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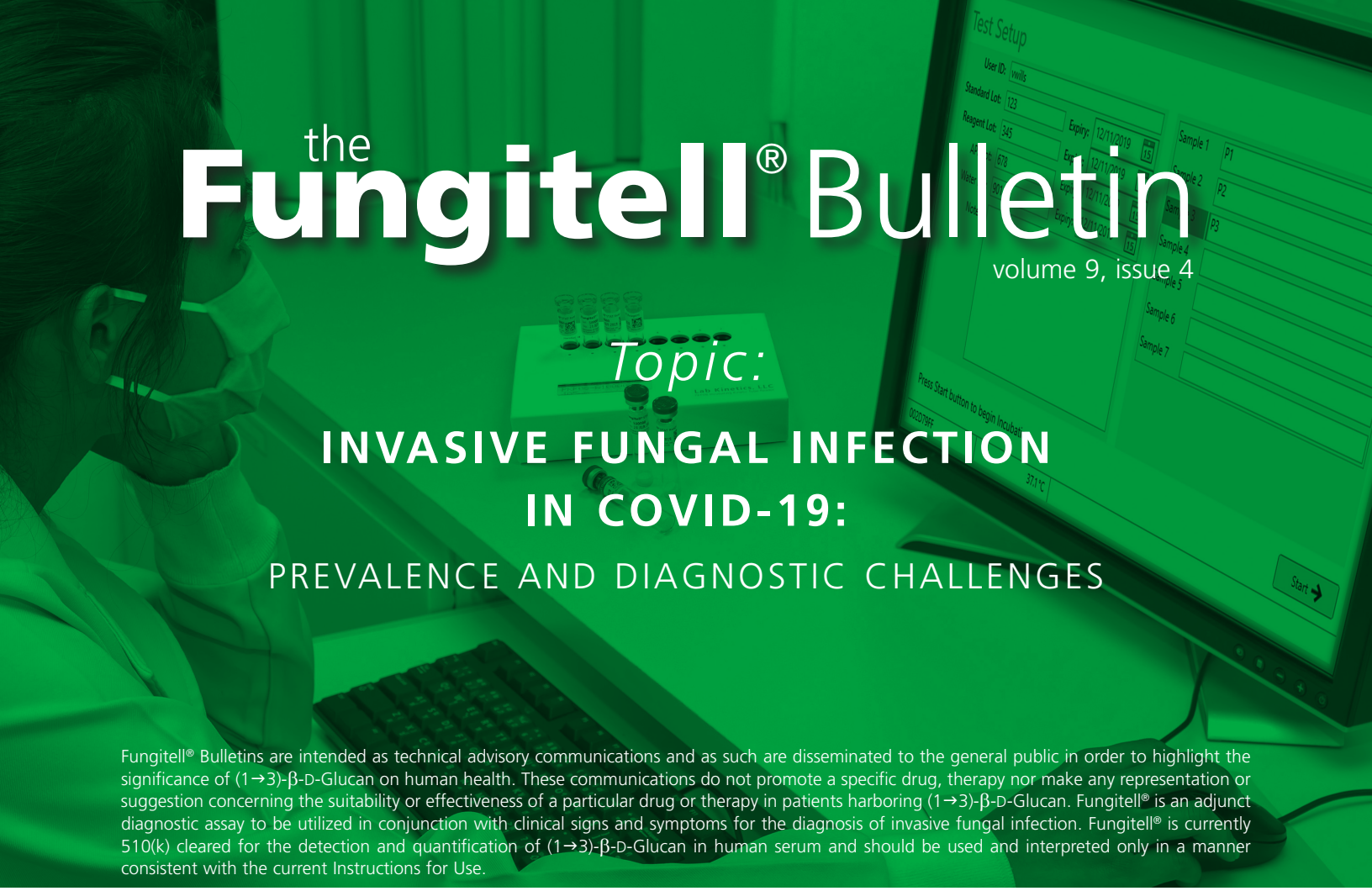

Topic:

INVASIVE FUNGAL INFECTION IN COVID-19:

PREVALENCE AND DIAGNOSTIC CHALLENGES

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 and quantification 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.

Discussion:

In the last few years, invasive fungal infection in the setting of severe influenza has been noted with a widely variable regional prevalence (Verweij, P.E. *et al.,* 2020). With the SARS-COV-2 pandemic, similar findings have been observed in COVID-19 patients with severe disease (Armstrong-James, D. *et al.,* 2021). Secondary or superinfections have been documented to occur in the ICU setting of COVID-19 patient care, especially in the ICU. Secondary fungal infection has been reported in many publications with highly variable attack rates and it is associated with greatly increased morbidity and mortality. The principal genera associated with these infections include *Aspergillus, Pneumocystis,* and *Candida* (Peman *et al.,* 2020; Frias De Leon, 2021). As with any invasive fungal disease, early diagnosis and appropriate antifungal therapy are key to better outcomes, however, in the setting of severe COVID-19, these are a complex challenge. (1→3)-β-D-Glucan (BDG) detection, employing Fungitell®, has been used as an aid to diagnosis in the setting of COVID-19 and suspected fungal coinfection. Selected aspects of this complication of COVID-19 are briefly reviewed below.

Aspergillosis:

The observation of COVID-19-associated pulmonary aspergillosis (CAPA) occurred early in the pandemic as a serious secondary infection (van Arkle *et al.,* 2020; Bruno et al, 2020; Bartoletti *et al.,* 2020; Verweij *et al.,* 2020; Beer *et al.,* 2020). Similarities with influenza-associated pulmonary aspergillosis were noted along with key diagnostic performance differences (lower serum galactomannan sensitivity), strong association with immunosuppressive therapy, and greatly increased morbidity and mortality (Bartoletti *et al.,* 2020; Hoenig, 2020). The incomplete understanding of diagnostic approaches were such that very early in the pandemic (May, 2020), Verweij *et al.,* (2020) called for evaluation of the performance of *Aspergillus* PCR, galactomannan, and BDG for COVID-19 patients suspected of aspergillosis and empirical therapy for patients with evidence of *Aspergillus* in bronchoalveolar lavage or serum. Similarly, White *et al.,* (2020) screened 135 adult COVID-19 patients and found evidence of invasive fungal disease in 26.7%; of these, 14.1% had aspergillosis and 12.6%, had yeast infections. A multi-pronged diagnostic strategy was employed including radiology, blood culture, PCR, galactomannan and BDG, but test combinations varied with subsets of patients. The criticality of diagnostic sensitivity and appro-

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priate antifungal therapy (AFT) to patient management was indicated by the observed mortality rates which were: Overall, 38%; CAPA, 57.9%; CAPA with AFT, 46.7%; CAPA absent AFT, 100%. Much debate concerning the prevalence of CAPA has resulted from diagnostic imprecision. However, in a COVID-19 autopsy series reported by Fortarezza et al (2021) 9/45 (20%) of the deceased had autopsy-proven histological evidence of invasive pulmonary aspergillosis. By contrast, Kula *et al.,* (2021) reviewed 50 studies with autopsy data for 677 decedents in whom invasive mould disease occurred at a level of 2% (11 cases), 8 of which were CAPA. In an autopsy series reported by Evert (2021), 8/17 patients who succumbed to were autopsied and 6 of the 8 were reported to have invasive mould disease, 3/8 had invasive pulmonary aspergillosis. All of the studies discussed the heterogeneity of methodologies, clinical settings, regions, host cohorts, etc. that might be associated with the wide range of their findings. Accordingly, while the problem of CAPA is recognized, the extent, the risk factors, and the most effective diagnostic strategies remain to be ascertained.

Pneumocystosis:

The overlap of clinical signs and symptoms observed in COVID-19 and *Pneumocystis jirovecii* pneumonia (PJP) patients has been much discussed in the literature (Peman *et al.,* 2020; Rubiano *et al.,* 2021; Jeican *et al.,* 2021; Broadhurst *et al.,* 2021; Mouren *et al.,* 2021). Case reports of secondary PJP in COVID-19 began appearing in the literature relatively early in the pandemic (De Francesco *et al.,* 2020; Menon A.A. *et al.,* 2020; Sajjad *et al.,* 2020; Kelly *et al.,* 2020). Accordingly, and especially in severe COVID-19 disease where patients might be intubated and immunosuppressed, diagnostic procedures capable of aiding in the establishment or rule-out of PJP are critical to its early recognition and appropriate patient management (Broadhurst, 2021). In addition, if *Pneumocystis* is determined to be present, the question of colonization or clear infection becomes pressing. Chong *et al.,* (2021) have reviewed case reports of PJP in the setting of COVID-19 and describe the diagnostic approaches utilized by various investigators in addressing this medical dilemma. Of the 12 cases presented, only three (25%) had utilized serum (BDG) in establishing the diagnosis of PJP. In all three cases, the BDG was very elevated, and in two of the three, the BDG titer was extremely elevated at 500 pg/mL. Both did not survive. The complexities of *Pneumocystis* infection in COVID-19 patients is considered in detail in an observational two center study by Alanio *et al.,* (2021). They reported *Pneumocystis* nucleic acid PCR positivity of respiratory specimens (BAL, tracheal aspirates, or sputum) in 10/108 patients (9.3%). Serum BDG was tested in four qPCR-positive patients and the results were <120 pg/mL which the authors described as being in line with the low qPCR results for these patients. Of nine *Pneumocystis*-PCR-negative tested for serum BDG titer, two had titers of 450 and 500 pg/mL, respectively which supported a diagnosis of pulmonary aspergillosis. This study presents the diagnostic difficulties associated with severe pulmonary disease, immunosuppression, the question of fungal colonization versus disease, and identification of organism. The findings clearly demonstrate the need for integration of multiple diagnostic modalities. While positive BDG titers are helpful in supporting a diagnosis of fungal infection, additional efforts to identify the genus are required in order to refine therapeutic strategies.

Candidemia:

In a single center study, Kayaaslan *et al.,* (2021) compared the incidence of ICU candidemia in non-COVID-19 patients during the period of Mar. 1, 2019 to Mar. 1, 2021 and of COVID-19 patients during Mar. 1, 2020 through Mar. 1, 2021. The candidemia rate per 100 patients was 1.9 and 0.5 for COVID-19, and non-COVID, respectively ($p<0.001$). The incidence rate was 2.16 and 1.06 per 1,000 patient days, respectively ($p<0.001$). The time to a diagnosis of candidemia was 13 and 27 days in COVID-19 and non-COVID-19, respectively ($p<0.001$) and mortality rates were 92.5% and 79.4%, respectively. Corticosteroid use in the COVID-19 patients was considered to be a major factor in the fungal attack. Similarly poor relative outcomes were observed by Seagle *et al.,* (2021) in a USA-based, ten state candidemia surveillance-based study of 251 candidemia patients. Those with a diagnosis of COVID-19 in the 30 days prior to positive *Candida* culture had approximately twice the mortality as those without a COVID-19 diagnosis, 62.5% vs. 32.1%, respectively. Of significant interest, 25% of the institutional candidemia cases reported for the study period, April to August, 2020, had a positive COVID-19 diagnosis. The authors observed a significantly longer length of stay prior to positive *Candida* culture for the COVID-19 patients, suggesting a health care-associated etiology. The development of candidemia in the later stages of COVID-19-related ICU stay was also observed in a single center study In another single center study by Kokkoris *et al.,* (2021) in which, during a nine week period with 50 ICU admissions, 7/50 (14%) patients were diagnosed with candidemia beginning at Day 34. Nucci *et al.,* (2020) reported that pre- and post-pandemic candidemia rates were 1.54 and 7.44 per 1,000 admissions, respectively. Detailed analysis showed that factors affecting the rise in the candidemia rates included sicker patients admitted during the pandemic period and higher rates of candidemia among the COVID-19 patients. In a similar vein, Mastrangelo *et al.,* (2020) reported that in an admitted for any reason cohort study, non-COVID-19 vs. COVID-19-associated candidemia had a frequency of 1.48 and 10.97 per 10,000 person-days of follow-up, respectively. When only ICU patients were considered, the frequency was 14.46 and 81.68, respectively. Appropriate diagnostic and therapeutic approaches are critical to outcome as observed by White et al (2020) who observed that COVID-19 patients with invasive *Candida* infections had an overall mortality rate of 47.1%. Those with appropriate antifungal therapy had a mortality rate of 27.3% while mortality for those without was 83.3%. Accordingly, whether originating from single center or broad survey studies, the pattern remains the same, candidemia in the setting of COVID-19 is a serious concern, especially in the ICU, with longer stays.

Conclusion:

The significant invasive fungal attack rate in COVID-19 patients, the very high morbidity and mortality, the diversity of genera involved, and the clear benefits of early and appropriate antifungal therapy where indicated represent a need for prompt, aggressive use of all available diagnostic modalities.

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