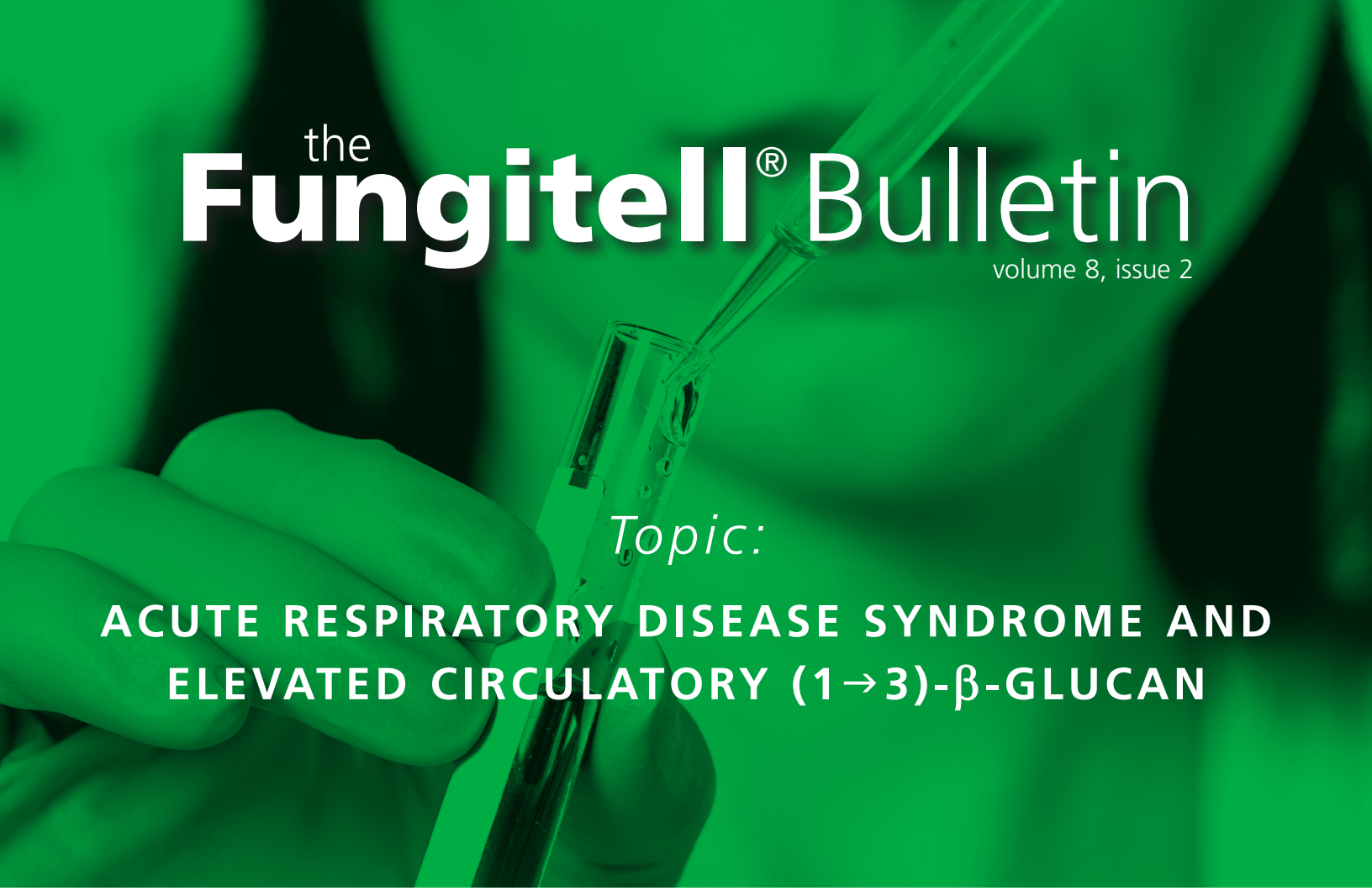

the Fungitell® Bulletin

volume 8, issue 2

Topic:

ACUTE RESPIRATORY DISEASE SYNDROME AND ELEVATED CIRCULATORY (1→3)-β-GLUCAN

Discussion:

Observations of elevated serum (1→3)-β-glucan (BG) in the absence of evidence of invasive fungal disease (IFD) have been noted in diagnostic performance investigations.[1,2,3,4] These observations have been described in a variety of clinical conditions and are associated with increased symptom severity and worse outcomes. As these BG titer determinations are analytically correct, and with IFD ruled out, investigators have been interested in establishing the source of the circulating BG. To date, the association of elevated serum BG, in the absence of IFD, has been observed in septic shock, hepatitis C infection, cystic fibrosis, chronic kidney disease, large surface area burns, HIV positivity, systemic lupus erythematosus, and mechanically ventilated patients.[5,6,7,8,9,10,11,12] At this point, in human patients, definitive proof of the origin of the (1→3)-β-glucan has been lacking, but a number of factors suggest that translocation from the intestinal lumen is the source, due to a damaged intestinal mucosal permeability barrier. Data from animal studies support translocated, gut-originating BG as a factor exacerbating inflammation, pathophysiology, and mortality.[5,13] Fungitell-detectable BG is a high molecular weight material, with a molecular weight of at least 6,800 Daltons being required for activation.[14] Thus, it is reasonable to assume that if BG is entering the bloodstream by translocation from the intestinal lumen, other pathogen-associated molecular patterns (PAMPs) such as Toll-Like Receptor (TLR) ligands and nucleotide-binding oligomerization domain-like (NOD) receptor ligands may also be translocating. Co-exposure to ligands of any two classes of PAMP has been demonstrated to elicit synergistic inflammatory responses in a human blood exposure model.[15] Similar findings were observed in human macrophage culture exposure models.[16,17] Accordingly, a mechanistic basis exists for exacerbated inflammatory pathophysiology due to leaky gut.

The setting of invasive mechanical ventilation (IMV) is of particular interest due to its prevalence among critical care patients and high morbidity and mortality.[18] Mehta et al (2015) reported an IMV rate of 310.9/100,000 adults in the USA.[19] Serum BG in the setting of IMV has been investigated and elevated BG titers were observed to be associated with poor outcomes. Heyland et al (2011) evaluated the outcomes of 57 patients suspected of ventilator-associated pneumonia, but without IFD. They found that serum BG titers ≥ 80 pg/ml (Fungitell® assay) were associated with an overall mortality odds ratio of 4.2, relative to BG-negative patients (< 80 pg/ml).[20] Similarly, Kotok et al (2019) presented data from a study of 220 mechanically ventilated critically ill patients.[21]

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43/220 (20%) were considered BG-positive with titers ≥ 60 pg/ml. Among patients with positive BG titers, the 30 day mortality was 44% while among those with negative titers, the mortality rate was 19%. Ventilator-free days were significantly lower among the BG-negatives versus positive ($p<0.001$).

Intestinal hypotension, one of the sequelae of pulmonary insufficiency, is associated with mucosal barrier injury as routinely observed in ischaemia-reperfusion injury (IRI) models. Further, the addition of *Candida albicans*, a human intestinal commensal, to the gut in a rat IRI model has been shown to exacerbate inflammatory markers and markers of gut mucosal barrier damage.[22]

Taken together, the above-described observations suggest that, in the setting of IMV, elevated serum BG may be driven by intestinal mucosal barrier impairment and participate in the exacerbation of pathophysiology. These observations may help to understand the so-called false positive serum beta-glucan titers observed with certain critical care patients. Additional studies are warranted and several are ongoing.

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