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GIARDIA/CRYPTO (S SINGER, SECTION EDITOR)

Central Nervous System Cryptococcosis due to *Cryptococcus gattii* in the Tropics

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Abstract

Purpose of Review Cryptococcosis of the central nervous system due to *Cryptococcus gattii* species complex is a serious mycosis with worldwide distribution but of great importance in the tropics. This article aims to review the progress made in these regions in the knowledge of this disease and its etiological agent.

Recent Findings They can be summarized in the presence in apparently immunocompetent patients of autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF), which is a hidden risk factor for acquiring *C. gattii* infection; this finding strengthens the concept that *C. gattii* is an opportunistic pathogen. A greater knowledge of the clinical and molecular epidemiology of *C. gattii* infection and of the different environmental niches of this fungus in the tropics. The discovery of a new lineage of *C. gattii*, VGV, in environmental samples from Africa. Until now, the COVID-19 pandemic has not meant an increase in cryptococcosis cases.

Summary Advances have been made in the identification of risk factors for cryptococcosis due to *C. gattii* as well as in the knowledge of its etiological agent and its relationship with the environment. Remarkably, there have been no significant achievements in diagnosis and treatment notwithstanding the documented importance.

Keywords *Cryptococcus gattii* species complex · Cryptococcosis · Meningitis · Encephalitis · Cryptococcoma · AIDS

Introduction

Cryptococcosis is a systemic mycosis caused by two fungal species complexes *Cryptococcus neoformans* and *Cryptococcus gattii*, belonging to the *Basidiomycota* phylum. They are easily distinguishable from other pathogenic yeasts due to the presence of a polysaccharide capsule, which constitutes one of their main studied virulence factors. The most serious and frequent clinical form of presentation is meningoencephalitic and is preceded by the inhalation of infective propagules that inhabit the environment, reach the lungs, and subsequently spread to the central nervous system (CNS) [1].

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History

In 1894, Sanfelice isolated *C. neoformans* from peach juice for the first time, and in the same year, Busse and Buschke described the first case of cryptococcosis in a woman with a bone lesion. For decades, pathogenic isolates of *Cryptococcus* were treated as a single species: *C. neoformans*; however, the heterogeneity between the isolates led in the 1960s to the recognition of four serotypes (A, B, C, and D) based on polysaccharide epitopes of the capsule. The discovery of two different teleomorphs, *Filobasidiella neoformans* (anamorph: *C. neoformans*) and *Filobasidiella bacillospora* (anamorph: C. *gattii*) confirmed the species split, which has been subsequently verified by genome studies [1]. In 2002, isolates with serotypes B and C were classified as *C. gattii* and serotypes A, AD, and D as *C. neoformans* [2].

The first case of cryptococcosis due to *C. gattii* was described in 1970 in an African child with leukemia who developed meningitis [3, 4]; however, already at the end of the nineteenth century, Curtis described an isolate from a lumbar tumor mass of a young man. The isolate was recovered in cultures and inoculated in animals where the

subcutaneous lesion reproduced (Fig. 1). Curtis named it *Saccharomyces subcutaneous tumefaciens* that was later identified as *C. gattii* [5, 6].

In this century, analysis of the two species using molecular typing methods such as simple restriction fragment length polymorphism (RFLP) analysis to DNA and PCR fingerprinting, amplified fragment length polymorphism (AFLP), multilocus microsatellite typing (MLMT), multilocus sequence typing (MLST), and whole-genome sequence typing (WGST) has shown that both species *C. neoformans* and *C. gattii* contain genetically different lineages, leading to consider them as two species complexes. These in turn have been subdivided into numerous molecular types. Until now, four main lineages have been recognized for *C. gattii* called VGI/AFLP4, VGII/AFLP6, VGIII/AFLP5, and VGIV/AFLP7 [7]. Recently, a new lineage, VGV, has been identified in environmental isolates in Zambia, Africa [8•]. Different names have been proposed for the 4 main lineages: *C. gattii* (VGI), *C. deuterogattii* (VGII), *C. bacillisporus* (VGIII), and *C. tetragattiii* (VGIV) [9]. This taxonomy is controversial because the known genotypes of *C. gattii* have revealed greater diversity than the 4 proposed species, which will lead to continued instability in the nomenclature. In the absence of biological differences between the clades and of consensus about which DNA sequence represents a species, a group of researchers has recommended continuing to use the term *C. gattii* species complex; this also applies to *C. neoformans* [10].

Epidemiology

Meningoencephalitic cryptococcosis is very frequently associated with advanced HIV infection, and an annual incidence of 223,000 cases and 180,000 deaths is estimated in this population, most of whom live in sub-Saharan Africa [11].

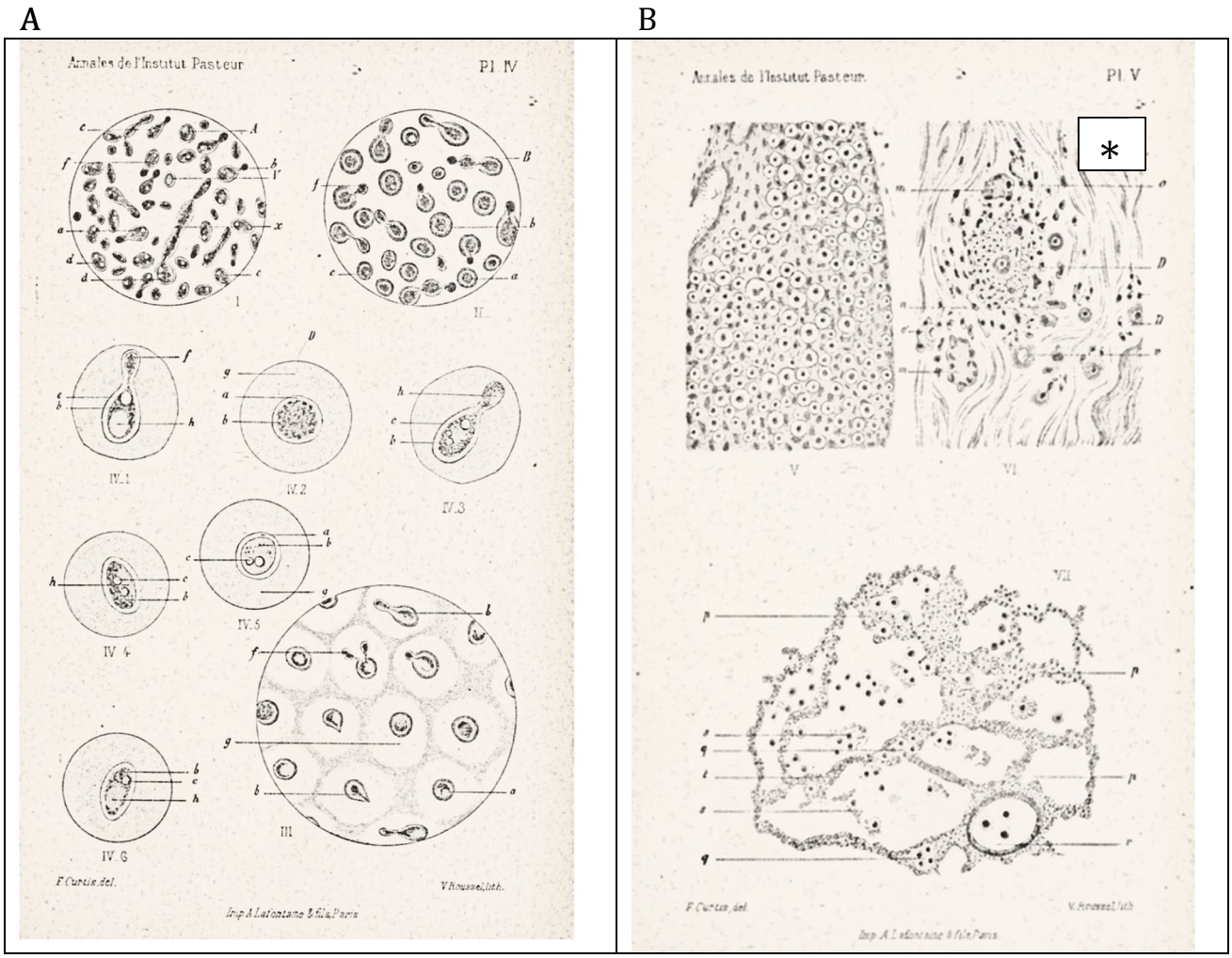

Fig. 1 Original drawings by Ferdinand Curtis describing *Saccharomyces subcutaneous tumefaciens*. **A** From culture in different media. **B** Histopathology from rats inoculated with the yeast and from the human case diagnosed (*). *Annales de l'Institut Pasteur* (1895) [5]

Globally, it is estimated that *C. neoformans* causes 95% of cases of cryptococcosis and *C. gattii* the remaining 5% [12]. For decades, it has been accepted that *C. neoformans* has a global distribution and that it especially affects immunosuppressed patients, the vast majority HIV infected and that *C. gattii* is distributed in tropical and subtropical areas and mainly affects individuals without HIV infection, with a significant percentage of apparently immunocompetent patients. In relation to *C. gattii*, this situation changed in 1999 with the appearance of the cryptococcosis outbreak in the Vancouver region, Canada, a temperate region, caused by the VGII lineage [13] and by the subsequent observation of cases of cryptococcosis due to *C. gattii* in the Pacific Northwest of the USA [14].

To date, it is known that the distribution of *C. gattii* is more global although minor compared to *C. neoformans*. Cases of *C. gattii* infections have been reported for all molecular lineages in a wide range of regions including Australia, Papua New Guinea, South America, Southeast Asia, Central and Southern Africa, the USA, and Canada. Sporadic cases have been described in Europe, most of them imported. However, there is evidence of the emergence of *C. gattii* in Europe in the last two decades, especially in Portugal, France, and Southern Italy [15].

C. neoformans, with a global distribution, causes disease in both immunocompetent and immunosuppressed hosts; however, most reported cases show compromise of the immune system, mainly due to infection by HIV but also due to the use of corticosteroids or other conditions that produce immunosuppression. For this reason, *C. neoformans* is known as an opportunistic pathogen, although there are countries such as China, Korea, and Japan where most of the *C. neoformans*-infected patients are not infected by HIV [1]. Until a few years ago, studies showed that *C. gattii* more frequently affected individuals without known risk factors, regardless of geographic region and was therefore considered a primary pathogen [1]. Significantly, HIV-infected patients rarely present cryptococcosis due to *C. gattii*, except for lineages VGIII and VGIV, a situation well known in Africa [16]. Infection of apparently immunocompetent individuals with *C. gattii* was thought to be the result of increased environmental exposure to the fungus and was based on the high prevalence of *C. gattii* infection in rural Aboriginal Australians, where they are daily exposed to the natural reservoir of this fungus, such as eucalyptus and other trees, organic debris, and other soil components. This concept began to change when it was shown that patients from British Columbia, Canada, in addition to their environmental exposure, had medical conditions that caused immunosuppression such as steroid use, chronic obstructive pulmonary disease and other noninfectious lung pathologies, and pneumonia [17]. Despite the high exposure to *C. gattii* in endemic regions such as South America, Southeast Asia and Vancouver, Canada, the number of cases of cryptococcosis is very low, and in a tropical country such as Colombia, the annual incidence is less than one case per million [18].

This has led to the belief that certain risk factors must exist in these individuals, which allow the appearance of the disease. New evidence has been obtained in recent years, and it has been detected that a significant percentage of apparently healthy patients have autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF) [19, 20••]. This factor is essential for the differentiation of monocytes into macrophages and in modulating the immune response [21]. Other subtle defects in immunity are likely to be risk factors for *C. gattii* cryptococcosis in apparently healthy individuals. In short, it is time to consider *C. gattii* as an opportunistic pathogen [21].

Regarding the clinical manifestations, the high percentage of patients in Papua New Guinea with meningitis due to *C. gattii* who lost their vision initially drew attention [22], a fact that we can attribute to the lack of aggressive management of intracranial hypertension, which is very common in these patients [23]. The first clinical studies from Australia and New Zealand on cryptococcosis due to *C. gattii* showed, in addition to the state of apparent immunocompetence, the higher frequency of pulmonary and cerebral cryptococcomas, lower mortality but greater neurological sequelae that required surgery, and prolonged therapy [24–26].

The appearance of the COVID-19 pandemic has generated an increase in the diagnosis of some systemic mycoses such as aspergillosis and mucormycosis [27]; the latter has occurred with an unusually high frequency in India [28]. The occurrence of these mycoses has been favored by different factors or comorbidities associated with COVID-19, such as hypoxemia, diabetes mellitus, steroid use, increased ferritin and free serum iron levels, mechanical ventilation, and CD4 lymphopenia (total cells, CD4+ and CD8+). However, only a handful of cases of cryptococcosis associated with COVID-19 have been described (two of them in the tropics), and no *C. gattii* infection has been reported [27].

Progress has been made in the knowledge of the molecular epidemiology of the etiological agents of cryptococcosis in Latin America [29, 30]. In this region, *C. neoformans* molecular-type VNI is the main cause of this mycosis (76%), followed by *C. gattii* molecular-type VGII. Africa, the continent with the highest number of cases of cryptococcosis in the world has the lowest proportion of isolates subjected to molecular typing [31]. Table 1 shows the distribution of molecular types of *C. gattii* isolates in Latin America and Africa. In India, *C. neoformans* VNI also predominates, and the representation of *C. gattii* is scarce (1,4% of the isolates) and with the molecular patterns VGI and VGIV [32].

A recent publication [33] of the study of strains obtained before 1975 showed that the HIV pandemic altered both the molecular epidemiology and the virulence of *C.*

Table 1 Distribution of the major molecular types of *Cryptococcus gattii* species complexes isolates reported from Latin America and Africa

Region	Source	VGI	VGII	VGIII	VGIV	Total
		n	*n*	*n*	*n*	*n*
Latin America [30]	Clinical	60	492	93	10	655
	Environmental	34	350	90	11	485
	Veterinary	1	14	1	-	16
	Total	**95**	**856**	**184**	**21**	**1156**
Africa [31]	Clinical	17	11	-	55	83
	Environmental*	12	-	-	-	12
	Veterinary	-	-	-	1	1
	Total	**29**	**11**	**-**	**56**	**96**

*Six environmental isolates of the molecular type VGV from Zambia, Africa

neoformans/C. gattii species complexes. Before the pandemic, VNI predominated to a lesser extent (64%) and VGIII (7.5%). Overall, high genetic variability and recombination rates were found for the pre-HIV-pandemic era among strains of the *C. neoformans/C. gattii* species complexes.

Ecology

The natural habitat of *C. gattii* is trees. Since the end of the last century, the association of serotype B molecular pattern VGII with eucalyptus (*Eucalyptus camaldulensis*) in Australia [34] and serotype C molecular pattern VGIII with almond trees (*Terminalia catappa*) in Colombia [35] was established. Since then, an increasing number of trees have been identified as environmental reservoirs of *C. gattii*, many of these studies have been carried out in Latin America [29, 30] and in Africa [31]. Extensive environmental sampling in Zambia, Africa, allowed to recognize a new lineage of *C. gattii*, the molecular pattern VGV [8•].

The study of household dust in the Rio Negro microregion in the Brazilian Amazon suggests that humans may be exposed to the agents of cryptococcosis (*C. neoformans* VNI and *C. gattii* VGII) and that this continuous exposure could lead to the development of clinical or subclinical infections [36, 37].

Genomic analyzes have pointed to the origin of *C. gattii* VGII in the South American Amazon rainforest [38, 39] while the origin of *C. neoformans* is in Africa [40, 41]. It is presumed that these two species separated about 80–100 million years ago [41]. The study of environmental isolates of *C. gattii* and its relationship with the different regions of the world has been recently reviewed [42].

It has been postulated that global warming in recent years has significantly affected the distribution of *C. gattii* VGI in the European Mediterranean basin. Niche modeling using Maxent analysis showed a gradual expansion of the fundamental niche that has been more noticeable since 2010. This model predicts that the distribution of this pathogen will increase its distribution area towards more internal areas of the continent [43].

Diagnosis and Treatment

The diagnosis of meningeal cryptococcosis is made by identifying the fungus in the cerebrospinal fluid on direct examination using India ink exclusion, by determining the capsular antigen by lateral flow test, by detecting nucleic acid by PCR, and by cultivation in media for fungi and even in basic bacteriology media such as blood agar. Once the isolation is obtained, the differentiation of *C. gattii* from *C. neoformans* is easily done with the use of the canavanine glycine bromothymol blue (CGB) agar, a medium in which *C. gattii* grows, but *C. neoformans* not. Molecular methods allow a more precise identification indicating molecular lineages [44]. Also, proteomics with the MALDI-TOF-MS test allows differentiating species in a fast, sensitive, and less expensive way than molecular tests [45].

The treatment of meningeal cryptococcosis in patients with HIV, where the vast majority are caused by *C. neoformans*, has been established through controlled studies carried out in Africa, a continent where thousands of cases of this disease occur, which makes possible the conducting of these studies [46, 47]. In contrast, the treatment of *C. gattii* meningitis is based on extrapolation from studies of AIDS patients [48] and on retrospective case series studies [49] (Table 2) or expert recommendations [50]. Basically, the treatment of CNS cryptococcosis is based on 3 antifungals: amphotericin B, 5-fluorocytosine, and fluconazole. In many tropical countries, fluorocytosine or amphotericin B is not available, which makes treatment difficult. In addition, amphotericin deoxycholate is used, which is more toxic and difficult to handle, due to its lower cost than liposomal presentations. Prospective studies are needed to determine the best antifungal treatment for CNS cryptococcosis due to *C. gattii*. Cerebral cryptococomas, which are more frequent in patients with *C. gattii*, require longer therapies [48].

Table 2 Antifungal treatment recommendations for CNS cryptococcosis due to *Cryptococcus gattii* [49]

Regimen	Time
Induction therapy	
AMB plus 5 FC	6 weeks
Consolidation/maintenance therapy	
Fluconazole	6–12 months

Abbreviations: AMB, amphotericin; 5-FC, 5-flucytosine

Aggressive management of intracranial hypertension, which occurs in most patients, is necessary to improve patient survival. The recommendation of repeated lumbar punctures and in refractory cases of cerebrospinal fluid diversion also comes from observational studies [49]. In summary, no new advances have been made in the antifungal treatment of *C. gattii* CNS cryptococcosis. Recently, neurocritical and neurosurgical management of *C. gattii* cryptococcosis has been emphasized due to frequent intracranial hypertension [51]. These patients do not present the classic radiological signs of increased intracranial pressure such as ventriculomegaly, cerebral edema, or effacement of the basal cisterns. Therefore, the diagnosis is based on symptoms such as disabling headache, progressive vision loss, and papilledema and is confirmed by measuring the opening of the cerebrospinal fluid during lumbar puncture. The intraparenchymal deposition of the abundant capsular polysaccharide causes poor brain compliance, which leads to the so-called frozen brain state. If we want to reduce mortality and improve clinical outcomes, early diagnosis, antifungal therapy, and aggressive management of intracranial hypertension are necessary [51]. The benefit of steroids in these patients remains to be demonstrated. Traditionally, cryptococcosis management guidelines did not consider it necessary to establish the species of *Cryptococcus* in clinical practice [48, 52, 53]. The most recent guidelines recommend doing this speciation in the clinical laboratory due to the differences in the morphology, biology, and phylogenetics of the two species [54, 55]. Mortality and sequelae of CNS cryptococcosis due to *C. gattii* remain high (20.2%) [56]. The limitations in the diagnosis and treatment of this serious mycosis in many tropical countries mean that the poor outcomes are perpetuated.

However, there is renewed interest in the development of new antifungal drugs whose targets are essential genes or cellular functions, the blocking of virulence factors or the inhibition of the stress-response signaling, the use of drug combinations, and the development of therapeutics immunomodulatory and vaccines [57•]. We hope that in the near future the fruit of these investigations will be beneficial for patients affected by cryptococcosis.

Conclusion

Progress has been made in the knowledge of *C. gattii* and in the epidemiological and ecological aspects of cryptococcosis. Unfortunately, no significant progress has been made in the management of patients with CNS cryptococcosis, a situation that is more evident in the tropics.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Kwon-Chung KJ, Fraser JA, Doering TL, Wang Z, Janbon G, Idnurm A, Bahn YS. *Cryptococcus neoformans* and *Cryptococcus gattii,* the etiologic agents of cryptococcosis. Cold Spring Harb Perspect Med. 2014;4(7):a019760. https://doi.org/10.1101/cshperspect.a019760.
2. Kwon-Chung KJ, Boekhout T, Fell JW, Diaz M. (1557) Proposal to conserve the name *Cryptococcus gattii* against *C. hondrianus* and *C. bacillisporus* (Basidiomycota, Hymenomycetes, Tremellomycetidae). Taxon. 2002;51:804–6.
3. Gatti F, Eeckels R. An atypical strain of *Cryptococcus neoformans* (San Felice) Vuillemin 1894. I. Description of the disease and of the strain. Ann Soc Belges Med Trop Parasitol Mycol. 1970;50(6):689–93.
4. Vanbreuseghem R, Takashio M. An atypical strain of *Cryptococcus neoformans* (San Felice) Vuillemin 1894. II. *Cryptococcus neoformans* var. *gattii* var. nov. Ann Soc Belges Med Trop Parasitol Mycol. 1970;50(6):695–702.
5. Curtis F. Contribution a l'etude de la saccharomycosen humaine [Contribution to the study of human saccharomycosis]. Ann Inst Pasteur. 1896;10:449–68.
6. Barnett JA. A history of research on yeasts 14: medical yeasts part 2, *Cryptococcus neoformans*. Yeast. 2010;27(11):875–904. https://doi.org/10.1002/yea.1786.
7. Meyer W. *Cryptococcus gattii* in the age of whole-genome sequencing. mBio. 2015;6(6):e01761–15. https://doi.org/10.1128/mBio.01761-15.
8. • Farrer RA, Chang M, Davis MJ, van Dorp L, Yang DH, Shea T, et al. A new lineage of *Cryptococcus gattii* (VGV) discovered in the Central Zambezian Miombo Woodlands. mBio. 2019;10(6):e02306–19. https://doi.org/10.1128/mBio.02306-19. **The discovery of a new molecular pattern of *C. gattii* in Africa.**
9. Hagen F, Khayhan K, Theelen B, Kolecka A, Polacheck I, Sionov E, et al. Recognition of seven species in the *Cryptococcus gattii*/*Cryptococcus neoformans* species complex. Fungal

Genet Biol. 2015;78:16–48. https://doi.org/10.1016/j.fgb.2015.02.009.
10. Kwon-Chung KJ, Bennett JE, Wickes BL, Meyer W, Cuomo CA, Wollenburg KR, et al. The case for adopting the "species complex" nomenclature for the etiologic agents of cryptococcosis. mSphere. 2017;2(1):e00357–16. https://doi.org/10.1128/mSphere.00357-16.
11. Rajasingham R, Smith RM, Park BJ, Jarvis JN, Govender NP, Chiller TM, et al. Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. Lancet Infect Dis. 2017;17(8):873–81. https://doi.org/10.1016/S1473-3099(17)30243-8.
12. Stott KE, Loyse A, Jarvis JN, Alufandika M, Harrison TS, Mwandumba HC, et al. Cryptococcal meningoencephalitis: time for action. Lancet Infect Dis. 2021;21(9):e259–71. https://doi.org/10.1016/S1473-3099(20)30771-4.
13. 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):251–7. https://doi.org/10.3201/eid1602.090900.
14. Datta K, Bartlett KH, Baer R, Byrnes E, Galanis E, Heitman J, et al. & *Cryptococcus gattii* working group of the Pacific Northwest. Spread of *Cryptococcus gattii* into Pacific Northwest region of the United States. Emerg Infect Dis. 2009;15(8):1185–91. https://doi.org/10.3201/eid1508.081384.
15. Paccoud O, Bougnoux ME, Desnos-Ollivier M, Varet B, Lortholary O, Lanternier F. *Cryptococcus gattii* in patients with lymphoid neoplasms: an illustration of evolutive host-fungus interactions. J Fungi (Basel). 2021;7(3):212. https://doi.org/10.3390/jof7030212.
16. Montoya MC, Magwene PM, Perfect JR. Associations between *Cryptococcus* genotypes, phenotypes, and clinical parameters of human disease: a review. J Fungi (Basel). 2021;7(4):260. https://doi.org/10.3390/jof7040260.
17. MacDougall L, Fyfe M, Romney M, Starr M, Galanis E. Risk factors for *Cryptococcus gattii* infection, British Columbia, Canada. Emerg Infect Dis. 2011;17(2):193–9. https://doi.org/10.3201/eid1702.101020.
18. Lizarazo J, Escandón P, Agudelo CI, Firacative C, Meyer W, Castañeda E. Retrospective study of the epidemiology and clinical manifestations of *Cryptococcus gattii* infections in Colombia from 1997-2011. PLoS Negl Trop Dis. 2014;8(11):e3272. https://doi.org/10.1371/journal.pntd.0003272.
19. Saijo T, Chen J, Chen SC, Rosen LB, Yi J, Sorrell TC, et al. Anti-granulocyte-macrophage colony-stimulating factor autoantibodies are a risk factor for central nervous system infection by *Cryptococcus gattii* in otherwise immunocompetent patients. mBio. 2014;5(2):e00912–4. https://doi.org/10.1128/mBio.00912-14.
20.•• Yang DH, England MR, Salvator H, Anjum S, Park YD, Marr KA, et al. *Cryptococcus gattii* species complex as an opportunistic pathogen: underlying medical conditions associated with the infection. mBio. 2021;12(5):e0270821. https://doi.org/10.1128/mBio.02708-21. **The authors demonstrated the presence of Anti-granulocyte-macrophage colony-stimulating factor autoantibodies (GM-CSF) in the majority of a group of apparently immunocompetent *C. gattii* cryptococcosis patients.**
21. Kwon-Chung KJ, Saijo T. Is *Cryptococcus gattii* a primary pathogen? J Fungi (Basel). 2015;1(2):154–67. https://doi.org/10.3390/jof1020154.
22. Lalloo D, Fisher D, Naraqi S, Laurenson I, Temu P, Sinha A, et al. Cryptococcal meningitis (*C. neoformans* var. *gattii*) leading to blindness in previously healthy Melanesian adults in Papua New Guinea. Q J Med. 1994;87(6):343–9.
23. McCabe GA, McHugh JW, Goodwin T, Johnson DF, Fok A, Campbell TG. Ophthalmic manifestations of *Cryptococcus gattii* species complex: a case series and review of the literature. Int J Ophthalmol. 2022;15(1):119–27. https://doi.org/10.18240/ijo.2022.01.18.
24. Mitchell DH, Sorrell TC, Allworth AM, Heath CH, McGregor AR, Papanaoum K, et al. Cryptococcal disease of the CNS in immunocompetent hosts: influence of cryptococcal variety on clinical manifestations and outcome. Clin Infect Dis. 1995;20(3):611–6. https://doi.org/10.1093/clinids/20.3.611.
25. Speed B, Dunt D. Clinical and host differences between infections with the two varieties of *Cryptococcus neoformans*. Clin Infect Dis. 1995;21(1):28–34. https://doi.org/10.1093/clinids/21.1.28.
26. Chen S, Sorrell T, Nimmo G, Speed B, Currie B, Ellis D, et al. Epidemiology and host- and variety-dependent characteristics of infection due to *Cryptococcus neoformans* in Australia and New Zealand. Australasian Cryptococcal Study Group. Clin Infect Dis. 2000;31(2):499–508. https://doi.org/10.1086/313992.
27. Amin A, Vartanian A, Poladian N, Voloshko A, Yegiazaryan A, Al-Kassir AL, et al. Root causes of fungal coinfections in COVID-19 infected patients. Infect Dis Rep. 2021;13(4):1018–35. https://doi.org/10.3390/idr13040093.
28. Sen M, Honavar SG, Bansal R, Sengupta S, Rao R, Kim U, et al. members of the Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC) Study Group. Epidemiology, clinical profile, management, and outcome of COVID-19-associated rhino-orbital-cerebral mucormycosis in 2826 patients in India - Collaborative OPAI-IJO Study on Mucormycosis in COVID-19 (COSMIC), Report 1. Indian J Ophthalmol. 2021;69(7):1670–92. https://doi.org/10.4103/ijo.IJO_1565_21.
29. Firacative C, Lizarazo J, Illnait-Zaragozí MT, Castañeda E. Latin American Cryptococcal Study Group. The status of cryptococcosis in Latin America. Mem Inst Oswaldo Cruz. 2018;113(7):e170554. https://doi.org/10.1590/0074-02760170554.
30. Firacative C, Meyer W, Castañeda E. *Cryptococcus neoformans* and *Cryptococcus gattii* species complexes in Latin America: a map of molecular types, genotypic diversity, and antifungal susceptibility as reported by the latin american cryptococcal study group. J Fungi (Basel). 2021;7(4):282. https://doi.org/10.3390/jof7040282.
31. Edwards HM, Cogliati M, Kwenda G, Fisher MC. The need for environmental surveillance to understand the ecology, epidemiology, and impact of *Cryptococcus* infection in Africa. FEMS Microbiol Ecol. 2021;97(7):fiab093. https://doi.org/10.1093/femsec/fiab093.
32. Xess I, Pandey M, Dabas Y, Agarwal R, Das S, Srivastava PMV, et al. Multilocus Sequence Typing of Clinical Isolates of *Cryptococcus* from India. Mycopathologia. 2021;186(2):199–211. https://doi.org/10.1007/s11046-020-00500-6.
33. Pharkjaksu S, Kwon-Chung KJ, Bennett JE, Ngamskulrungroj P. Population diversity and virulence characteristics of *Cryptococcus neoformans*/*C. gattii* species complexes isolated during the pre-HIV-pandemic era. PLoS Negl Trop Dis. 2020;14(10):e0008651. https://doi.org/10.1371/journal.pntd.0008651.
34. Ellis DH, Pfeiffer TJ. Natural habitat of *Cryptococcus neoformans* var. *gattii*. J Clin Microbiol. 1990;28(7):1642–4. https://doi.org/10.1128/jcm.28.7.1642-1644.1990.
35. Callejas A, Ordoñez N, Rodriguez MC, Castañeda E. First isolation of *Cryptococcus neoformans* var. *gattii*, serotype C, from the environment in Colombia. Med Mycol. 1998;36(5):341–4.
36. Brito-Santos F, Barbosa GG, Trilles L, Nishikawa MM, Wanke B, Meyer W, et al. Environmental isolation of *Cryptococcus gattii* VGII

from indoor dust from typical wooden houses in the deep Amazonas of the Rio Negro basin. PLoS One. 2015;10(2):e0115866. https://doi.org/10.1371/journal.pone.0115866.
37. Brito-Santos F, Trilles L, Firacative C, Wanke B, Carvalho-Costa FA, Nishikawa MM, et al. Indoor dust as a source of virulent strains of the agents of cryptococcosis in the rio negro microregion of the Brazilian amazon. microorganisms. 2020;8(5):682. https://doi.org/10.3390/microorganisms8050682.
38. Hagen F, Ceresini PC, Polacheck I, Ma H, van Nieuwerburgh F, Gabaldón T, et al. Ancient dispersal of the human fungal pathogen *Cryptococcus gattii* from the Amazon rainforest. PLoS One. 2013;8(8):e71148. https://doi.org/10.1371/journal.pone.0071148.
39. Souto AC, Bonfietti LX, Ferreira-Paim K, Trilles L, Martins M, Ribeiro-Alves M, et al. Population genetic analysis reveals a high genetic diversity in the Brazilian *Cryptococcus gattii* vgii population and shifts the global origin from the Amazon rainforest to the semi-arid desert in the northeast of Brazil. PLoS Negl Trop Dis. 2016;10(8):e0004885. https://doi.org/10.1371/journal.pntd.0004885.
40. 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. https://doi.org/10.1371/journal.pone.0019688.
41. Casadevall A, Freij JB, Hann-Soden C, Taylor J. Continental drift and speciation of the *Cryptococcus neoformans* and *Cryptococcus gattii* species complexes. mSphere. 2017;2(2):e00103–17. https://doi.org/10.1128/mSphere.00103-17.
42. Acheson ES, Galanis E, Bartlett K, Mak S, Klinkenberg B. searching for clues for eighteen years: deciphering the ecological determinants of *Cryptococcus gattii* on Vancouver Island, British Columbia. Med Mycol. 2018;56(2):129–44. https://doi.org/10.1093/mmy/myx037.
43. Cogliati M. Global warming impact on the expansion of fundamental niche of *Cryptococcus gattii* VGI in Europe. Environ Microbiol Rep. 2021;13(3):375–83. https://doi.org/10.1111/1758-2229.12945.
44. Chen SC, Meyer W, Sorrell TC. *Cryptococcus gattii* infections. Clin Microbiol Rev. 2014;27(4):980–1024. https://doi.org/10.1128/CMR.00126-13.
45. Bernhard M, Worasilchai N, Kangogo M, Bii C, Trzaska WJ, Weig M, et al. CryptoType - public datasets for MALDI-TOF-MS based differentiation of *Cryptococcus neoformans/gattii* complexes. Front Cell Infect Microbiol. 2021;11:634382. https://doi.org/10.3389/fcimb.2021.634382.
46. Day JN, Chau TTH, Wolbers M, Mai PP, Dung NT, Mai NH, et al. Combination antifungal therapy for cryptococcal meningitis. N Engl J Med. 2013;368(14):1291–302. https://doi.org/10.1056/NEJMoa1110404.
47. Molloy SF, Kanyama C, Heyderman RS, Loyse A, Kouanfack C, Chanda D, et al. ACTA Trial Study Team. Antifungal combinations for treatment of cryptococcal meningitis in Africa. N Engl J Med. 2018;378(11):1004–17. https://doi.org/10.1056/NEJMoa1710922.
48. Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ. 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. https://doi.org/10.1086/649858.
49. Chen SC, Korman TM, Slavin MA, Marriott D, Byth K, Bak N, 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):543–51. https://doi.org/10.1093/cid/cit341.
50. Franco-Paredes C, Womack T, Bohlmeyer T, Sellers B, Hays A, Patel K, et al. Management of *Cryptococcus gattii* meningoencephalitis. Lancet Infect Dis. 2015;15(3):348–55. https://doi.org/10.1016/S1473-3099(14)70945-4.
51. Akins PT, Jian B. The frozen brain state of *Cryptococcus gattii*: a globe-trotting, tropical, neurotropic fungus. Neurocrit Care. 2019;30(2):272–9. https://doi.org/10.1007/s12028-018-0538-4.
52. WHO. Guidelines for the diagnosis, prevention and management of cryptococcal disease in HIV-infected adults, adolescents and children. March, 2018. http://www.who.int/hiv/pub/guidelines/cryptococcal-disease/en/ (accessed January 20, 2021).
53. Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019;20(1):1030. https://doi.org/10.4102/sajhivmed.v20i1.1030.
54. Baddley JW, Forrest GN. AST infectious diseases community of practice. Cryptococcosis in solid organ transplantation-Guidelines from the American Society of Transplantation Infectious Diseases Community of Practice. Clin Transpl. 2019;33(9):e13543. https://doi.org/10.1111/ctr.13543.
55. Chang CC, Hall V, Cooper C, Grigoriadis G, Beardsley J, Sorrell TC, and the Australasian Antifungal Guidelines Steering Committee, et al. Consensus guidelines for the diagnosis and management of cryptococcosis and rare yeast infections in the haematology/oncology setting, 2021. Intern Med J. 2021;51(Suppl 7):118–42. https://doi.org/10.1111/imj.15590.
56. Baddley JW, Chen SC, Huisingh C, Benedict K, DeBess EE, Galanis E, et al. MSG07: An International Cohort Study Comparing Epidemiology and Outcomes of Patients with *Cryptococcus neoformans* or *Cryptococcus gattii* Infections. Clin Infect Dis. 2021;73(7):1133–41. https://doi.org/10.1093/cid/ciab268.
57.• Iyer KR, Revie NM, Fu C, Robbins N, Cowen LE. Treatment strategies for cryptococcal infection: challenges, advances and future outlook. Nat Rev Microbiol. 2021;19(7):454–66. https://doi.org/10.1038/s41579-021-00511-0. **Excellent article about the treatment of cryptococcosis and potential therapeutic strategies.**

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