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Case report

Therapeutic role of fluconazole in immunocompetent patients with pulmonary cryptococcosis: A case report

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ABSTRACT

The present investigation examines the potential for customized treatment of pulmonary cryptococcosis using fluconazole in an immunocompetent individual. Therapeutic drug monitoring (TDM) was utilized throughout treatment to assess fluconazole levels. Research indicated that the MIC_{90} for cryptococcus in China is around 8 mg/L. We evaluated the area under the curve (AUC) relative to the minimal inhibitory concentration (MIC), focusing on the AUC from 0 to 24 h (AUC0–24 h/MIC). Fluconazole's dosage was adjusted according to pharmacokinetics/pharmacodynamics (PK/PD) principles to enhance therapeutic efficacy. Post-treatment evaluation showed marked improvement in the patient's condition, with lesions exhibiting partial absorption.

Introduction

Cryptococcus, a conditionally pathogenic fungus, tends to infect those with compromised immune systems [1]. However, a concerning trend has emerged, with a rising number of cases reported among immunocompetent patients in recent years [2,3]. In October 2022, the World Health Organisation (WHO) placed Cryptococcus neoformans at the top of its list of fungal pathogens to focus on [4]. The clinical signs of pulmonary cryptococcosis (PC) are typically non-specific, presenting as fever, cough, dyspnea, chest pain, and abdominal discomfort, which can often lead to misdiagnosis as other respiratory infections like community-acquired pneumonia or tuberculosis; moreover, some individuals may remain asymptomatic [5]. Fluconazole, a triazole antifungal medication, effectively inhibits fungal sterol synthesis. It is commonly used for treating Candida and Cryptococcus infections and is prized for its strong antimicrobial efficacy, bioavailability, and low cost [6]. Despite its widespread use, there is a paucity of data on the pharmacokinetic/pharmacodynamic (PK/PD) target attainment for fluconazole in cryptococcosis treatment. This is primarily due to the difficulty of culturing Cryptococcus in vitro and obtaining its minimum inhibitory concentration (MIC) values [7]. Secondly, there are geographic and environmental epidemiologic differences in Cryptococcus, which may result in isolates from hospitals in different regions exhibiting varying degrees of pharmacologic sensitivity [8–10].

This article details a case involving the management approach for pulmonary cryptococcosis in an immunocompetent patient utilizing therapeutic drug monitoring (TDM) to optimize fluconazole and presents a review of the MIC_{90} values of the currently prevalent Cryptococcus in our country. We aim for an $AUC_{0-24\ h}$/MIC as its PK/PD sterilization target value and dynamically assessed compliance, contributing valuable information for individualized treatment strategies for pulmonary cryptococcosis [11].

Case information

The patient, a 56-year-old female weighing 74 kg, previously in good health, presented to the hospital with a 2-month history of cough and sputum production. The symptoms began two months prior after exposure to poultry, including chickens, ducks, and pigeons. The cough was characterized by white mucoid sputum, worsening nocturnally, and was associated with mild chest tightness, sore throat, and rhinorrhea. An outpatient chest CT revealed mild bilateral pulmonary inflammation, and laboratory tests showed an elevated C-reactive protein (CRP) level of 25.3 mg/L. The patient was treated with intravenous levofloxacin sodium chloride 0.5 g once daily for 10 days, resulting in normalization of CRP and inflammation markers upon follow-up. Subsequently, oral

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moxifloxacin 0.4 g once daily was initiated for continuation therapy. Despite initial improvement, two months later, the patient experienced a recurrence of cough and sputum production. A repeat chest CT demonstrated extensive deterioration in the right lung compared to the prior imaging (Fig. 1). Upon admission for further evaluation, the physical examination was unremarkable, as were laboratory analyses including complete blood count, urinalysis, stool examination, coagulation profile, biochemical tests, and tumor markers. The final diagnosis upon admission was community-acquired pneumonia, classified as non-severe.

Following admission, the patient underwent a series of diagnostic examinations. Tuberculosis-related assessments revealed the absence of acid-fast bacilli in smears, while the T-cell test for tuberculosis infection returned positive. Fungal investigations indicated negative results for the Aspergillus galactomannan antigen test on two separate occasions. Additionally, the analysis of bronchoalveolar lavage fluid (BALF) yielded negative findings for cryptococcal ink staining and smears, with both fungal cultures also returning negative results. Furthermore, metagenomic next-generation sequencing (mNGS) and real-time fluorescence PCR targeting BALF fluid did not identify any Cryptococcus sequences. However, the peripheral blood cryptococcal polysaccharide antigen test was positive. The patient's medical history revealed recent contact with poultry species, including chickens, ducks, and pigeons, approximately two months prior. Coupled with clinical manifestations such as cough and sputum production, these findings led to a suspicion of cryptococcal infection. Literature indicates that in immunocompetent individuals, 67 % of cases of pulmonary cryptococcal disease may progress to central nervous system involvement, resulting in cryptococcal meningitis [12]. Therefore, a lumbar puncture was performed, which showed normal cerebrospinal fluid biochemistry. Both the ink staining and cryptococcal podoplanin antigen test were negative, and cranial enhancement CT scans did not reveal any abnormalities, leading to a temporary exclusion of cryptococcal central nervous system dissemination.

Following the diagnosis of pulmonary cryptococcosis, the patient commenced intravenous antifungal therapy with fluconazole, starting with a loading dose of 800 mg, followed by 400 mg once daily for maintenance. For TDM purposes, concentrations measured 0.5 h before and 1 h after administration are designated as the trough concentration (C_{min}) and peak concentration (C_{max}), respectively. Additionally, the concentration measured 4 h post-administration ($C_{4\ h}$) is also recorded, considering that the infusion lasts for 0.5 hours. On the fifth day post-initiation of therapy, TDM revealed fluconazole serum concentrations of 16.50 mg/L (C_{min}), 27.40 mg/L (C_{max}), and 24.15 mg/L ($C_{4\ h}$). The patient exhibited persistent cough and sputum production, leading the clinical pharmacist to conclude that the PK/PD target had not been achieved, indicating the fluconazole dose was inadequate. As a result, the dose was increased to 800 mg daily on the fifth day.

After 12 days of therapy, podoconjugate antigen testing remained positive; however, the patient reported significant improvement in cough and sputum as well as other clinical symptoms. The patient was subsequently discharged to continue oral fluconazole at 800 mg daily. Outpatient follow-up TDM revealed fluconazole levels of 28.1 mg/L (C_{min}), 36.9 mg/L ($C_{4\ h}$), 42.6 mg/L (C_{max}), and 29.2 mg/L (C_{min}), 37.2 mg/L ($C_{4\ h}$), and 43.2 mg/L (C_{max}), on days 20 and 35 post-treatment, respectively (Table 1). Imaging on day 25 showed significant improvement compared to baseline imaging findings (Fig. 2).

Discussion

Cryptococcus is not a typical colonizer of the respiratory tract. In clinical settings across China, the detection of Cryptococcus polysaccharide antigen has emerged as a widely utilized immunological

Table 1
Dose of fluconazole, blood concentration, and PK/PD target levels.

Time (d)	Dosage (mg)	TDM (mg/L)			PK/PD ($AUC_{0-24\ h}$/MIC)
		C_{min}	C_{max}	4 h post-dose ($C_{4\ h}$)	
5	400	16.5	27.40	24.2	59.3
20	800	28.1	42.6	36.9	94.1
35	800	29.2	43.2	37.2	96.0

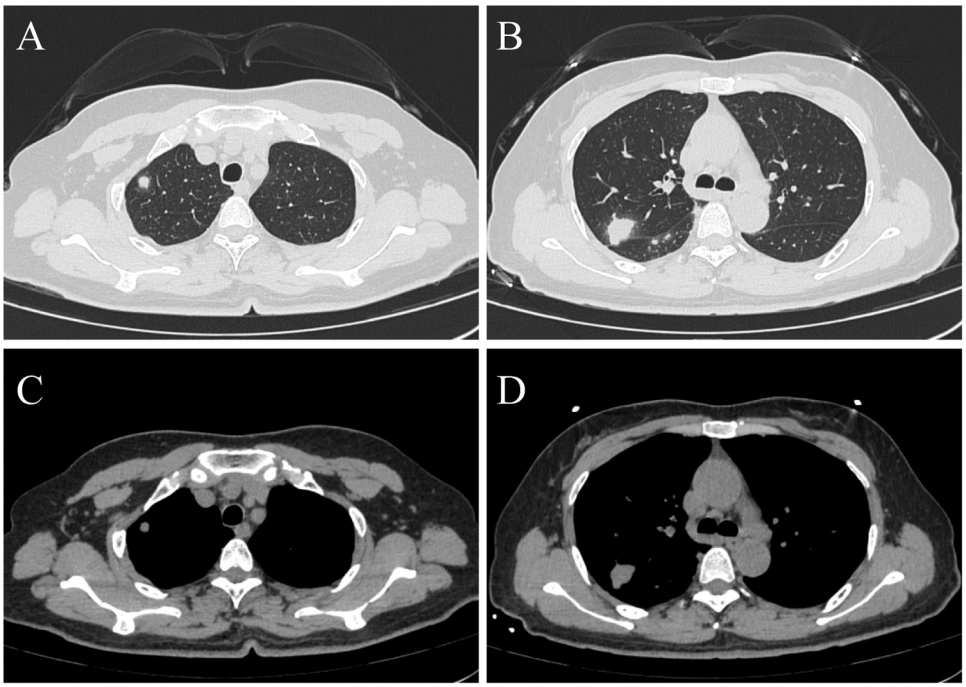

Fig. 1. Patient's pre-admission chest CT: multiple patchy, rounded solid slightly hyperdense shadows in the right lung(A~ B: Lung window; C~D: mediastinal window).

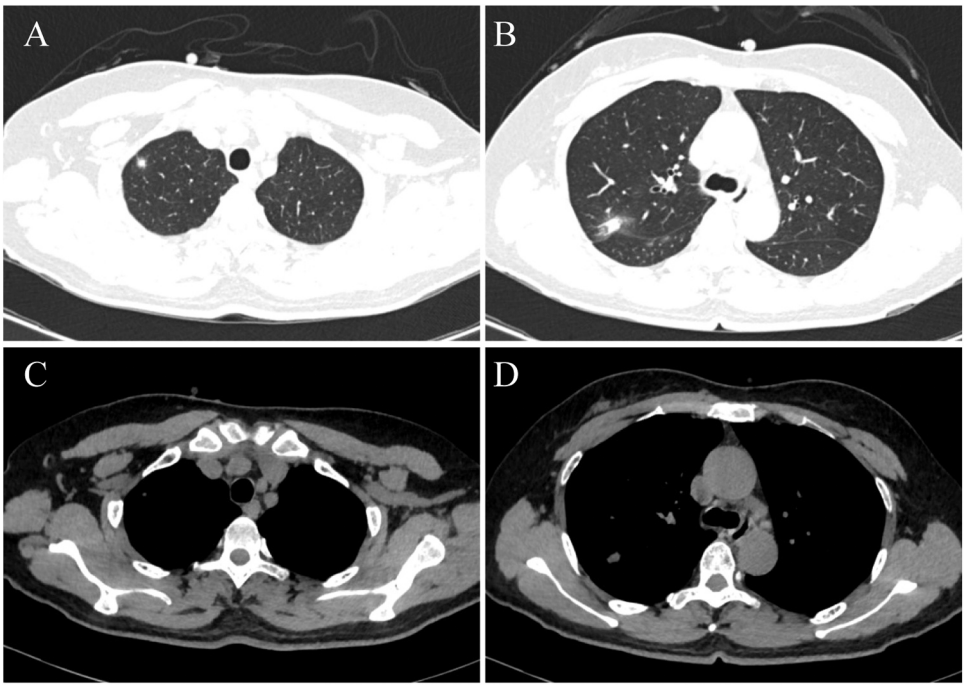

Fig. 2. Chest CT of the patient after 25 d of treatment: right lung solid shadow is absorbed compared to the previous one (A–B: Lung window; C–D: mediastinal window).

diagnostic method for cryptococcosis. A meta-analysis indicated that the lateral flow immunoassay (LFA) for detecting Cryptococcus achieved a diagnostic specificity of 98.1 % and a sensitivity of 97.6 % [13].

Recently, with the expanded use of mNGS in cases of complicated and critical infections, particularly in cases with unexplained lung shadows. However, the patient admitted to the hospital, both fungal cultures and smears were negative, and no cryptococcal sequences were identified through mNGS or real-time fluorescence PCR in the BALF. Nevertheless, the patient's Cryptococcus polysaccharide antigen result was positive. This discrepancy may be attributed to the challenges associated with the thick outer wall of Cryptococcus, which is rich in lipids, complicating nucleic acid extraction and full recovery of genomic material. Furthermore, the pathogen load in the sample may have been below the minimum detection threshold for mNGS, or the quantity of sequencing data might have been insufficient to cover the target microorganisms[14]. As such, false-negative results in mNGS assays are a clinical reality; a negative mNGS result does not definitively exclude cryptococcal infection. Therefore, antigen detection in BALF should be regarded as a valuable diagnostic tool for pulmonary cryptococcosis, enabling timely initiation of anti-infective therapy.

Based on both domestic and international guidelines [15], fluconazole is the preferred antifungal treatment for pulmonary cryptococcosis. Although there is no established clinical breakpoint for fluconazole against Cryptococcus, some studies have explored drug sensitivity testing for this pathogen. Wang et al.conducted a multicenter in vitro drug susceptibility testing for a new type of Cryptococcus in East China, determining the MIC_{90} values of strains for various antifungal agents: fluconazole 8 mg/L, voriconazole 0.12 mg/L, amphotericin B 1 mg/L, 5-fluorocytosine 8 mg/L, esaconazole 0.06 mg/L, posaconazole 0.25 mg/L, and itraconazole 0.25 mg/L [16]. Comparatively, the fluconazole dilution gradient in this region aligns with the Clinical and Laboratory Standards Institute (CLSI) standards, while the epidemiological cutoff values (ECVs) for fluconazole against Cryptococcus neoformans have not been provided by EUCAST in 2023. Further domestic research, including studies by Zhou et al. [14] from Tongji University in 2022, indicated the molecular epidemiology and drug resistance profiles of Cryptococcus neoformans among HIV-positive and negative individuals in East China [17]. Their findings demonstrated that 93.98–100 % of Cryptococcus neoformans strains exhibited high susceptibility to fluconazole, 5-fluorocytosine, and voriconazole, with MIC_{90} values for fluconazole consistently reported at 8 mg/L in both HIV-positive and negative cohorts. Thus, the prevalent MIC_{90} for Cryptococcus neoformans in our country appears to align with the CLSI ECV of 8 mg/L. Additionally, a significant multicenter prospective study of cryptococcal infections in France found no correlation between fluconazole resistance and adverse clinical outcomes. While in vitro fluconazole resistance may not predict clinical treatment response, further investigation is warranted [18]. According to the ECMM/ISHAM/ASM guidelines for managing cryptococcosis [15], patients with mild to moderate pulmonary cryptococcosis, regardless of their immune status, are advised to receive fluconazole at a dosage of 400 mg daily. Considering the clinical presentation of this patient, characterized by isolated pulmonary cryptococcosis, it was determined that an initial therapeutic regimen of fluconazole 400 mg IV once daily would be appropriate for treatment.

Fluconazole is a time-dependent triazole antifungal drug that exhibits prolonged antifungal effects. The PK/PD index for fluconazole is typically represented by the AUC to MIC ratio ($AUC_{0-24\ h}$/MIC) [19]. While there are limited reports on TDM of fluconazole during cryptococcal treatment, a study by Sudan et al. established a target $AUC_{0-24\ h}$/MIC greater than 389 mg/(L·h) for a murine model of cryptococcal meningitis[20]. However, the target value for pulmonary cryptococcal infection in humans remains unclear. Evidence suggests that when the cryptococcal MIC $\leq$ 2 mg/L, achieving an $AUC_{0-24\ h}$/MIC greater than 100 with a fluconazole dose of 400 mg/day during the consolidation phase can yield improved clinical outcomes [21]. Therefore, the recommended PK/PD target for pulmonary cryptococcosis is approximately $AUC_{0-24\ h}$/MIC $>$ 100. Fluconazole's pharmacokinetics are comparable regardless of oral or intravenous administration, with plasma concentrations peaking around 1 h after dosing. The plasma concentration is directly proportional to the administered dose. In this paper, fluconazole was subjected to TDM by LC-MS/MS method which has been established in the laboratory. The trapezoidal area computed from these three concentration values can be used to estimate $AUC_{0-24\ h}$. The trapezoidal

area constructed from the values of C_{min}, $C_{4\,h,}$ and C_{max} was used to estimate the value of fluconazole $AUC_{0–24\,h}$ in the patient[22]. Fluconazole $AUC_{0–24\,h}$/MIC = (S1 + S2)/MIC= $[(C_{min} + C_{max})/2 \times t_1 + (C_{max} + C_{4\,h})/2 \times t_2]$/MIC in this patient ($t_1$, t_2 were the three times respectively) blood collection intervals), as shown in Fig. 3.

The patient underwent TDM for fluconazole for the first time on day 5 of treatment. The clinical pharmacist estimated an $AUC_{0–24\,h}$/MIC ratio of approximately 59.3 (Table 1), which fell short of the clinical therapeutic target. In light of the patient's clinical symptoms, it was concluded that the fluconazole dose was insufficient. According to the management guideline from the ECMM/ISHAM/ASM [15], for mild-to-moderate cases of isolated pulmonary cryptococcosis, a recommended daily fluconazole dose ranges from 400 to 800 mg. Research has indicated that fluconazole is dose-dependent, with some studies revealing that 33 % of patients treated with a standard daily dosage of 400 mg experienced clinical treatment failures due to inadequate dosing [23]. The national expert consensus on PK/PD recommends an adult fluconazole dose of 6–12 mg/kg/day for candidiasis treatment; hence, higher doses may be necessary for cryptococcosis management. Initially, this patient was administered a standard fluconazole dose of 400 mg daily. Given the patient's weight of 74 kg, this dosage equated to approximately 5.4 mg/kg/day, which is below the suggested range of 6–12 mg/kg/day, potentially contributing to the failure in achieving PK/PD objectives. After a thorough evaluation, the fluconazole dose was increased to 800 mg daily on day 5 of treatment. Subsequent TDM conducted on days 20 and 30 revealed estimated $AUC_{0–24\,h}$/MIC ratios of 94.1 and 96.0, respectively, indicating proximity to the target value (Table 1). Alongside improvements in the patient's clinical symptoms and imaging results, the adjusted fluconazole dosage was deemed reasonable and clinically effective.

This case study highlights the importance of pharmacological exploration in the treatment of pulmonary cryptococcosis with fluconazole. By monitoring fluconazole blood concentrations throughout the treatment process and adjusting the dosage based on PK/PD principles, we achieved more favorable outcomes. This approach may serve as a valuable reference for individualized and precise management of pulmonary cryptococcosis in clinical settings. Nevertheless, the extant evidence for fluconazole TDM remains limited, particularly to immunocompromised patients, those with disseminated cryptococcosis, and patients with meningitis. Furthermore, additional evidence is required from multiple cases, particularly data on immunocompromised patients, disseminated cryptococcosis, and patients with meningitis. The objective of future clinical work is to collect a greater number of cases to verify the clinical efficacy of fluconazole TDM to a greater extent and to provide a stronger evidence base for its application in different patient groups.

Author contribution

Yuzhu.Cao, Huimin Yu, and Tang Tan designed and wrote the manuscript. Huimin Yu performed the experiments, Yuzhu.Cao and Huimin Yu analyzed the data. All authors contributed to data collection and manuscript writing.

Ethical Approval Statement

This study was approved by the Clinical Trials Ethics Committee of the General Hospital of the EasternTheater Command (Approval Number: 2020NZKY-029-01). The study was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants were informed about the study's purpose, procedures, potential risks, and benefits, and their consent was obtained prior to participation.

Consent Statement

Informed consent was obtained from all individual participants included in the study. Participants were provided with detailed information about the study's purpose, procedures, potential risks, and benefits. They were assured of their right to withdraw from the study at any time without any consequences. Written consent was obtained from each participant prior to their involvement in the study.

CRediT authorship contribution statement

Yu Huimin: Writing – original draft, Methodology, Formal analysis, Data curation. **Cao Yuzhu:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition. **Tang Tang:** Writing – original draft, Visualization, Data curation. **Sha Qifei:** Visualization, Project administration, Methodology. **Hua Shuang:** Methodology, Formal analysis, Data curation.

Author Statement

All authors have seen and approved the final version of the manuscript as submitted. We guarantee that the article is an original work, has not been previously published, and has not been considered for publication elsewhere.

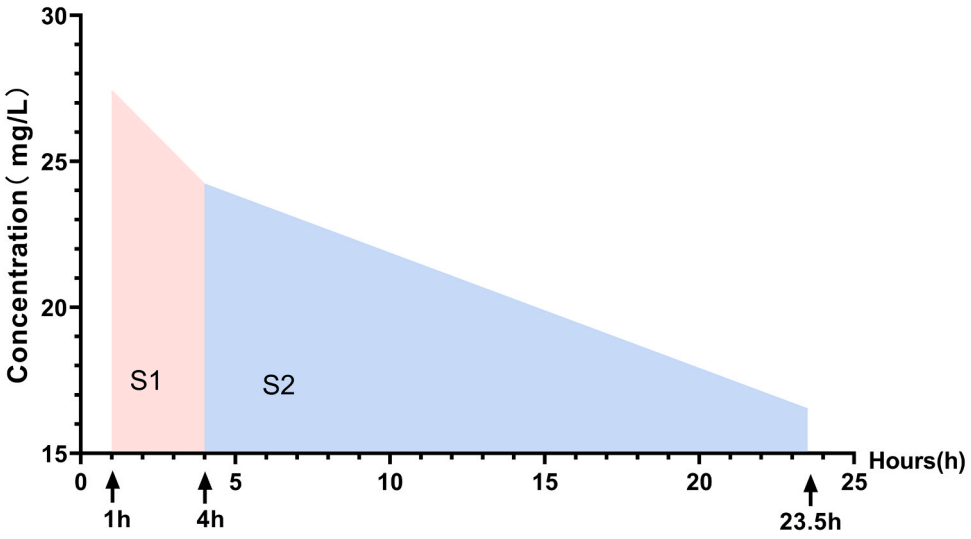

Fig. 3. Estimation of the area under the blood concentration-time curve (AUC) of fluconazole by trapezoidal approximation.

Author agreement

All authors agreed to publish the manuscript entitled "Therapeutic Role of Fluconazole in Immunocompetent Patients with Pulmonary Cryptococcosis: A Report of One Case and An Overview of Current Evidence" in IDcases.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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References

[1] Zhao Y, Ye L, Zhao F, Zhang L, Lu Z, Chu T, et al. Cryptococcus neoformans, a global threat to human health. Infect Dis Poverty 2023;12(1):20.
[2] Setianingrum F, Rautemaa-Richardson R, Denning DW. Pulmonary cryptococcosis: a review of pathobiology and clinical aspects. Med Mycol 2019;57(2):133–50.
[3] Dai Q, Wang Y, Ying Q, Ye Q. Cryptococcosis with pulmonary cavitation in an immunocompetent child: a case report and literature review. BMC Infect Dis 2024;24(1):162.
[4] Fisher MC, Denning DW. The WHO fungal priority pathogens list as a game-changer. Nat Rev Microbiol 2023;21(4):211–2.
[5] Hung MS, Tsai YH, Lee CH, Yang CT. Pulmonary cryptococcosis: clinical, radiographical and serological markers of dissemination. Respirology 2008;13(2):247. 51.
[6] Janowski M, Demchuk OM, Wujec M. Fluconazole analogs and derivatives: an overview of synthesis, chemical transformations, and biological activity. Molecules 2024;29(12).
[7] Luco RF, Allo M, Schor IE, Kornblihtt AR, Misteli T. Epigenetics in alternative pre-mRNA splicing. Cell 2011;144(1):16–26.
[8] Cogliati M. Global molecular epidemiology of cryptococcus neoformans and Cryptococcus gattii: an atlas of the molecular types. Science 2013;2013:675213.
[9] Chen M, Wang Y, Li Y, Hong N, Zhu X, Pan W, et al. Genotypic diversity and antifungal susceptibility of environmental isolates of Cryptococcus neoformans from the Yangtze River Delta region of East China. Med Mycol 2021;59(7):653–63.
[10] Paes HC, Derengowski LDS, Peconick LDF, Albuquerque P, Pappas Jr GJ, Nicola AM, et al. A Wor1-like transcription factor is essential for virulence of Cryptococcus neoformans. Front Cell Infect Microbiol 2018;8:369.
[11] Melhem MSC, Leite Junior DP, Takahashi JPF, Macioni MB, Oliveira L, de Araujo LS, et al. Antifungal resistance in cryptococcal infections. Pathogens 2024;13(2).
[12] Suwatanapongched T, Sangsatra W, Boonsarngsuk V, Watcharananan SP, Incharoen P. Clinical and radiologic manifestations of pulmonary cryptococcosis in immunocompetent patients and their outcomes after treatment. Diagn Interv Radiol 2013;19(6):438. 46.
[13] Huang HR, Fan LC, Rajbanshi B, Xu JF. Evaluation of a new cryptococcal antigen lateral flow immunoassay in serum, cerebrospinal fluid and urine for the diagnosis of cryptococcosis: a meta-analysis and systematic review. PLoS One 2015;10(5):e0127117.
[14] Thoracic S Chinese. Consensus of clinical pathways of metagenomic next-generation sequencing test in diagnosis of lower respiratory tract infections in China]. Zhonghua Jie He He Hu Xi Za Zhi 2023;46(4):322–35.
[15] Chang CC, Harrison TS, Bicanic TA, Chayakulkeeree M, Sorrell TC, Warris A, et al. Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM. Lancet Infect Dis 2024;24(8):e495–512.
[16] Lili W, Ziyi Z, Ziwen W, Wenjie T, Yan Z, Lingbing Z, et al. Establishment of the epidemiological cut-off value for antifungal drugs against Cryptococcus neoformans in East China from 2017 to 2022. Chin J Lab Med 2024:639–43.
[17] Zhou Z, Zhu C, Ip M, Liu M, Zhu Z, Liu R, et al. Molecular epidemiology and antifungal resistance of Cryptococcus neoformans from human immunodeficiency virus-negative and human immunodeficiency virus-positive patients in Eastern China. Front Microbiol 2022;13:942940.
[18] Bassetti M, Vena A, Bouza E, Peghin M, Munoz P, Righi E, et al. Antifungal susceptibility testing in Candida, Aspergillus and Cryptococcus infections: are the MICs useful for clinicians? Clin Microbiol Infect 2020;26(8):1024–33.
[19] Sudan A, Livermore J, Howard SJ, Al-Nakeeb Z, Sharp A, Goodwin J, et al. Pharmacokinetics and pharmacodynamics of fluconazole for cryptococcal meningoencephalitis: implications for antifungal therapy and in vitro susceptibility breakpoints. Antimicrob Agents Chemother 2013;57(6):2793. 800.
[20] Vanherp L, Poelmans J, Weerasekera A, Hillen A, Croitor-Sava AR, Sorrell TC, et al. Trehalose as quantitative biomarker for in vivo diagnosis and treatment follow-up in cryptococcomas. Transl Res 2021;230:111–22.
[21] Chesdachai S, Rajasingham R, Nicol MR, Meya DB, Bongomin F, Abassi M, et al. Minimum inhibitory concentration distribution of fluconazole against cryptococcus species and the fluconazole exposure prediction model. Open Forum Infect Dis 2019;6(10).
[22] Xu Y, Jin L, Liu N, Luo X, Dong D, Tang J, et al. Evaluation of the ratio of the estimated area under the concentration-time curve to minimum inhibitory concentration (estimated AUIC) as a predictor of the outcome for tigecycline treatment for pneumonia due to multidrug-resistant bacteria in an intensive care unit. Int J Infect Dis 2019;82:79–85.
[23] Sinnollareddy MG, Roberts JA, Lipman J, Akova M, Bassetti M, De Waele JJ, et al. Pharmacokinetic variability and exposures of fluconazole, anidulafungin, and caspofungin in intensive care unit patients: data from multinational Defining Antibiotic Levels in Intensive care unit (DALI) patients study. Crit Care 2015;19(1):33.