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Letter to the Editor

Antifungal cerebrospinal levels and susceptibility profile in cryptococcal meningitis in the context of intracranial hypertension

Dear Editor,

Cryptococcus (C.) gattii is a fungal pathogen of humans and animals that can affect immunocompromised and immunocompetent hosts[1]. Cryptococcosis is known to occur upon inhalation of airborne infectious propagules, such as spores or dried yeast cells, which allows the pathogen to settle in the lungs, where it can survive and proliferate within alveolar macrophages[2,3]. If the pathogen reaches the central nervous system, it can lead to meningoencephalitis, the most severe form of cryptococcosis, which is always lethal if not treated rapidly. These manifestations might lead to excessive neurological morbidity due to the associated intracranial hypertension. We describe a patient with cryptococcal meningitis caused by *C. gattii* and highlight the importance of antifungal levels and sensitivity profiles for appropriate management in the setting of intracranial hypertension.

A 65-year-old HIV-negative patient presented to the emergency department with a 4-week history of headache, vomiting and weight loss. Previous underlying diseases included systemic arterial hypertension and hypothyroidism. A lumbar puncture (LP) was performed with an opening pressure of 325 mm H_2O. The LP revealed the following: yeast cells (India ink stain), glucose (36 mg/dL), protein (63 mg/dL), cryptococcal antigen titer (1:1000) by CrAg lateral flow assay (Immuno-Mycologics, OK, USA), and 140 leukocytes/μL (90% polymorphonucleocytes). The cerebrospinal fluid culture grew *Cryptococcus gattii* molecular type VGII (20,000 UFC/mL) based on phenotypic canavanine-glycine-bromothymol blue medium and genotypic characterization as previously described[4]. The patient was treated with intravenous amphotericin B deoxycholate (1.0 mg/kg) and fluconazole (800 mg/day) on the same day. Despite routine daily lumbar punctures, the patient continued to experience intracranial hypertension (IH) (Table I). The microdilution minimum inhibitory concentration (MIC) determination of *C. gattii* was 1.0 μg/mL for amphotericin B deoxycholate, 4.0 μg/mL for fluconazole and 0.03 μg/mL for voriconazole (VRC). The checkerboard assay demonstrated synergism between amphotericin B deoxycholate and fluconazole and between amphotericin B deoxycholate and voriconazole. These antifungal combinations were used in the antifungal treatment. This test was performed according to the protocol described by Saiman in 20075.

Opening and closing intracranial pressures from days 1 to 14 of antifungal therapy are shown in Table I. Amphotericin B deoxycholate and fluconazole CSF levels were measured by HPLC as previously described[6,7]. As shown in Figure 1, despite high intracranial pressure, the concentrations of fluconazole and voriconazole exceeded the MIC of *C. gattii*. As expected, based on previous publications, amphotericin B deoxycholate concentrations in the CSF were low (<0.05 μg/mL) after administration of intravenous amphotericin B[8]. Amphotericin B shows limited penetration into the CSF, and little is known about the factors affecting its efficacy in central nervous tissue. CSF cultures grew *C. gattii* after 14 days of incubation. Due to the lack of response, therapy with fluconazole was replaced by intravenous voriconazole (200 mg every 12 hours) in combination with amphotericin B deoxycholate.

During the course of therapy with voriconazole, the patient's intracranial pressure was generally lower than it had been during the induction phase. Despite voriconazole CSF levels above

Corresponding Author: Luciano Zubaran Goldani, MD; email: lgoldani@ufrgs.br

Table I. Opening and closing intracranial pressures from days 1 to 14 of antifungal therapy.

Day	Opening pressure (mm H_2O)	Closure pressure (mm H_2O)
1	325	125
3	450	190
4	525	200
5	350	175
6	270	170
7	260	160
10	360	240
11	180	110
14	320	80

the MIC, the CSF cultures were positive for *C. gattii* on day 5 after the beginning of voriconazole therapy. The CSF culture was positive, and after 15 days of voriconazole and amphotericin B therapy, the VRC was suspended, and fluconazole was reinstated. High intracranial pressure persisted despite multiple daily lumbar drainages. The patient died of persistent intracranial pressure and multiple organ failure.

The *C. gattii* mortality rate is still high, ranging from 18.2 to 50% in early studies of *C. gattii* meningitis[9]. Elevated intracranial pressure is another significant and predictive factor for morbidity and mortality in patients with HIV-associated cryptococcal meningitis. Previous data suggest that dose modifications of antifungal agents, including amphotericin B and fluconazole, are not necessary for patients with cryptococcal meningitis, including *C. gattii* infection, and intracranial hypertension[10]. However, information on the correlation between amphotericin B and CSF concentration and efficacy in the treatment of CNS fungal infections is still limited[11]. High fungal burden appeared to be necessary but not sufficient for the development of high pressure[12]. Despite appropriate antifungal therapy, including fluconazole and amphotericin B, adequate CSF levels, and CSF sterilization, intracranial hypertension persisted, resulting in a fatal outcome in our patient. It is well known that intracranial hypertension may persist after CSF sterilization. In this context, aggressive management of elevated opening pressure through repeated CSF drainage is required to prevent any adverse impact of elevated opening pressure on outcome in patients with cryptococcal meningitis[13].

This study contributes to the understanding of the pharmacokinetics of antifungal agents and clinical management in cryptococcal meningoencephalitis in the context of intracranial hypertension.

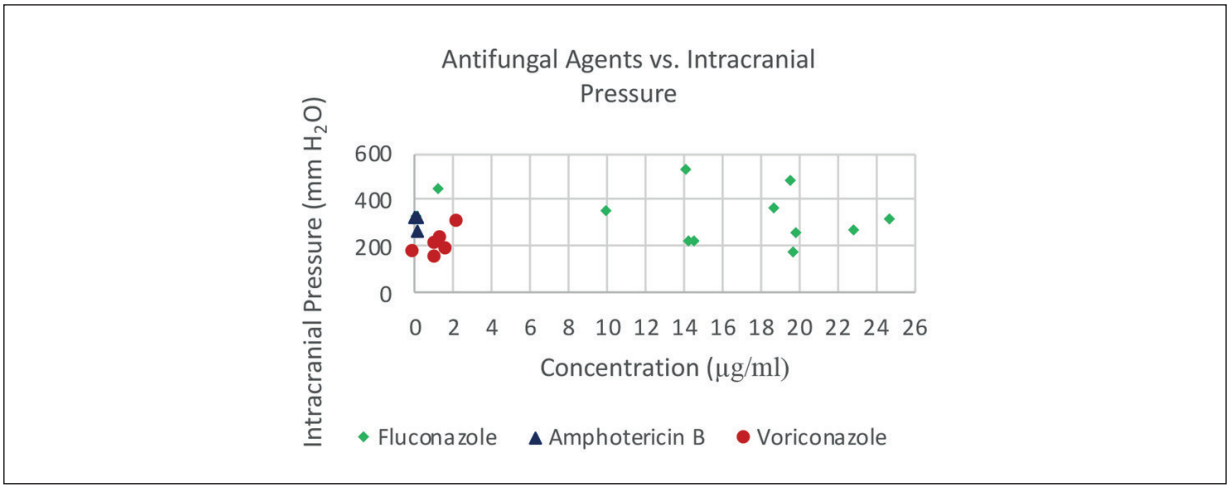

Figure 1. Amphotericin B deoxycholate levels from days 1 to 14 of therapy.

Conflict of Interest
The Authors declare that they have no conflict of interests.

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Authors' Contribution
PDR collected the clinical data and patient history. VA collected the clinical specimens and the clinical data. FW performed the chromatography analysis and helped with the drafting of the manuscript and all fungal culturing and analyses. LZG supervised the coordination and conception of the manuscript. All authors have read and approved the manuscript.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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F. Wirth, D. Príscila, P. Rosa, A. Valério, L.Z. Goldani

Infectious Diseases Section, Hospital de Clínicas de Porto Alegre,
Universidade Federal do Rio Grande do Sul, Brazil