

Non-*neoformans* Cryptococcal Infections: a Systematic Review

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Abstract

Non-*neoformans* cryptococci have been generally regarded as saprophytes and rarely reported as human pathogens. However, the incidence of infection due to these organisms has increased over the past 40 years, with *Cryptococcus laurentii* and *Cryptococcus albidus*, together, responsible for 80% of reported cases. Conditions associated with impaired cell-mediated immunity are important risks for non-*neoformans* cryptococcal infections and prior azole prophylaxis has been associated with antifungal resistance. The presence of invasive devices was a significant risk factor for *Cryptococcus laurentii* infection (adjusted OR = 8.7; 95% CI = 1.48–82.9; $p = 0.003$), while predictors for mortality included age ≥ 45 years (aOR = 8.4; 95% CI = 1.18–78.82; $p = 0.004$) and meningeal presentation (aOR = 7.0; 95% CI = 1.85–60.5; $p = 0.04$). Because clinical manifestations of non-*neoformans* cryptococcal infections are most often indistinguishable from *Cryptococcus neoformans*, a high index of suspicion remains important to facilitate early diagnosis and prompt treatment for such infections.

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Introduction

Cryptococcal infections are serious and life-threatening, with presentations most often caused by *Cryptococcus neoformans* in immunocompromised hosts [1]. Other cryptococcal species have traditionally been considered non-pathogenic; however, there has been an incremental rise in non-*neoformans* cryptococcal infections over the past four decades [2–5]. This increase may reflect enhanced awareness of such infections, improved laboratory detection of non-*neoformans* species in the *Cryptococcus* genus and a rise in the number of at-risk patients. We conducted a systematic review of the literature to characterize the epidemiology, risk factors, pathogenesis, clinical manifestations and treatment of non-*neoformans* cryptococcal infection in humans.

Methods

A comprehensive search was performed for cases reported in the English literature using the Pubmed databases from inception through April 2006. Search terms included “fungus”, “infection”, “*Cryptococcus*”, “non-*neoformans*”, “*adeliensis*”, “*albidus*”, “*curvatus*”, “*humicolus*”, “*laurentii*”, “*luteolus*”, “*macerans*” and “*uniguttulatus*”. References in each manuscript were reviewed to identify additional cases of non-*neoformans* cryptococcal infection. Thirty-eight articles were identified, reporting a total of 44 human cases of non-*neoformans* cryptococcal infection.

Statistical Analysis

Categorical variables were compared using Chi-square or Fisher’s exact test, as appropriate. Continuous variables were compared using the Mann-Whitney U Test. Multivariate analysis was used to adjust for confounders of risk factors and mortality. All tests were two-tailed, with p value < 0.05 considered significant.

Epidemiology

Non-*neoformans* species have generally been identified from various environmental sources and are widely distributed geographically, inclusive of the Caribbean, Antarctic and the Himalaya regions (Table 1). Some non-*neoformans* species, such as *Cryptococcus laurentii* and *Cryptococcus uniguttulatus*, had been reported to colonize humans [3, 6].

The prevalence of cryptococcal infection, in particular *C. neoformans* infection, increased during the acquired immune deficiency syndrome (AIDS) pandemic. After the first report of *Cryptococcus luteolus* in a child with measles [7], more sporadic non-*neoformans* cases were reported.

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Table 1
Epidemiological features of *Cryptococcus neoformans* and non-*neoformans* cryptococci.

Cryptococcal species	Environmental sources	Geographic distribution	Prevalence rate
<i>C. neoformans</i>	Soil, pigeon nests, excreta of pigeons, canaries, milk and cockatoos (var. <i>neoformans</i>)	Worldwide (var. <i>neoformans</i>)	2.9–13.3% (HIV-infected individuals)
	<i>Eucalyptus camaldulensis</i> and related eucalyptus species, koalas and opossums (var. <i>gattii</i>)	Tropics and subtropical regions (var. <i>gattii</i>)	0.001% (non-HIV-infected individuals)
Non- <i>neoformans</i> cryptococci	Air, water, wood, soil, pigeon excreta food: cheese, fruits, pork products, beans, and wine	Worldwide including the Caribbean, Antarctica, and the Himalayas	NA ^a

^a 20 reported cases (*C. laurentii*), 18 reported cases (*C. albidus*), 1 reported case (*C. adeliensis*), 1 reported case (*C. curvatus*), 1 reported case (*C. humicolus*), 1 reported case (*C. luteolus*), 1 reported case (*C. macerans*), 1 reported case (*C. uniguttulatus*); NA: not available

However, the overall prevalence of non-*neoformans* cryptococcal infection, in comparison to *C. neoformans*, remains relatively low.

Pathogenesis

Cryptococcus laurentii Complex

C. laurentii has been reported to have a high degree of intraspecies heterogeneity and has been divided into phylogenetic groups I and II [8]. The physiologic and biochemical characteristics of the various species in the complex are very similar. However, the species in phylogenetic group I, such as *Cryptococcus flavescens* and *Cryptococcus aureus*, can be distinguished from phylogenetic group II, by their combination of assimilation patterns of D-glucosamine, N-acetyl-D-glucosamine, DL-lactic acid, 1,2-propanediol and sodium nitrite and vitamin requirements [8].

Transmission, Virulence Factors and Host Immune Response

There is general agreement that most cryptococcal infections are acquired by inhalation of infectious propagules. Notably, two cases of healthcare-associated infections have been reported with transmission either from direct inhalation of airborne yeast in close geographic proximity or through respiratory care procedures with contaminated instruments by medical personnel [9, 10]. In addition, one case of mother-to-child transmission of *C. neoformans* has been reported [11]. The virulence factors of *Cryptococcus* spp. have been ascribed to capsule formation against phagocytosis, the expression of the laccase enzyme, and production of melanin [12–14]. The presence of the polysaccharide capsule in non-*neoformans* cryptococci shares common features with that of *C. neoformans* [3]. The process of melanin deposition observed in non-*neoformans* cryptococci is responsible for the alteration in cell wall integrity, immune evasion and decreased susceptibility

to antifungal therapy [14]. However, the level of laccase activity expressed in these non-*neoformans* cryptococci is lower than that seen in *C. neoformans* [3, 14]. Once the yeast enters the human host, macrophages are responsible for phagocytosis and the production of proinflammatory cytokines for recruitment of inflammatory cells [13, 15]. T-cell lymphocytes, especially Th-1 subtypes, then produce cytokines to activate fungicidal activity of macrophages and the transformation of alveolar macrophages into giant cells from which the ingestion of large encapsulated yeast cells occur as part of granuloma formation [13, 15].

Risk Factors

The likelihood of *neoformans* cryptococcal infection rises dramatically in individuals with impaired cell-mediated immunity, inclusive of lymphoproliferative disorders, advanced HIV infection (CD4 counts < 100 cells/ μ l) and hematologic malignancies [13, 16, 17]. Other recognized risk factors include use of steroid or chemotherapeutic agents, organ transplantation [13], impaired humoral immunity such as hyper-IgM syndrome [18–20], non-HIV lymphopenia [21], and direct or indirect exposures to pigeon excreta [22, 23]. The majority (48%) of non-*neoformans* cryptococcal cases had impaired cell-mediated immunity (i.e., neutropenia, hematologic malignancy, steroid or immunosuppressive drug use, or organ transplantation) while 16% had comorbid HIV infection with a mean CD4 count < 100 cells/ μ l.

From our analysis, the presence of invasive devices (aOR = 8.7; 95% CI = 1.48–82.9; $p = 0.003$) was a significant risk factor associated with *C. laurentii* infection. Clinical presentations for patients with *C. laurentii* and *C. albidus* were similar (Table 2), yet patients with *C. laurentii* infection were younger ($p = 0.01$) and more likely to survive ($p = 0.01$).

Table 2
Patient characteristics, underlying diseases, risk factors, clinical manifestations, treatment and outcome of *C. laurentii* and *C. albidus*, infections.

Characteristics	<i>C. laurentii</i> (n = 20)	<i>C. albidus</i> (n = 18)	p value
Age, mean years \pm SD	30 \pm 19	46 \pm 21	0.01
Male sex	12 (60)	12 (67)	NS
Underlying diseases			
Hematologic malignancy	3 (15)	5 (28)	NS
HIV diseases	3 (15)	3 (17)	NS
Solid tumor	3 (15)	1 (5)	NS
Other ^a	9 (45)	8 (44)	NS
Risk factors			
Invasive devices ^b	11 (55)	0 (0)	0.003
Prior steroid exposure	4 (20)	3 (17)	NS
Prior immunosuppressant exposure	0 (0)	4 (23)	NS
Prior azole or amphotericin B exposure	4 (20)	1 (5)	NS
CD4 count < 100 cells/ μ l	2 (10)	2 (11)	NS
Exposure to pigeon excreta	1 (5)	1 (5)	NS
Non-medication-associated neutropenia ^c	3 (15)	0 (0)	NS
Clinical manifestations			
Blood stream infection	11 (55)	6 (33)	NS
Neurological ^d	4 (20)	6 (33)	NS
Pulmonary ^e	1 (5)	2 (11)	NS
Ophthalmologic ^f	2 (10)	2 (11)	NS
Cutaneous infection	2 (10)	2 (11)	NS
Peritonitis	2 (10)	0 (0)	NS
Treatment			
Amphotericin B \pm flucytosine	9 (45)	7 (39)	NS
Fluconazole	6 (30)	3 (17)	NS
Ketoconazole	1 (5)	1 (5)	NS
Non-antifungal treatment ^g	1 (5)	5 (28)	NS
Outcome			
Died	0 (0)	5 (28)	0.01

Data are no. (%) of patients, unless otherwise indicated. Categorical variables were compared using Chi-square or Fisher exact test, as appropriate. Continuous variables were compared using the Mann-Whitney U test. All p values were two-tailed; $p < 0.05$ was considered statistically significant; NS: non-significance; ^a Includes juvenile rheumatoid arthritis, alcoholic liver disease, chronic kidney disease, diabetes mellitus, prematurity, dermatomyositis, X-linked hyper IgM syndrome and chronic renal allograft dysfunction; ^b Includes insertion of central venous catheter, peripheral intravenous central catheter, urinary catheter, peritoneal dialysis catheter and intraventricular drain; ^c Neutropenia caused by hematologic malignancy itself, unrelated to immunosuppressive agents; ^d Includes meningitis; ^e Includes pneumonia, lung abscess and empyema thoracis; ^f Includes keratitis, scleral ulcer and endophthalmitis; ^g Includes catheter removal + peritoneal irrigation with normal saline solution, infected cornea removal and no treatment

Clinical Manifestations

Non-*neoformans* cryptococci has been reported to cause infection in many organ systems (Table 2). The bloodstream (17/44; 39%) and central nervous system (CNS) (14/44; 32%) were the most common sites of non-*neoformans* cryptococcal infection. The CNS manifestations were more commonly recognized in HIV-infected hosts (4/7; 57%) than in hosts without HIV infection (10/37; 27%) ($p = 0.05$).

Bloodstream Infection

Seventeen patients with non-*neoformans* cryptococemia presented with either fever, hypothermia or septic shock [2, 4, 5, 9, 24–35]. Risk factors included the presence of an invasive device (9/17; 53%), neutropenia (7/17; 41%) and AIDS (3/17; 18%). The latex agglutination test was performed in four cases (24%); only one (1/4; 25%) had a positive cryptococcal antigen titer (titer of 1:40). The reduced sensitivity of antigen testing (25% in non-*neoformans* vs. 99% in *C. neoformans*) may be related to the antigenic differences among the species, a lower organism burden in non-*neoformans* cryptococemia, or limitations of the assay [3, 24, 36].

Central Nervous System Infection

Among the 14 patients with CNS infection [2, 3, 5, 22, 37–43], meningeal signs were reported for 50% of the cases. Clinical presentations were protean and included fever, headache, nausea, vomiting, paresthesia, gait disturbance, flaccid or spastic paralysis and altered mental status. The organisms were isolated from cerebrospinal fluid (CSF) in all cases and CSF findings were similar to those reported for *neoformans* infections.

Pulmonary Infection

With the exception for one case that had acute respiratory distress syndrome (ARDS) [30], most cases manifested as chronic, indolent illnesses [9, 25, 44–46]. The type and extent of pulmonary involvement included pneumonia, lung abscess and empyema [9, 26, 44–46]. The diagnoses were confirmed by positive culture results from different sources including bronchial swab or biopsy, sputum, or fluid from abscess and pleural space. Chest radiograph findings included localized opacities, disseminated nodular infiltration mimicking miliary patterns, cavity lesions, hilar node enlargement, pleural fluid and diffuse bilateral opacification with or without a pattern similar to that seen in ARDS. Notable, the investigators of one report suggested that *C. albidus* may be an etiologic agent of summer-type hypersensitivity pneumonitis [47].

Other Body Site Infections

Non-*neoformans* cryptococci can infect other organ systems such as skin, eyes, the gastrointestinal (GI) tract and lymph nodes [25]. Skin infections included cutaneous nodules, erythematous patches and plaque [23, 27, 30, 48, 49].

Ocular manifestations included deteriorating vision, painless scleral ulcer and corneal infiltrates [50–53]. Two patients receiving chronic ambulatory peritoneal dialysis had peritonitis [25, 54, 55].

Treatment

The choices and duration of treatment for non-*neoformans* cryptococci infections depend on the anatomical sites of involvement, the host-immune status and the severity of infection. Recommendations regarding the treatment for non-*neoformans* cryptococcal infections are limited to date due to the small number of empirically treated cases and lack of controlled trial data.

Cryptococcus laurentii

Amphotericin B alone was used for treatment of fungemia, meningitis, lung abscess, cutaneous infection and peritonitis with 100% cure in nine cases. The mean induction period was 14 days followed by fluconazole treatment for meningitis [5]. In patients with fungemia, the mean duration of treatment was 25 days (ranged 14–33 days) [31–35], while it was longer for lung abscess (42 days) [46] and peritonitis (60 days) [54]. In one patient with peritonitis, successful treatment was restricted to removal of the peritoneal catheter followed by peritoneal irrigation with saline solution [55]. In one patient with fungemia, a 14-day course of amphotericin B plus flucytosine was successful [4]. Fluconazole was successfully used in six patients with fungemia (mean duration 17 days) [4, 35], meningitis (mean duration 36 days) [18, 42] and endophthalmitis (150 days) [52].

Cryptococcus albidus

Amphotericin B alone was used in pneumonia, empyema, meningitis and fungemia cases with 86% treatment success (6/7 cases). The mean duration of treatment for meningitis was 60 days [22], with 17 days (ranged 14–20 days) for fungemia [28, 29] and 90 days for empyema [47]. One patient developed leukopenia and anemia as side effects of conventional amphotericin B (1 mg/kg/day) and therapy was switched to itraconazole [52]. A non-pharmacological intervention involving removal of infected tissue was used successfully in a patient with keratitis after corneal transplantation. Fluconazole was used successfully in all patients with cutaneous infections with a 56-day mean treatment period [48].

Overall, spontaneous recovery of non-*neoformans* cryptococcal infection may occur in less severe cases with non-CNS infections. In these cases, non-pharmacologic treatments, such as catheter or infected-tissue removal, were successful alone or in combination with antifungal agents [51, 54, 55]. Amphotericin B, at the similar dose and duration recommended for *C. neoformans* infection, [56] seemed effective for non-*neoformans* cryptococcal infection. Fluconazole has been used as initial therapy in selected patients with non-CNS infection. However, longer

duration of treatment, drug susceptibility, and the host-immune status are factors to consider for optimal CNS treatment. Newer azoles, such as voriconazole and posaconazole has been shown to be active against *C. neoformans* in in-vitro studies [57–60], although their clinical efficacy has not been well studied in clinical trials. Echinocandins, such as caspofungin, micafungin and anidulafungin have demonstrated potent antifungal activity toward a variety of fungi but not *Cryptococcus* spp. [61–63].

Predictors of Mortality

Characteristics of patients with non-*neoformans* cryptococcal infection, stratified by survival, are compared in table 3. However, the attributable mortality could not be determined due to limited clinical data for each report. Predictors for overall mortality included age ≥ 45 years (adjusted OR = 8.4; 95% CI = 1.18–78.82; $p = 0.004$) and CNS infection (aOR = 7.0; 95% CI = 1.85–60.5; $p = 0.04$).

Drug Resistance

Host comorbidities, drug intolerance, poor drug compliance and pharmacokinetic issues can each contribute to anti-cryptococcal drug resistance. For most *C. neoformans* clinical isolates, primary drug resistance to the standard antifungal agents, such as the polyenes and azoles, was uncommon while drug resistance to flucytosine has been increasingly observed [64]. The widespread use of azoles in immunocompromised hosts has contributed to the apparent azole resistance [64]. For non-*neoformans* cryptococci, antifungal susceptibility testing has been reported for 16/44 (36%) cases, 15 (94%) of whom had clinical isolates susceptible to amphotericin B. The exception was a case with *C. laurentii* who had two subsequent episodes of *C. neoformans* meningitis followed by *C. laurentii* meningoencephalitis. Prior exposure to amphotericin B for the treatment of *C. neoformans* meningitis may have contributed to the emergence of amphotericin B-resistant *C. laurentii* [42].

Table 3
Factors associated with overall mortality among patients with non-*neoformans* cryptococcal infection.

Characteristics	Non-survival (n = 6)	Survival (n = 37)	P value
Age, mean years \pm SD	55 \pm 19	33 \pm 21	0.004
Male sex	2 (33)	24 (65)	NS
Underlying diseases and risk factors			
Hematologic malignancy	3 (50)	6 (17)	NS
HIV diseases	1 (17)	6 (17)	NS
Solid tumor	1 (17)	4 (11)	NS
Invasive devices ^a	0 (0)	10 (27)	NS
Prior immunosuppressant or steroid exposure	3 (50)	9 (24)	NS
Organ infections			
Blood stream	2 (33)	14 (38)	NS
Meningitis	4 (67)	8 (22)	0.04
CSF findings ^b			
CSF glucose < 50% of blood glucose	1 (50)	1 (20)	NS
Protein > 45 g/dl	2 (100)	3 (60)	NS
WBC > 100 cells/ μ l	1 (50)	3 (60)	NS
Positive Indian Ink smear	1 (50)	2 (40)	NS
Length of hospital stay, mean days \pm SD	39 \pm 35	36 \pm 29	NS
Fluconazole resistance	1 (17)	6 (16)	NS
Treatment			
Amphotericin B \pm flucytosine	4 (67)	20 (54)	NS
Fluconazole	0 (0)	10 (29)	NS
Non-treatment	2 (33)	3 (8)	NS

Data are no. (%) of patients, unless otherwise indicated. Categorical variables were compared using Chi-square or Fisher exact test, as appropriate. Continuous variables were compared using the Mann–Whitney U test. All p values were two-tailed; $p < 0.05$ was considered statistically significant; NS: non-significance; CSF: cerebrospinal fluid; WBC: white blood cell count; ^a Includes central venous catheter and urinary catheter; ^b Total number of patients with meningitis that had available lumbar puncture information was two in non-survival group and five in survival group

Table 4
Reports of failure of primary prophylaxis in patients with non-*neoformans* cryptococcal infections.

Species	Diagnosis	Underlying diseases	Prophylactic drug	Dose	Duration ^a	Reasons of failure	References
<i>C. adeliensis</i>	Meningitis	AML, lymphoma	Itraconazole	400 mg/day	NA	Reduced susceptibility to itraconazole	38
<i>C. albidus</i>	Fungemia	AML, status post APCT	Fluconazole	200 mg/day	NA	Resistance to fluconazole	29
<i>C. laurentii</i>	Fungemia	Leukemia post BMT	Ketoconazole	400 mg/day	22 days	Resistance to ketoconazole	9
<i>C. laurentii</i>	Fungemia	AML	Amphotericin B	1 mg/kg/day	14 days	NA	31
<i>C. laurentii</i>	Fungemia	Solid tumor	Ketoconazole	200 mg/day	4 days	Resistance to ketoconazole	31
<i>C. laurentii</i>	Fungemia	NHL	Itraconazole	1,200 mg/day	5 days	Resistance to ketoconazole	31

^a Duration of therapy before the onset of infections; AML: acute myelogenous leukemia; APCT: autologous progenitor cell transplantation; BMT: bone marrow transplantation; NA: not available; NHL: non-Hodgkin lymphoma

For non-*neoformans* cryptococci, primary resistance was most frequent for fluconazole and flucytosine [4, 32, 37–39, 46–39, 50]. Fluconazole resistance was more common in patients who previously received azole prophylaxis (83%) than azole-naïve patients (50%). Itraconazole, ketoconazole and voriconazole susceptibility testing was reported for only a few cases [2, 32, 34, 37, 38]. In a small subset of cases with available data, amphotericin B was active against non-*neoformans* cryptococci. Hence, in patients with prior azole exposure, fluconazole susceptibility testing seems prudent.

Prevention

Three general strategies have been recommended for prevention of *C. neoformans* infection: (1) avoidance of close contact with pathogen-rich environments, (2) improvement of host defenses, i.e., by using granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte colony-stimulating factor (G-CSF) or use of combination antiretroviral therapy in HIV-infected patients and (3) antifungal prophylaxis.

Antifungal Prophylaxis

Data relevant to antifungal prophylaxis for non-*neoformans* cryptococci is sparse. There are no guideline recommendations for non-*neoformans* cryptococcal prophylaxis in HIV-infected patients. Until additional data become available, we suggest that the prophylaxis of non-*neoformans* cryptococcal infections in HIV-infected persons be similar to that for *C. neoformans* infections.

For high-risk patients without HIV infection, precise recommendations for primary prophylaxis of non-*neoformans* cryptococcal infections are non-existent. In this systematic review, six patients who received primary prophylaxis for fungal infections developed non-*neoformans* cryptococcal infections (Table 4). The reasons for failure were possibly due to drug intolerance, reduced suscepti-

bility or resistance to the prophylactic agents. Large comparative clinical trials would help characterize the “high risk” patients most likely to benefit from anti-cryptococcal prophylaxis.

Conclusion

With the increase in immunocompromised patients worldwide and the widespread use of immunosuppressive agents, non-*neoformans* cryptococci have been increasingly recognized as human pathogens. Epidemiological studies suggest that non-*neoformans* cryptococci have a diverse geographic distribution and that persons with impaired cell-mediated immunity or invasive devices are predisposed to these infections. Infection can involve many organ systems with clinical manifestations similar to *C. neoformans* infection. Amphotericin B remains the mainstay of the treatment and azole agents are reasonable alternatives for patients with less severe, non-disseminated infection. Drug susceptibility testing should guide treatment. Patients with advanced age and meningitis may have higher risk for mortality and should be promptly diagnosed and treated. Avoidance of organism-rich environments, improvement of host defenses and antifungal prophylaxis may help prevent non-*neoformans* cryptococcal disease.

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