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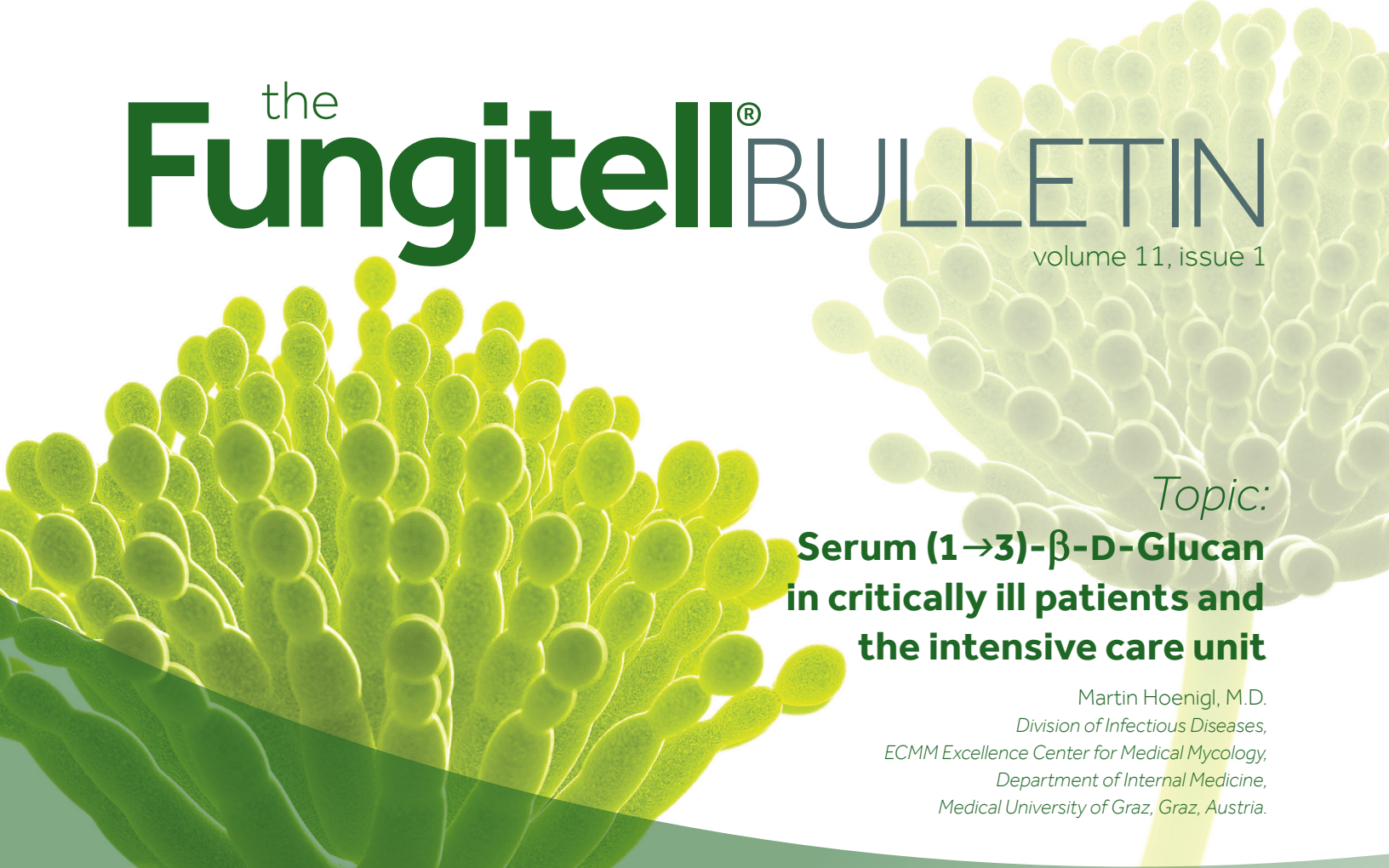

Topic:

Serum (1→3)-β-D-Glucan in critically ill patients and the intensive care unit

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Discussion:

Invasive fungal infections, particularly those caused by *Candida, Aspergillus* and *Pneumocystis* species, pose a significant threat to critically ill patients, requiring prompt antifungal treatment. Serum 1,3-β-D-Glucan (BDG) testing, using the Fungitell® assay, has proven to be a reliable method for diagnosing candidemia and invasive candidiasis in ICU patients, patients with underlying hematologic malignancies [Prüller 2014] [Lamoth 2021], and other hospitalized patients [Ostrosky-Zeichner 2005]. One common characteristic feature shared by those fungi is the production of the polysaccharide BDG, a component of the fungal cell wall that serves as a diagnostic marker for invasive fungal infection. While BDG testing has a high negative predictive value (NPV), making it especially useful for safely discontinuing empirical antifungal therapy, it also plays a role in antifungal stewardship by helping reduce unnecessary treatment. This article explores the diagnostic role of BDG in managing invasive *Candida* infections in the ICU, its limitations with other fungi like *Aspergillus*, and its potential broader applications in gut health and emerging research areas.

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Diagnosis in the ICU - *Candida*

Invasive *Candida* infections are life-threatening and require immediate initiation of antifungal treatment at the time of suspicion, to give patients a reasonable chance of survival and prevent serious complications such as *Candida* endocarditis [Clancy 2018] [Thompson 2023]. This observation naturally results in overtreatment, including empirical antifungal treatment of patients who in fact don't develop invasive *Candida* infections. The high sensitivity and negative predictive value (NPV) for invasive *Candida* infections, may make this marker an ideal candidate for utilization in antifungal stewardship efforts. Serum BDG has proven to be a reliable tool for antifungal treatment stratification [Posteraro 2016], particularly useful for guiding the cessation of empirical antifungal therapy [Sandhar 2022] [Bassetti 2024] due to its high NPV of ~90-95% [Bassetti 2024]. Given that serum BDG tests become negative under appropriate antifungal therapy (and are therefore also used for treatment monitoring) [Jaijakul 2012] it is important to obtain a sample for serum BDG testing before initiation of antifungal therapy, otherwise the NPV would decrease [Rautemaa-Richardson 2018]. Of note, sensitivity of serum BDG may be lower for diagnosing infections caused by *Candida auris* or *Candida parapsilosis* when compared to other *Candida spp.* [Mikulska 2016] [Farooqi 2021]. Multiple studies have demonstrated that negative serum BDG levels, if tested from samples drawn before initiation of systemic antifungal treatment, can be used to safely discontinue empirically initiated antifungal therapy in patients [Prattes 2014] [Nucci 2016].

Conversely, while serum BDG testing is valuable when used in a targeted approach, positive results from broad screening in ICU patients may not reliably justify initiating antifungal therapy in suspected cases of *Candida* infection. Data from a recent randomised controlled trials examining the use of antifungal therapy in ICU patients with sepsis at a high risk of *Candida* infection determined that, in this select group of at-risk patients, serum BDG guided initiation of antifungal therapy did not improve 28-day mortality and may be associated with overtreatment (i.e., treating patients with antifungals without invasive *Candida* infection) [Bloos 2022]. This suggests that the effectiveness of BDG as a diagnostic lies in its use within a more targeted approach. Serum BDG testing has also shown promise in diagnosing neonatal candidiasis [Cornu 2018] [Cohen 2020], and also *Pneumocystis jirovecii* pneumonia [Mercier 2019]. Of note, serum BDG has also proven reliable for predicting outcome in patients with candidemia [Agnelli 2020] [Esteves 2021]. The diagnostic potential of BDG in other patient materials remains limited, but CSF BDG testing has shown high sensitivity for diagnosing CNS *Candida* infections [Forster 2022], while high BDG titers in peritoneal fluid were associated with intra-abdominal candidiasis [Nourry 2023].

Diagnosis in the ICU - *Aspergillus*

The role of serum BDG for diagnosing invasive aspergillosis in the ICU is limited. This is primarily due to the invasive growth pattern of *Aspergillus*, which tends to remain localised in the airways, particularly in non-neutropenic ICU patients [Egger 2022], rather than disseminating into the bloodstream where BDG could be detected. As a result, serum BDG testing may not capture all cases of invasive pulmonary aspergillosis effectively. The challenges in diagnosing *Aspergillus* infections in non-neutropenic patients are well described [Colombo 2017], and while BDG may be useful as part of a broader strategy, its specificity limits utility for diagnosing *Aspergillus* infections. Furthermore, while BDG testing from urine has been explored as a potential adjunct to diagnosis, it has shown limited diagnostic potential [Raggam 2015], likely due to the variability in fungal dissemination and clearance patterns in the body. Consequently, alternative diagnostic tools, such as galactomannan combined with direct imaging, may be more effective for detecting invasive aspergillosis, especially in ICU patients.

Additional Considerations

While the high sensitivity of BDG testing is considered the main strength in the ICU setting, a positive result only indicates fungal cell wall components in the blood, which can occur even without invasive *Candida* infection. Fungi, alongside bacteria, are major components of the gut microbiome [Hallen-Adams 2017], including *Candida spp., Saccharomyces spp.* and other yeasts, as well as molds like *Aspergillus spp.* and *Fusarium spp.* [Witherden 2017]. The role of the fungal gut microbiome, the mycobiome, has garnered increasing attention in recent years. Researchers are now focusing on the mycobiome's role and dynamics in health and disease, as well as the important interactions between its microorganisms - bacteria, viruses, archaea, fungi [Zhang 2022] [Egger 2024]. For example, Kusakabe and colleagues recently found elevated anti-*Candida* IgG antibodies in severe COVID-19 patients with intestinal dysbiosis, *Candida* overgrowth and systemic neutrophilia [Kasakabe 2023], indicating that the mycobiome may contribute to lung hyperinflammation. This finding highlights that gut dysbiosis of the mycobiome may be a contributing factor to the immunopathology of severe COVID-19 disease. Although fewer studies have evaluated the lung mycobiome's role in driving hyperinflammation, both *Candida* colonization of the lung and higher levels of BDG in bronchioalveolar lavage fluid, where BDG has limited diagnostic utility due to frequent *Candida* and *Pneumocystis* colonization [Mutschlechner 2015], have been shown to predict mortality in ICU patients in the absence of any association with lung infection [Reischies 2016]. The mechanisms underlying these associations remains unclear. However, in another context, the fungal cell wall component BDG has not only been shown to be elevated in serum from patients living with chronic HIV [Hoenigl 2019] [Farhour 2018], advanced liver cirrhosis [Egger 2023], and other conditions associated with microbial translocation, including after abdominal surgery [Szyszkowitz 2018], but has also been identified as a marker of immune activation and thereby a driver of persistent inflammation, that correlates with clinical outcomes [Hoenigl 2019] [Weiner 2019] [Yang 2017] [Gianella 2019].

In Closing

In conclusion, serum BDG testing has a variety of important roles in the ICU population. Besides its diagnostic potential for invasive *Candida* and also *Pneumocystis* infections, serum BDG testing may be an effective tool for antifungal stewardship informing discontinuation of empirical antifungal therapy in patients that don't actually have *Candida* disease. For all indications a fast turnaround of the test, eg by utilizing the Fungitell STAT® assay [White 2021] or an automated Fungitell® assay protocol [Prüller 2014], can assure early discontinuation of antifungal therapy, thereby benefitting the patients and saving costs.

Hoenigl Bio:

Martin Hoenigl, M.D., Assoc. Prof., FECMM is an Associate Professor of Translational Mycology at the Division of Infectious Diseases, Medical University of Graz, Austria. He has obtained his venia docendi in internal medicine in 2012, and is author to over 300 pub med listed publications in the field of infectious diseases, the majority in leading authorships (i.e. first or last author; ORCiD: 0000-0002-1653-2824). Dr. Hoenigl has particular expertise in conducting research on clinical mycology, including fungal diagnostics and pharmacology of antifungal drugs and correlation with clinical findings. He is a past president of the European Confederation of Medical Mycology (ECMM), and the delegate of the Austrian Society for Medical Mycology (OEGMM). Dr. Hoenigl is also the founder of the ECMM Academy (together with Prof. Cornely) and serves as an associate editor for the journal Mycoses and deputy editor of Mycopathologia. Dr. Hoenigl has been awarded with the Researcher of the year 2011 award at the Medical University of Graz, and with the Research Promotion award 2014 of the German Speaking mycological society.

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