminary analysis shows minimum inhibitory concentrations to antifungal medications differ even amongst *C. gattii* subtypes [personal correspondence].

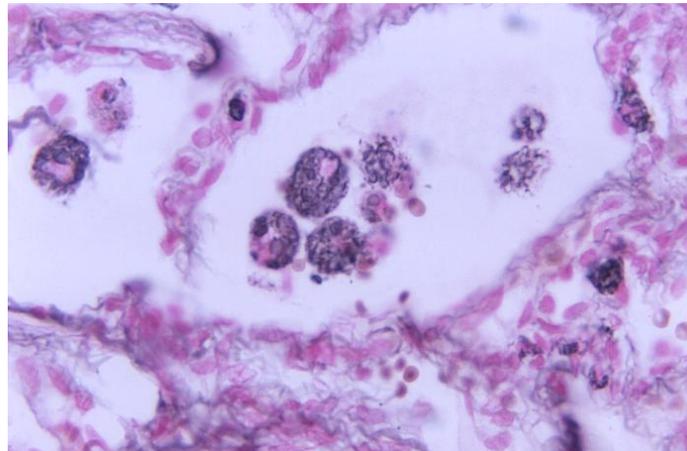
Based on these differences between *C. neoformans* and *C. gattii* infections, species identification at the time of diagnosis and treatment may provide guidance for clinical care and may affect expectations for both the treating physician and patient. The Infectious Diseases Society of America provides a brief treatment guideline specific to *C. gattii* (Pages 296-7, bullets 82-86): http://www.idsociety.org/uploadedFiles/IDSA/Guidelines-Patient_Care/PDF_Library/Cryptococcal.pdf

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Cryptococcal infection of the lung (CDC)

Laboratory Testing for *Cryptococcus*

Automated clinical laboratory systems such as Microscan and Vitek do not have the capability to distinguish *C. gattii* from *C. neoformans*. Both species are reported by these systems as *C. neoformans*, so results from automated systems should not be considered as confirming species. Cryptococcal isolates should be submitted to a reference laboratory with the capability to distinguish species using canavanine-glycine-bromothymol blue (CGB) agar, a chromogenic culture medium.

The Washington State Department of Health (WA DOH) is working with CDC as well as other public health agencies in the Pacific Northwest to conduct surveillance for *C. gattii*. The goals of surveillance are to better describe the epidemiology of this emerging infection and ultimately to identify disease prevention strategies for the public. To support this effort, the notifiable conditions reporting requirements in the Washington State Administrative Code (WAC) were revised in February 2011 to require specifically that laboratories must submit all *Cryptococcus* isolates not identified as *C. neoformans* to the Washington State Public Health Laboratories (PHL). This includes isolates identified as *C. neoformans* only through automated systems. Isolates received at WA PHL are sent to CDC for species confirmation and molecular subtyping by multi-locus sequence typing (MLST).

Accumulating evidence suggests that *C. gattii* exhibits important differences in presentation, clinical course, and response to treatment when compared to *C. neoformans*. WA DOH and CDC strongly urge clinical laboratories to obtain species identification of isolates identified as *Cryptococcus* as that information may be important for the medical care of the patient, particularly duration of treatment. Furthermore, we encourage clinicians and laboratorians to consider the possibility that a cryptococcal infection is due to *C. gattii*, particularly when the patient is HIV-negative, and request appropriate testing for that organism.