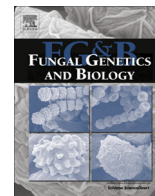




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journal homepage: www.elsevier.com/locate/yfgbiEpidemiology of *Cryptococcus* and cryptococcosis in ChinaWei Fang^a, Zhenzong Fa^b, Wanqing Liao^{a,b,*}^a Department of Dermatology and Venereology, Changzheng Hospital, Shanghai, China^b Shanghai Key Laboratory of Molecular Medical Mycology, Changzheng Hospital, Shanghai, China

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ABSTRACT

Cryptococcosis is a significant invasive fungal infection with noteworthy morbidity and mortality, primarily caused by *Cryptococcus neoformans* and *Cryptococcus gattii*. In China, *C. neoformans* var. *grubii* (especially molecular type VNI) is the most common variety in the environment and responsible for the majority of cryptococcal infections. *C. gattii* infections are quite rare in China and the primary molecular type is VGI, which is closely related to *C. gattii* isolates in Australia. Interestingly, the majority of cryptococcosis in China were reported in the HIV-uninfected patients (especially immunocompetent hosts). This unique phenomenon may be attributed to multiple polymorphisms in the genes encoding mannose-binding lectin (MBL) and Fc-gamma receptor 2B (*FCGR2B*) in the Han population, the major ethnic group in China. Compared to immunocompromised patients, immunocompetent patients with cryptococcal meningitis often presented with more intense inflammatory responses and more severe neurological complications, but less fungal burdens and disseminated infection. The overall prognosis, which is independently associated with amphotericin B-based initial therapy, is similar between immunocompetent and immunocompromised patients. In addition, intrathecal administration of amphotericin B has been proved to be an effective adjunctive treatment for cryptococcosis in China.

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1. Introduction

Cryptococcus is an important fungal pathogen causing life-threatening meningitis of significant morbidity and mortality. Among the 70 identified species of *Cryptococcus*, *Cryptococcus neoformans* and *Cryptococcus gattii* are the major causative agents of human cryptococcosis (Kurtzman et al., 2010). While *C. neoformans* is a major fungal pathogen causing infections in immunocompromised individuals such as AIDS patients, *C. gattii* has long been considered as the culprit causing cryptococcosis in immunocompetent hosts, recently highlighted in the outbreaks in Canada (British Columbia) and the United States Pacific Northwest (Datta et al., 2009; Galanis et al., 2010; Heitman et al., 2010; Sorrell, 2001). These two species are genetically related to each other, however, they vary in ecological niches, geographic distribution, and pathogenic characteristics. *C. neoformans* has a global distribution and is closely associated with avian habitats, while most *C. gattii* strains have been isolated from North America and Australia, and are commonly identified in Eucalyptus trees in the environment (Ellis and

Pfeiffer, 1990). In addition, *C. gattii* infections often cause more frequent neurological complications than *C. neoformans*. It seems *C. gattii* is less sensitive to antifungal therapy than *C. neoformans*, therefore, more aggressive interventions are usually required in the treatment of *C. gattii* infections (Newton et al., 2002; Perfect et al., 2010; Speed and Dunt, 1995).

China is the third largest and the most populous (over 1.3 billion people) country in the world. The majority of people in China reside in the temperate and subtropical regions, a climate amenable for fungal growth and spread. In fact, the increasing number of immunocompromised population including patients with HIV infection, malignant tumors, organ or stem-cell transplantation, and autoimmune diseases during the past several decades in China has led to a rapid elevation of the incidence of invasive fungal infections such as cryptococcosis, which become a serious threat to the public health (Trey et al., 2011; Wang and Wang, 2010; Wu et al., 2011a; Wu and Lu, 2008; Yang et al., 2010). Unfortunately, relatively little is known about the diversity and epidemiology of the pathogenic *Cryptococcus* species complex in China. In this article, the ecology, epidemiology, and population genetics of *C. neoformans* and *C. gattii* in China will be reviewed and compared with data from other countries. In addition, the unique clinical features and epidemiology of cryptococcosis in China, and the Chinese physicians' management experience on cryptococcosis will also be discussed in the present review.

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2. Geographic distribution and environmental niches of *C. neoformans* and *C. gattii* in China

Human cryptococcal infections are thought to be acquired by inhalation of airborne spores or desiccated yeast cells from the environment (Lin and Heitman, 2006). Therefore, investigation of the geographic distribution and environmental niches of *C. neoformans* and *C. gattii* allows us to better understand the potential impacts of these environmental pathogenic fungi on human health.

In China, ecological studies of *C. neoformans* and *C. gattii* were initiated relatively late, and most studies were focused on the identification of cryptococcal strains from avian excreta. In 1993, Li et al. isolated 51 *C. neoformans* isolates from 36 samples of pigeon droppings in Nanjing city, East China (Li et al., 1993). Among them, 40 (78%) and 11 (22%) isolates were identified as serotype A and serotype AD, respectively, based on slide agglutination assays. Interestingly, both *C. neoformans* serotype A and serotype AD isolates were concurrently isolated from some samples. In 2000, Li et al. isolated 32 *C. neoformans* serotype A isolates from 144 samples of pigeon droppings in private and public pigeon shelters in Shanghai, China (Li et al., 2000). In 2011, five *C. neoformans* serotype A strains were identified from 143 samples of fresh domestic pigeons droppings in Beijing (Wu and Li, 2011). In 2012, a total of 358 *C. neoformans* isolates were isolated from 620 samples of avian excreta in 10 major cities from 20° to 50° North latitude (Li et al., 2012). Mycological tests of 101 isolates showed that all of them were *C. neoformans* serotype A and mating type α , which was consistent with the geographic distribution of cryptococcosis in China. The isolation rate of *C. neoformans* in the G2 region (30–40°N) was the highest (50%), followed by the G3 region (20–30°N) (29%) and the G1 region (40–50°N) (13%). Unfortunately, the molecular types of these environmental isolates were not determined. Recently, Lin et al. isolated 80 cryptococcal strains from 1372 avian fecal samples collected from 15 provinces in mainland China (Lin et al., 2013). All the 80 strains were identified as *C. neoformans* molecular type VN1c based on PCR fingerprinting, which is consistent with the major molecular type of clinical isolates in China (Chen et al., 2008).

Taken together, avian habitats were an important natural reservoir for *C. neoformans* in China, and *C. neoformans* serotype A strains (96%) were the predominant species in this environment. In total, 283 cryptococcal isolates were isolated from pigeon droppings in 16 provinces in mainland China (Fig. 1). The average isolation rate was 12.9%, which is significantly lower than that in other countries (Castanon-Olivares and Lopez-Martinez, 1994; Romeo et al., 2012). The significant difference of isolation rates of cryptococcal isolates between China and other countries may be attributed to differences in the isolation methods, sample quality, and some environmental factors. In addition, the geographic distribution of *C. neoformans* is associated with the longitude and climate. The southeastern region (tropical and subtropical regions with warm and wet climate) appears to be more appropriate for fungal growth and propagation compared with other regions in China. However, the ecological data from West China is currently not available, which highlights ecological and epidemiological studies in this area in the future.

Unlike *C. neoformans* that is mainly associated with pigeons droppings, *C. gattii* strains are mostly isolated from trees and decayed wood. For example, *C. gattii* strains, especially strains of the molecular type VGI, were closely associated with Eucalyptus trees in Australia and elsewhere (Chakrabarti et al., 1997; Ellis and Pfeiffer, 1990; Montenegro and Paula, 2000; Sorrell, 2001). *Eucalyptus camaldulensis* trees were imported from Australia to China and widely distributed between 17°N and 33°N, including Jiangxi, Guangdong, Guangxi, and Zhejiang provinces. Currently, there is only one report on *C. gattii* ecology in China. Li et al. collected 819 samples of flower, bud, leaf, decayed wood, and bark from 40 *E. camaldulensis* trees in the Jiangxi province, China (Li et al., 2012). However, no *C. gattii* strains were isolated from these tree samples, which may be due to the physiological adaptation of *E. camaldulensis* to the changes of climate or ecological environment. Molecular identification methods, which are more sensitive than culture-dependent approaches, may be useful in ecological studies of *C. gattii* in China. In addition, identification and characterization of other ecological niches of *C. gattii* should also be

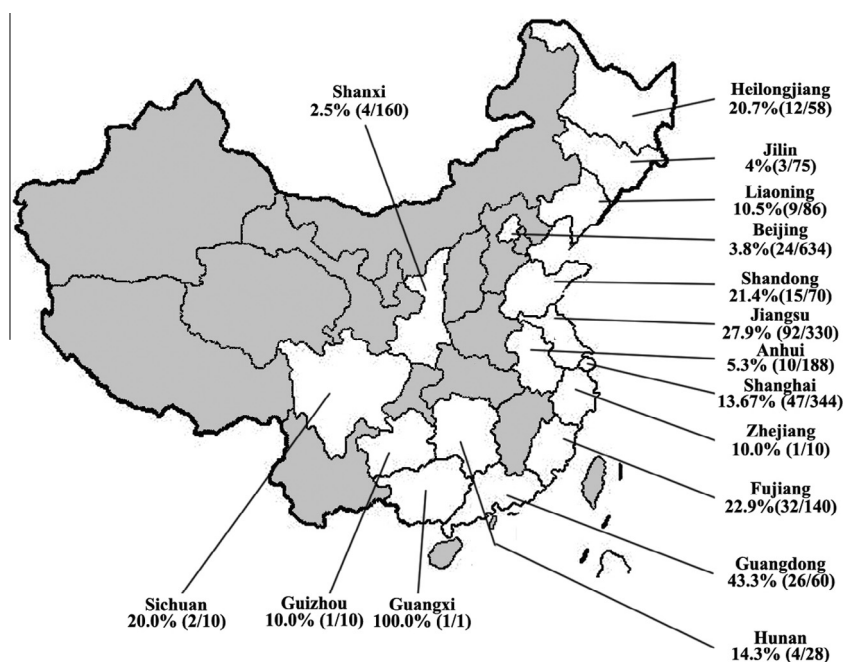


Fig. 1. Summary of ecological studies on *C. neoformans* conducted in mainland China between 1993 and 2013. A total of 283 cryptococcal strains were isolated from 2194 avian fecal samples from 16 provinces in China (Li et al., 1993, 2012; Li et al., 2000; Lin et al., 2013; Wu et al., 2011b). The positive rate of isolation was variable in different regions, which was relatively higher in Southeast regions. The shadowed areas represented those provinces where no ecological data about *C. neoformans* were available.

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