Clinical Infectious Diseases

INVITED COMMENTARY

Emerging Roles of (1→3)-β-D-Glucan in Cerebrospinal Fluid for Detection and Therapeutic Monitoring of Invasive Fungal Diseases of the Central Nervous System

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Keywords. CSF (1→3)-beta-D-glucan; Candida meningoencephalitis; cerebral Aspergillosis; cryptococcal meningitis; Fusarium meningitis.

Invasive fungal diseases (IFDs) of the central nervous system (CNS) caused by *Candida* spp. and molds are associated with severe morbidity and high mortality [1–5]. Early detection and prompt initiation of antifungal therapy are essential to a successful outcome of IFDs of the CNS. Direct microscopic examination and detection of cryptococcal capsular polysaccharide antigen in cerebrospinal fluid (CSF) have been paramount for the early-detection therapeutic monitoring of cryptococcal meningitis [6–8].

There is a paucity of biomarkers for the detection of non-cryptococcal IFDs of the CNS. Diagnosis of non-cryptococcal IFDs of the CNS, such as hematogenous *Candida* meningoencephalitis (HCME), cerebral aspergillosis, and other mold infections of the CNS, is clinically and microbiologically challenging. Direct examination, culture, white blood cell count, and chemistries of CSF in patients with HCME and cerebral aspergillosis are relatively insensitive in the detection and therapeutic monitoring of non-cryptococcal IFDs of the CNS [1, 4, 9–12].

The cell walls of *Candida* spp., and medically important Ascomycetous molds, including *Aspergillus* spp., *Fusarium*, *Scedosporium* spp., and *Exserohilum* spp., are composed of (1→3)-β-D-glucan and other polysaccharides [13]. The potential clinical utility of (1→3)-β-D-glucan is predicated on the unique structural characteristics of this cell wall polysaccharide being present in fungal cells but not that of mammalian cells. The core chain of the (1→3)-β-D-glucan polysaccharide is estimated to be 1500 glucose subunits in length for a molecular weight of approximately 2.7×10^5 Da. However, as (1→3)-β-D-glucan has multiple (1–>4) and (1–>6) branches, the molecular weight of the complete (1→3)-β-D-glucan molecule is larger. These properties are important, as this relatively large polysaccharide is not normally detected in noninflamed CSF and an intact blood–brain barrier above a certain analytical lower limit of quantitation. Consistent with the observations of the high molecular weight of circulating (1→3)-β-D-glucan, the values for most samples of normal human CSF (1→3)-β-D-glucan are less than 30 pg/mL.

The paper by Bigot and colleagues [14] in *Clinical Infectious Diseases* expands our understanding of (1→3)-β-D-glucan in the CSF as a biomarker for the diagnosis of HCME and mold infections of the CNS. While the study by Bigot et al advances our understanding of the potential utility of CSF (1→3)-β-D-glucan, their analysis aggregates the diagnostic sensitivity of the assay for non-cryptococcal fungal infections of the CNS, such that a more in-depth discussion of its clinical utility in each of the major CNS IFDs is warranted. Among these non-cryptococcal CNS IFDs are HCME, aspergillosis, and *Exserohilum rostratum* meningitis. Of note, cryptococcal meningoencephalitis and CNS infections by endemic dimorphic fungi were also not assessed. Moreover, a discussion of the utility for therapeutic monitoring through serial CSF (1→3)-β-D-glucan also warrants discussion as a biomarker for response to antifungal therapy.

Hematogenous *Candida* meningoencephalitis occurs disproportionally as a complication of candidemia in neonates and immunocompromised children [2, 3, 9, 10, 15–18]. Establishing a clinical diagnosis of HCME is difficult, as CSF cultures are insensitive, changes in CSF cell count and chemistries are nonspecific, and there are no widely available biomarkers. A diagnosis of HCME is important, as this disease requires an extended course of therapy beyond the standard 14 days for primary treatment of candidemia. Inadequate treatment of HCME is associated with recurrent infection, seizures, loss of developmental milestones, and developmental delays.

Petraitiene et al [19] demonstrated that CSF (1→3)-β-D-glucan would be a

Received 03 August 2023; editorial decision 16 August 2023; published online 31 August 2023

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Clinical Infectious Diseases® **2024;78(1):11–4**

https://doi.org/10.1093/cid/ciad520

useful biomarker of HCME disease and that the level of polysaccharide would correlate with organism burden within brain tissue. This was the first reported documentation of the utility of CSF (1→3)-β-D-glucan for the diagnosis of a fungal infection of the CNS. These investigators demonstrated that the level of (1→3)-β-D-glucan in CSF correlated directly with the residual fungal burden in cerebral and cerebellar tissue by quantitative cultures in a rabbit model of experimental HCME. The study also demonstrated compartmentalization of significantly greater concentration of (1→3)-β-D-glucan in CSF than in serum, which further facilitates a diagnosis of HCME. Further investigation demonstrated that the CSF (1→3)-β-D-glucan levels in experimental HCME were significantly higher than those within serum. Antifungal therapy also was associated with a simultaneous reduction in CSF (1→3)-β-D-glucan levels and quantitative cultures. These preclinical studies established an experimental foundation for utilizing CSF (1→3)-β-D-glucan as a biomarker for the detection of HCME, as well as for monitoring CNS response to antifungal therapy.

Building upon these preclinical observations, Salvatore and colleagues [10] reported the clinical utility of CSF (1→3)-β-D-glucan for the detection of HCME in pediatric patients with previously documented candidemia. The study further demonstrated that CSF (1→3)-β-D-glucan declined in response to effective antifungal therapy and successful outcome from HCME. The detection of CSF (1→3)-β-D-glucan in HCME provides critical information on the presence or absence of *Candida* within the CNS, an indicator of relative burden, and a baseline value by which to monitor therapeutic response. That CSF cultures for *Candida* in patients with HCME may be negative underscores the importance of a non–culture-based technology for early identification of this disease. The use of CSF (1→3)-β-D-glucan for therapeutic monitoring of response to antifungal therapy permits personalizing individual treatment until resolution of the biomarker, particularly with respect to length of therapy.

Before the advent of CSF (1→3)-β-D-glucan monitoring, patients historically would receive a course of treatment for candidemia, which may consist of 2 weeks only to subsequently present with neurologic deficits associated with HCME, which had been undertreated. Data from the prospective study by Salvatore et al demonstrated that significantly longer times of treatment are necessary in order to resolve the elevated levels of CSF (1→3)-β-D-glucan, eradicate *Candida* from CNS tissue, and thereby prevent relapse. Thus, a diagnostic strategy of early detection of HCME with CSF (1→3)-β-D-glucan and subsequent therapeutic monitoring of response is supported by preclinical and clinical foundations allowing this biomarker to be used in a manner similar to that of capsule polysaccharide of cryptococcal antigen.

Mold infections of the CNS are associated with high mortality, difficulty in early diagnosis, relapsed infection, and the need for protracted courses of antifungal therapy [1, 4, 12, 20]. Serris et al [21] reported that, among 119 patients with CNS aspergillosis from 20 French hospitals, 7 (64%) of 11 patients had a positive (>80 pg/mL) CSF(1→3)-β-D-glucan. They further observed that CSF (1→3)-β-D-glucan, galactomannan, and polymerase chain reaction (PCR) had similar sensitivities but, when combined, yielded a greater diagnostic sensitivity of 80%. Davis and colleagues [22] found that 9 (100%) of 9 previously reported cases of proven *Aspergillus* meningitis had positive CSF (1→3)-β-D-glucan. Mikulska et al [23] documented elevated CSF (1→3)-β-D-glucan in 3 patients with probable CNS aspergillosis at elevated levels ranging from 103 to more than 523 pg/mL.

Serial sampling of CSF (1→3)-β-D-glucan may have advantages in monitoring of therapeutic response in CNS aspergillosis. One well-described case of CNS aspergillosis in a pediatric patient with *Aspergillus* ventriculitis was monitored for therapeutic response with both CSF galactomannan and CSF (1→3)-β-D-glucan [20]. Although CSF (1→3)-β-D-glucan and galactomannan were both elevated at baseline, CSF galactomannan resolved relatively rapidly within approximately 30 days after initiation of therapy, while CSF (1→3)-β-D-glucan remained persistently elevated during this early phase of antifungal therapy. When antifungal therapy was decreased in dose intensity or discontinued entirely, the patient's neurologic symptoms deteriorated, and antifungal therapy was re-initiated. Over an ensuing year of antifungal therapy for the patient's CNS aspergillosis, there was a gradual decline in CSF (1→3)-β-D-glucan in response to antifungal therapy.

Among the dematiaceous molds, CSF (1→3)-β-D-glucan was found to be an important biomarker for early detection of *Exserohilum rostratum* meningoencephalitis in patients who had received paraspinal injections of a contaminated formulation of methylprednisolone acetate [24–26]. During the early phase of the outbreak, early microbiological detection of the infection was challenging, given the delay in growth of *E. rostratum* and the lack of sensitivity of cultures [27, 28].

Subsequent clinical studies demonstrated that CSF (1→3)-β-D-glucan was a sensitive biomarker of approximately 95% in detecting the presence of *Exserohilum* meningoencephalitis [24–26]. Litvintseva and colleagues [24] calculated a receiver operator characteristic (ROC) area under the curve of 0.99 and found the assay to be more sensitive than PCR. The elevated ratio of CSF to serum (1→3)-β-D-glucan observed in CNS candidiasis was also demonstrated in *Exserohilum* meningoencephalitis by Lyons et al [26]. Moreover, the decline in CSF (1→3)-β-D-glucan in patients receiving antifungal therapy also proved to be a useful tool in monitoring therapeutic response to antifungal therapy. The utility of this biomarker in detecting this fungal pathogen and monitoring

therapeutic response was further defined in a rabbit model of *E. rostratum* meningoencephalitis where successful therapeutic responses were correlated with a significant decline in CSF (1→3)-β-D-glucan in animals treated with posaconazole and with liposomal amphotericin B [29, 30].

The study by Bigot and colleagues [14] excluded patients with CNS IFDs caused by endemic dimorphic fungi, as these are infrequently encountered in France. Other investigators have characterized CSF (1→3)-β-D-glucan in patients with CNS IFDs caused by *Coccidioides* spp. [31]. and *Histoplasma capsulatum* [22, 26, 32]. The studies by Myint and colleagues [22, 32] demonstrated a sensitivity of 63.8%, specificity of 79.7%, and an area under the ROC curve of 0.706. There are spare data for CNS blastomycosis, where CSF (1→3)-β-D-glucan may have limited sensitivity.

While CSF capsular polysaccharide antigen is the time-tested biomarker for laboratory diagnosis of CNS cryptococcosis, Rhein and colleagues [33] demonstrated an 89% sensitivity and 85% specificity of CSF (1→3)-β-D-glucan in 117 patients with human immunodeficiency virus (HIV) from Uganda and South Africa with cryptococcal meningitis, with an assay-positive threshold value of 80 pg/mL or greater. The median CSF (1→3)-β-D-glucan concentrations at the time of diagnosis was 343 (interquartile range: 200–597) pg/mL. CSF (1→3)-β-D-glucan values of 500 pg/mL or greater at baseline were associated with greater 10-week mortality. CSF (1→3)-β-D-glucan concentrations at the time of diagnosis also correlated with CSF cryptococcal antigen titers, CSF fungal burden by quantitative culture, and levels of CSF monocyte chemotactic protein 1 (MCP-1). By comparison, 6 patients, 3 of whom has HIV, from the United States with proven cryptococcal meningitis had a detectable but relatively low median CSF (1→3)-β-D-glucan level of 33 pg/mL (range: <4–53 pg/mL). The differences between the CSF (1→3)-β-D-glucan levels reported in the 2 reports may be attributable to a substantially greater burden of CNS cryptococcal organisms in the study of Rhein et al.

CSF cryptococcal antigen clearly remains the first-line biomarker in patients with suspected cryptococcal meningitis. Moreover, the aforementioned study of Rhein et al documented that the presence of elevated CSF (1→3)-β-D-glucan does not exclude a diagnosis of this CNS cryptococcosis.

Mucormycosis, which causes devastating damage to the CNS, is difficult to diagnose. Little is known about the expression of CSF (1→3)-β-D-glucan in CNS mucormycosis. Since (1→3)-β-D-glucan is present in relatively low concentrations in the fungal cell wall of *Rhizopus* spp. [34], relatively low levels of CSF (1→3)-β-D-glucan may be anticipated. However, recent studies suggest that some patients with mucormycosis may have low circulating levels of serum (1→3)-β-D-glucan [35]. However, these apparently inconsistent observations may be explained by a low but detectable level of (1→3)-β-D-glucan that may be sufficiently expressed in some isolates of Mucorales as to be detectable in clinical specimens [36].

As a reflection of its expanding utility in the detection of IFDs of the CNS, (1→3)-β-D-glucan is recommended in the panel of assays performed on CSF by the Centers for Diseases Control and Prevention for the initial identification of patients with *Fusarium* meningitis in response to the outbreak in those patients exposed to procedures performed under epidural anesthesia in Matamoros, Mexico [37, 38]. Moreover, CSF (1→3)-β-D-glucan is also recognized as a select key finding in patients with *Fusarium* meningitis. As of 29 June, there have been 15 suspected cases, 10 probable cases, 9 confirmed cases, and 7 deaths from meningitis caused by *Fusarium solani* species complex. Although serum (1→3)-β-D-glucan has been found to be a sensitive biomarker in the detection of deeply invasive fusariosis [39, 40], there are no previous reports of CSF (1→3)-β-D-glucan in detection of *Fusarium* meningitis.

Although the normal values of (1→3)-β-d-glucan in human CSF have been uncertain, the current data in the study by Bigot et al [14] were 33 pg/mL or less. This value is substantially lower than that of the negative value of (1→3)-β-d-glucan determined for serum at less than 60 pg/mL. As the relatively large polysaccharide of (1→3)-β-D-glucan does not appear to substantially penetrate the blood–brain barrier into the CSF, normal values indeed may be lower in patients with an intact blood–brain barrier and no CNS pathology. However, pending further studies, the threshold cutoff value of greater than 80 pg/mL for greater specificity may be a more for optimal cutoff value for the detection of most (1→3)-β-d-glucan-producing fungal pathogens causing IFDs of the CNS.

There are limitations to the use of CSF (1→3)-β-D-glucan. The assay for the detection of (1→3)-β-D-glucan is approved by the Food and Drug Administration for serum but not for CSF. Unlike galactomannan, PCR, and metagenomics, (1→3)-β-D-glucan lacks specificity for a given fungus. The cutoff of (1→3)-β-d-glucan in CSF for the diagnosis of CNS IFDs has not been defined for the common fungal pathogens. The serum (1→3)-β-D-glucan assay is not widely used in pediatric patients. Several factors, including infusion of intravenous immunoglobulin, may contribute to false-positive reactions. The assay also may not be readily available in resource-challenged regions.

In summary, CSF (1→3)-β-D-glucan is a valuable biomarker for the detection and monitoring of therapeutic response of HCME and a promising indicator for *Aspergillus* and non-*Aspergillus* mold infections of the CNS within the appropriate clinical context.

Notes

Disclaimer. The funders had no role in the writing of the manuscript.

Financial support. T. J. W. was supported in this work as the Henry Schueler Foundation

Scholar by the Henry Schuler Foundation and as an Investigator of Emerging Infectious Diseases of the Save Our Sick Kids Foundation.

Potential conflicts of interest. T. J. W. has received grants for experimental and clinical antimicrobial pharmacology, therapeutics, and diagnostics to his institutions from Amplyx, Astellas, F2G, Gilead, Lediant, Merck, Omeros, Scynexis, Shionogi, and T2 Biosystems and has served as a consultant to Abbott Laboratories, Astellas, F2G, Gilead, Karyopharm, Leadiant, Omeros, Partner Therapeutics, Scynexis, Shionogi, Statera, and T2 Biosystems. T. J. W. also reports participation on Data Safety Monitoring or Advisory Board for T2 Biosystems and Abbott Laboratories. S. X. Z. reports research funding from Vela Diagnostics, IMMY Diagnostics, T2 Biosystems, Pearl Diagnostics, Applied BioCode, GenMark, and Scanogen; consulting fees from KARIUS and T2 Biosystems; and travel support from GenMark. These funds did not support the present report.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Economides MP, Ballester LY, Kumar VA, et al. Invasive mold infections of the central nervous system in patients with hematologic cancer or stem cell transplantation (2000–2016): uncommon, with improved survival but still deadly often. J Infect **2017**; 75:572–80.
2. Xiao H, Miao Y, Liu L, et al. Clinical characteristics of central nervous system candidiasis due to Candida albicans in children: a single-center experience. BMC Infect Dis **2022**; 22:945.
3. Chaussade H, Cazals X, Desoubeaux G, et al. Central nervous system candidiasis beyond neonates: lessons from a nationwide study. Med Mycol **2021**; 59:266–77.
4. McCarthy M, Rosengart A, Kontoyiannis DP, Walsh TJ. Mold infections of the central nervous system. N Engl J Med **2014**; 371:150–60.
5. Williamson PR, Jarvis JN, Panackal AA, et al. Cryptococcal meningitis: epidemiology, immunology, diagnosis and therapy. Nat Rev Neurol **2017**; 13:13–24.
6. Rajasingham R, Wake RM, Beyene T, Katende A, Letang E, Boulware DR. Cryptococcal meningitis diagnostics and screening in the era of point-of-care laboratory testing. J Clin Microbiol **2019**; 57: e01238-18.
7. Temfack E, Rim JJB, Spijker R, et al. Cryptococcal antigen in serum and cerebrospinal fluid for detecting cryptococcal meningitis in adults living with human immunodeficiency virus: systematic review and meta-analysis of diagnostic test accuracy studies. Clin Infect Dis **2021**; 72:1268–78.
8. Greene G, Lawrence DS, Jordan A, Chiller T, Jarvis JN. Cryptococcal meningitis: a review of cryptococcal antigen screening programs in Africa. Expert Rev Anti Infect Ther **2021**; 19:233–44.
9. Cohen-Wolkowiez M, Smith PB, Mangum B, et al. Neonatal *Candida* meningitis: significance of cerebrospinal fluid parameters and blood cultures. J Perinatol **2007**; 27:97–100.
10. Salvatore CM, Chen T, Toussi SS, et al. (1→3)-β-D-glucan in cerebrospinal fluid as a biomarker for *Candida* and *Aspergillus* infections of the central nervous system in pediatric patients. J Pediatr Infect Dis Soc **2016**; 5:277–86.
11. Walsh TJ, Hier DB, Caplan LR. Fungal infections of the central nervous system: analysis of risk factors and clinical manifestations. Neurology **1985**; 35: 1654–7.
12. Viscoli C, Machetti M, Gazzola P, et al. Aspergillus galactomannan antigen in the cerebrospinal fluid of bone marrow transplant recipients with probable cerebral aspergillosis. J Clin Microbiol **2002**; 40: 1496–9.
13. Gow NAR, Latge JP, Munro CA. The fungal cell wall: structure, biosynthesis, and function. Microbiol Spectr **2017**; 5:1–25.
14. Bigot J, Leroy J, Chouaki T, et al. ß-D-Glucan assay in the cerebrospinal fluid for the diagnosis of non-cryptococcal fungal infection of the central nervous system: a retrospective multicentric analysis and a comprehensive review of the literature. Clin Infect Dis **2023**; 77:711–20.
15. Walsh TJ, Katragkou A, Chen T, Salvatore CM, Roilides E. Invasive candidiasis in infants and children: recent advances in epidemiology, diagnosis, and treatment. J Fungi (Basel) **2019**; 5:11.
16. Drummond RA, Lionakis MS. Candidiasis of the central nervous system in neonates and children with primary immunodeficiencies. Curr Fungal Infect Rep **2018**; 12:92–7.
17. Benjamin DK Jr, Poole C, Steinbach WJ, Rowen JL, Walsh TJ. Neonatal candidemia and end-organ damage: a critical appraisal of the literature using meta-analytic techniques. Pediatrics **2003**; 112: 634–40.
18. McCullers JA, Vargas SL, Flynn PM, Razzouk BI, Shenep JL. Candidal meningitis in children with cancer. Clin Infect Dis **2000**; 31:451–7.
19. Petraitiene R, Petraitis V, Hope WW, et al. Cerebrospinal fluid and plasma (1→3)-beta-D-glucan as surrogate markers for detection and monitoring of therapeutic response in experimental hematogenous Candida meningoencephalitis. Antimicrob Agents Chemother **2008**; 52:4121–9.
20. Chen TK, Groncy PK, Javahery R, et al. Successful treatment of *Aspergillus* ventriculitis through voriconazole adaptive pharmacotherapy, immunomodulation, and therapeutic monitoring of cerebrospinal fluid (1→3)-β-D-glucan concentrations. Med Mycol **2017**; 55:109–17.
21. Serris A, Benzakoun J, Danion F, et al. Cerebral aspergillosis in the era of new antifungals: the CEREALS national cohort study Nationwide CEREbral Aspergillosis Lesional study (CEREALS). J Infect **2022**; 84:227–36.
22. Davis C, Wheat LJ, Myint T, Boulware DR, Bahr NC. Efficacy of cerebrospinal fluid beta-d-glucan diagnostic testing for fungal meningitis: a systematic review. J Clin Microbiol **2020**; 58:e02094-19.
23. Mikulska M, Furfaro E, Del Bono V, et al. (1-3)-β-D-glucan in cerebrospinal fluid is useful for the diagnosis of central nervous system fungal infections. Clin Infect Dis **2013**; 56:1511–2.
24. Lyons JL, Roos KL, Marr KA, et al. Cerebrospinal fluid (1,3)-β-D-glucan detection as an aid for diagnosis of iatrogenic fungal meningitis. J Clin Microbiol **2013**; 51:1285–7.
25. Litvintseva AP, Lindsley MD, Gade L, et al. Utility of (1-3)-β-D-glucan testing for diagnostics and monitoring response to treatment during the multistate outbreak of fungal meningitis and other infections. Clin Infect Dis **2014**; 58:622–30.
26. Lyons JL, Thakur KT, Lee R, et al. Utility of measuring (1,3)-β-d-glucan in cerebrospinal fluid for diagnosis of fungal central nervous system infection. J Clin Microbiol **2015**; 53:319–22.
27. Kainer MA, Reagan DR, Nguyen DB, et al. Fungal infections associated with contaminated methylprednisolone in Tennessee. N Engl J Med **2012**; 367:2194–203.
28. Larone DH, Walsh TJ. *Exserohilum* meningitis: anatomy of a national outbreak of fungal meningitis. Clin Microbiol Newsl **2013**; 35:185–93.
29. Petraitiene R, Petraitis V, Maung BBW, Naing E, Kavaliauskas P, Walsh TJ. Posaconazole alone and in combination with caspofungin for treatment of experimental *Exserohilum rostratum* meningoencephalitis: developing new strategies for treatment of phaeohyphomycosis of the central nervous system. J Fungi (Basel) **2020**; 6:33.
30. Petraitis V, Petraitiene R, Katragkou A, et al. Antifungal efficacy of isavuconazole and liposomal amphotericin B for treatment of experimental *Exserohilum rostratum* meningoencephalitis: a preclinical paradigm for management of CNS phaeohyphomycosis. Med Mycol **2021**; 59: 189–96.
31. Stevens DA, Zhang Y, Finkelman MA, Pappagianis D, Clemons KV, Martinez M. Cerebrospinal fluid (1,3)-beta-d-glucan testing is useful in diagnosis of coccidioidal meningitis. J Clin Microbiol **2016**; 54:2707–10.
32. Myint T, Chow FC, Bloch KC, et al. Detection of (1,3)-β-d-glucan in cerebrospinal fluid in histoplasma meningitis. J Clin Microbiol **2018**; 56: e00663-18.
33. Rhein J, Bahr NC, Morawski BM, et al. Detection of high cerebrospinal fluid levels of (1→3)-β-d-glucan in cryptococcal meningitis. Open Forum Infect Dis **2014**; 1:ofu105.
34. Mélida H, Sain D, Stajich JE, Bulone V. Deciphering the uniqueness of Mucoromycotina cell walls by combining biochemical and phylogenomic approaches. Environ Microbiol **2015**; 17:1649–62.
35. Angebault C, Lanternier F, Dalle F, et al. Prospective evaluation of serum β-glucan testing in patients with probable or proven fungal diseases. Open Forum Infect Dis **2016**; 3:ofw128.
36. Kontoyiannis DP. A potential explanation of a positive serum β-glucan assay in mucormycosis. Open Forum Infect Dis **2016**; 3:ofw209.
37. Centers for Disease Control and Prevention. Fungal meningitis outbreak associated with procedures performed under epidural anesthesia in Matamoros, Mexico. Available at: https://www.cdc.gov/hai/outbreaks/meningitis-epidural-anesthesia.html. Accessed 15 August 2023.
38. Interim Recommendations for Diagnosis and Management of Fungal Meningitis Associated with Epidural Anesthesia Administered in Matamoros, Mexico. Available at: https://funguseducationhub.org/wp-content/uploads/2023/06/interim-recommendations-Matamoros-FM-outbreak-6_09_23.pdf. Accessed 15 August 2023.
39. Nucci M, Barreiros G, Reis H, Paixão M, Akiti T, Nouér SA. Performance of 1,3-beta-D-glucan in the diagnosis and monitoring of invasive fusariosis. Mycoses **2019**; 62:570–5.
40. Lamoth F, Nucci M, Fernandez-Cruz A, et al. Performance of the beta-glucan test for the diagnosis of invasive fusariosis and scedosporiosis: a meta-analysis. Med Mycol **2023**;61:myad061.