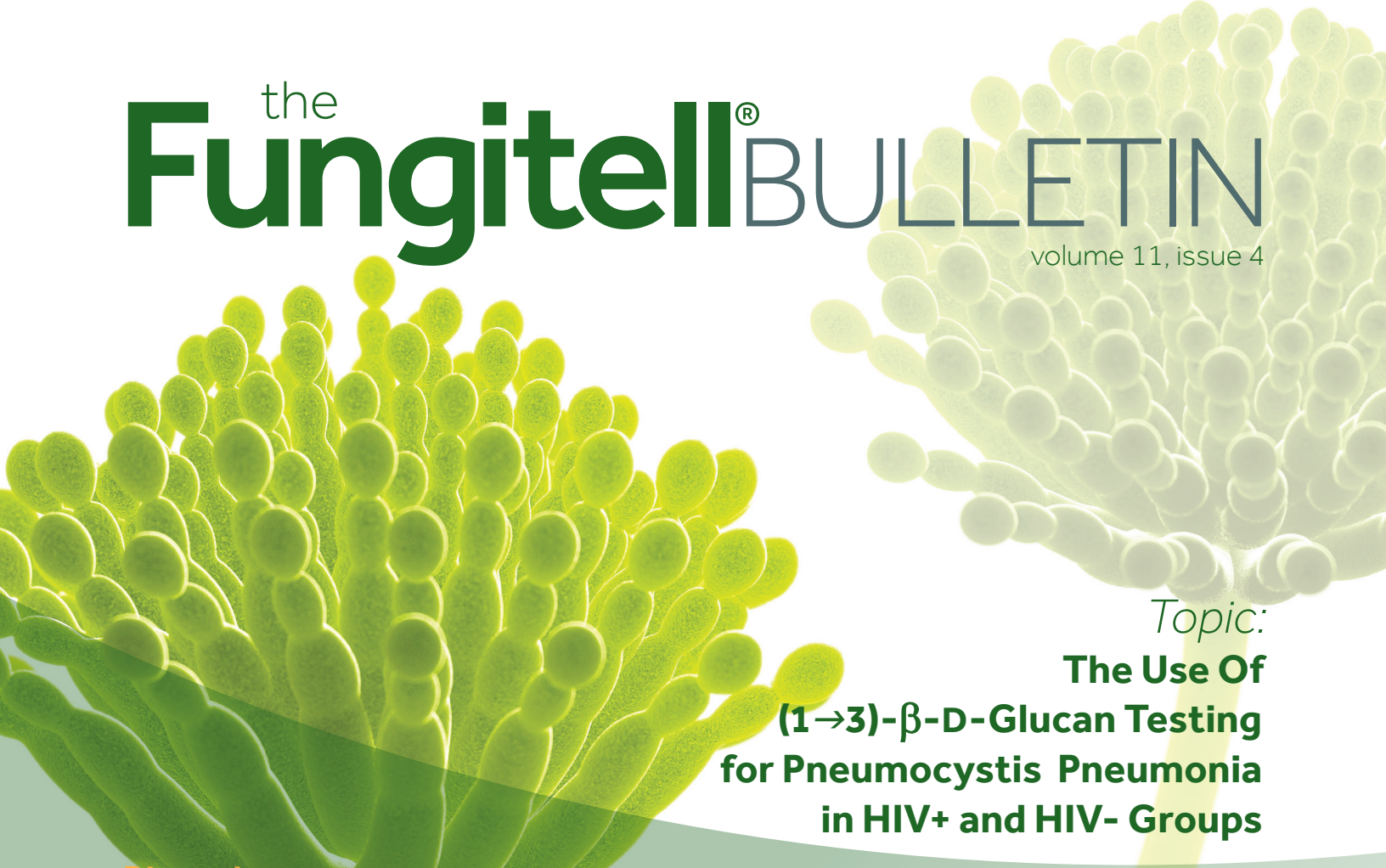
the Fungitell® BULLETIN
volume 11, issue 4



Topic:
The Use Of (1→3)-β-D-Glucan Testing for Pneumocystis Pneumonia in HIV+ and HIV- Groups

Discussion:

Pneumocystis pneumonia (PCP), caused by *Pneumocystis jirovecii*, is a life-threatening fungal infection that primarily affects immunocompromised individuals, particularly those with HIV/AIDS. Diagnosing PCP is challenging, as traditional methods like microscopy and PCR often require invasive specimens, such as biopsies or bronchoalveolar lavage (BAL), which are difficult to obtain. Consequently, non-invasive biomarkers like (1→3)-β-D-Glucan (BDG) have gained attention for their ability to facilitate quicker PCP diagnosis without the need for invasive procedures. BDG, a polysaccharide found in the cell walls of many pathogenic fungi, including *P. jirovecii,* acts as an indirect marker of infection. The Fungitell® assay, commonly used to measure serum BDG levels, has demonstrated its value in diagnosing suspected PCP, and was included in the European Conference on Infections in Leukaemia (ECIL) guidelines in 2016 (Alanio *et al.,* 2016).

A major advantage of the Fungitell assay for diagnosing PCP is its ability to use a simple serum sample, which is especially beneficial for HIV-positive patients with conditions that complicate the collection of deep-respiratory samples (Alanio *et al.,* 2016). This is particularly important in resource-limited settings where access to specialized equipment for real-time PCR or invasive sampling techniques is limited. BDG testing utilizes readily available serum, reducing the need for complex procedures and increasing accessibility in these settings.

Fungitell® Bulletins are intended as technical advisory communications and as such are disseminated to the general public in order to highlight the significance of (1→3)-β-D-Glucan on human health. These communications do not promote a specific drug, therapy nor make any representation or suggestion concerning the suitability or effectiveness of a particular drug or therapy in patients harboring (1→3)-β-D-Glucan. Fungitell® is an adjunct diagnostic assay to be utilized in conjunction with clinical signs and symptoms for the diagnosis of invasive fungal infection. Fungitell® is currently 510(k) cleared for the detection of (1→3)-β-D-Glucan in human serum and should be used and interpreted only in a manner consistent with the current Instructions for Use.

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Publication Date: October 2025
CORP_0810

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Pneumocystis Pneumonia in HIV Positive Patients

Sax *et al.* (2011) evaluated the Fungitell® assay in 252 HIV-positive patients for diagnosing PCP, reporting a sensitivity of 92%. Median BDG levels were notably higher in PCP patients (408 pg/mL) compared to non-PCP patients (37 pg/mL), with a moderate specificity of 65%, likely influenced by co-infections with other fungi. In an accompanying commentary, Morris and Mansur (2011) emphasized the significance of BDG levels in diagnosing HIV-associated PCP, highlighting the test's high sensitivity and its value as a diagnostic tool. A meta-analysis by Onishi *et al.* (2012), which included 12 PCP-related studies, confirmed similar sensitivity (96%) but higher specificity (84%), with little variation based on HIV status. The high sensitivity of BDG testing enhances its ability to detect early PCP in immunocompromised patients, where timely diagnosis is essential for improving outcomes.

Furthermore, a systemic review and meta-analysis by Del Corpo *et al.* (2020), as referenced in multiple subsequent papers, underscores the potential of BDG testing as a non-invasive adjunct marker of PCP. The 23 included studies examined a total of 997 patients diagnosed with PCP and 3,062 controls. Despite significant heterogeneity across studies, a bivariate meta-analysis estimated BDG highest sensitivity in HIV-positive patients (94%), while specificity remained similar at 83% irrespective of HIV status.

Pneumocystis Pneumonia in HIV Negative Patients

BDG testing is valuable for diagnosing PCP in HIV-positive individuals, but its use in HIV-negative patients is more complex. Del Corpo *et al.* (2020) found that sensitivity in HIV-negative patients was 86%, slightly lower than 94% in HIV-positive cases. Rhoads *et al.* (2024) noted challenges in diagnosing PCP in HIV-negative, non-transplant populations, where immunosuppressive medications are the primary risk factor. These patients experience less severe immunosuppression, making it harder to differentiate PCP from other pulmonary conditions. BDG testing has largely replaced serum LDH for PCP diagnosis, but refining cut-off values is critical, especially in HIV-negative patients where a higher BDG cut-off could improve specificity.

Li *et al.* (2024) highlighted the need to adjust BDG thresholds in HIV-negative patients, where factors like blood transfusions and hemodialysis can elevate BDG levels. Lahmer *et al.* (2017) found that using a 275 pg/mL cut-off improved PCP diagnosis, increasing sensitivity to 98% and specificity to 86-88%. BDG levels below 80 pg/mL effectively ruling out PCP with an NPV of 96%. However, Damiani *et al.* (2021) noted that BDG's sensitivity is reduced in patients with hematological malignancies due to lower fungal loads. Szvalb *et al.* (2020) also observed poor correlation between BDG and qPCR in HIV-negative cancer patients. Despite its strong NPV, BDG testing should be interpreted cautiously, and additional tests like qPCR or microscopy may be necessary to confirm or exclude PCP, especially in high-risk populations.

Pneumocystis Pneumonia and BDG Kinetics

The kinetics of BDG following PCP treatment may offer insights into its utility as a monitoring tool. Cuétara *et al.* (2008) showed that decreasing BDG levels after treatment with trimethoprim-sulfamethoxazole corresponded with a favorable response, while rising levels indicated treatment failure. However, Koga *et al.* (2011) found that, although BDG levels generally decreased after treatment, they did not consistently reflect disease severity or prognosis, with fluctuations observed even during clinical improvement. Larger studies would be needed to confirm these findings.

Closing Remarks

Fungitell® and β-D-glucan (BDG) testing represent a key advance in PCP diagnosis, especially in HIV-positive individuals, where its sensitivity and specificity are well-established. In HIV-negative patients, diagnostic accuracy varies, requiring careful interpretation of cut-off values and potential false positives and false negatives. Despite these limitations, BDG remains a valuable tool for early PCP detection, particularly when invasive procedures aren't feasible. Further research is needed to optimize BDG use across populations, especially regarding optimal cut-off values. BDG testing via Fungitell® offers promising potential for diagnosing PCP in both HIV-positive and HIV-negative patients.

References:

- Alanio A, Hauser PM, Lagrou K, *et al.* ECIL guidelines for the diagnosis of Pneumocystis jirovecii pneumonia in patients with haematological malignancies and stem cell transplant recipients. J Antimicrob Chemother. 2016;71(9):2386-2396. doi:10.1093/jac/dkw156.
- Cuétara MS, Alhambra A, Chaves F, Moragues MD, Pontón J, del Palacio A. Use of a serum (1->3)-beta-D-glucan assay for diagnosis and follow-up of Pneumocystis jiroveci pneumonia. Clin Infect Dis. 2008;47(10):1364-1366. doi:10.1086/592753.
- Damiani C, Demey B, Pauc C, Le Govic Y, Totet A. A Negative (1,3)-β-D-Glucan Result Alone Is Not Sufficient to Rule Out a Diagnosis of Pneumocystis Pneumonia in Patients With Hematological Malignancies. Front Microbiol. 2021;12:713265. Published 2021 Aug 11. doi:10.3389/fmicb.2021.713265: This research stresses that a negative β-glucan result should not be used alone to rule out PCP, providing important considerations for its use in clinical settings.
- Damiani C, Demey B, Pauc C, Le Govic Y, Totet A. A Negative (1,3)-β-D-Glucan Result Alone Is Not Sufficient to Rule Out a Diagnosis of Pneumocystis Pneumonia in Patients With Hematological Malignancies. Front Microbiol. 2021;12:713265. Published 2021 Aug 11. doi:10.3389/fmicb.2021.713265.
- Del Corpo O, Butler-Laporte G, Sheppard DC, Cheng MP, McDonald EG, Lee TC. Diagnostic accuracy of serum (1-3)-β-D-glucan for Pneumocystis jirovecii pneumonia: a systematic review and meta-analysis. Clin Microbiol Infect. 2020;26(9):1137-1143. doi:10.1016/j.cmi.2020.05.024.
- Karageorgopoulos DE, Qu JM, Korbila IP, Zhu YG, Vasileiou VA, Falagas ME. Accuracy of β-D-glucan for the diagnosis of Pneumocystis jirovecii pneumonia: a meta-analysis. Clin Microbiol Infect. 2013;19(1):39-49. doi:10.1111/j.1469-0691.2011.03760.x: Reviews the diagnostic accuracy of β-D-glucan for PCP in AIDS patients, underscoring its utility in diagnosing PCP in immunocompromised populations.
- Koga M, Koibuchi T, Kikuchi T, *et al.* Kinetics of serum β-D-glucan after Pneumocystis pneumonia treatment in patients with AIDS. Intern Med. 2011;50(13):1397-1401. doi: 10.2169/internalmedicine.50.5296: Examines the kinetics of serum β-D-glucan as a marker for monitoring the treatment of PCP in AIDS patients, discussing its role as a non-invasive adjunct marker.
- Lahmer T, da Costa CP, Held J, *et al.* Usefulness of 1,3 Beta-D-Glucan Detection in non-HIV Immunocompromised Mechanical Ventilated Critically Ill Patients with ARDS and Suspected Pneumocystis jirovecii Pneumonia. Mycopathologia. 2017;182(7-8):701-708. doi:10.1007/s11046-017-0132-x.
- Li YY, Chen Y, Li S, *et al.* Identifying optimal serum 1,3-β-D-Glucan cut-off for diagnosing Pneumocystis Jirovecii Pneumonia in non-HIV patients in the intensive care unit. BMC Infect Dis. 2024;24(1):1015. Published 2024 Sep 20. doi:10.1186/s12879-024-09873-1: This article delves into the appropriate serum cut-offs for β-D-glucan detection in HIV patients, helping refine diagnostic strategies for PCP.
- Morris AM, Masur H. A serologic test to diagnose pneumocystis pneumonia: are we there yet?. Clin Infect Dis. 2011;53(2):203-204. doi:10.1093/cid/cir348: This study investigates the diagnostic accuracy of β-glucan testing in patients with AIDS, highlighting the potential for β-glucan to support PCP diagnosis in immunocompromised individuals, including HIV-positive cohorts.
- Onishi A, Sugiyama D, Kogata Y, *et al.* Diagnostic accuracy of serum 1,3-β-D-glucan for pneumocystis jiroveci pneumonia, invasive candidiasis, and invasive aspergillosis: systematic review and meta-analysis. J Clin Microbiol. 2012;50(1):7-15. doi:10.1128/JCM.05267-11: This study reports the diagnostic accuracy of the Fungitell assay for PCP diagnosis, specifically in lung transplant and AIDS patients.
- Rhoads S, Maloney J, Mantha A, Van Hook R, Henao-Martínez AF. Pneumocystis jirovecii Pneumonia in HIV-Negative, Non-transplant Patients: Epidemiology, Clinical Manifestations, Diagnosis, Treatment, and Prevention. Curr Fungal Infect Rep. 2024; 18(2):125-135. doi:10.1007/s12281-024-00482-8: Focuses on the use of serum and bronchoalveolar lavage (BAL) β-D-glucan for diagnosing Pneumocystis pneumonia in HIV-negative patients, providing insights into the performance of the test across different populations.
- Sax PE, Komarow L, Finkelman MA, *et al.* Blood (1->3)-beta-D-glucan as a diagnostic test for HIV-related Pneumocystis jirovecii pneumonia. Clin Infect Dis. 2011;53(2):197-202. doi:10.1093/cid/cir335.
- Szvalb AD, Malek AE, Jiang Y, Bhatti MM, Wurster S, Kontoyiannis DP. Serum (1,3)-Beta-d-Glucan has suboptimal performance for the diagnosis of Pneumocystis jirovecii pneumonia in cancer patients and correlates poorly with respiratory burden as measured by quantitative PCR. J Infect. 2020;81(3):443-451. doi:10.1016/j.jinf.2020.07.003.