

References

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Reply to Blaize et al.

From the Authors:

We thank Dr. Blaize and colleagues for their interest and letter in response to our recent publication detailing a case of suspected coronavirus disease (COVID-19) and *Pneumocystis jirovecii* coinfection (1). The authors correctly note that the decline in serum (1,3)-β-D-glucan level observed in our patient was more rapid than is typically expected following initiation of appropriate therapy (2). Several studies have demonstrated that (1,3)-β-D-glucan is not a reliable biomarker of response to *P. jirovecii* treatment (3); however, in some patients, such as ours, decreasing (1,3)-β-D-glucan levels have been shown to correlate with improved clinical outcomes in *Pneumocystis pneumonia* (4). In our patient, the serum (1,3)-β-D-glucan level was elevated at 305 pg/ml on admission, remained persistently elevated at 268 pg/ml on hospital Day 3, at which point trimethoprim-sulfamethoxazole treatment was initiated, and then declined to 90 pg/ml 1 week after initiating treatment.

The diagnosis of *P. jirovecii* infection can be challenging, particularly in patients without HIV, in whom the fungal burden is generally lower (5). Furthermore, owing to the high sensitivity of *P. jirovecii* PCR (6), it may be difficult to differentiate between *Pneumocystis* colonization versus infection, particularly in the setting of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which may have similar clinical manifestations as *Pneumocystis pneumonia*. Nevertheless, the

constellation of an elevated (1,3)-β-D-glucan level on two occasions, positive tracheal aspirate qualitative PCR assay, presence of typical cystic changes of *P. jirovecii* on chest computed tomography, and rapid clinical improvement following initiation of trimethoprim-sulfamethoxazole therapy support our conclusion that our patient indeed had a true *P. jirovecii* infection. It is worth noting that several studies have suggested that quantitative *P. jirovecii* PCR and (1,3)-β-D-glucan may be used to distinguish between *Pneumocystis pneumonia* and colonization (7, 8). Specifically, a positive quantitative PCR from a BAL fluid sample ($>1.6 \times 10^3$ DNA copies/μl) and a (1,3)-β-D-glucan level cutoff of 100 pg/ml has been suggested to discriminate between *P. jirovecii* colonization versus infection (8). Gold-standard staining methods to detect *P. jirovecii* in respiratory specimens are also useful to confirm *P. jirovecii* infection, although the sensitivity is low compared with PCR, particularly in HIV-negative immunocompromised patients (9–11). Unfortunately, we do not have quantitative PCR or cytologic/immunofluorescent staining data from our patient, which would have further strengthened our argument for true *P. jirovecii* infection.

Dr. Blaize and colleagues performed quantitative *P. jirovecii* PCR testing on 423 respiratory samples obtained from 145 patients at their center with confirmed SARS-CoV-2 infection who required either mechanical ventilation or venovenous extracorporeal membrane oxygenation support. Despite the high prevalence of lymphocytopenia in this population of critically ill patients with COVID-19, there were no true cases of *P. jirovecii* coinfection. In our patient with SARS-CoV-2 and *P. jirovecii* coinfection, other than COVID-19-associated CD4⁺ lymphocytopenia, she did not have a known underlying immunodeficiency. She was on oral budesonide for treatment of her ulcerative colitis, which was well controlled, and an albuterol inhaler as needed for mild intermittent asthma (1), but not inhaled corticosteroids as suggested by the authors. Oral budesonide formulations provide topical antiinflammatory activity in the colon but have very little systemic bioavailability owing to their high first-pass hepatic metabolism. As such, oral budesonide formulations have not been associated with increased risk of *P. jirovecii* infection in patients with ulcerative colitis (12). Although our patient did not have any other classical risk factors for *P. jirovecii* infection, it is certainly possible that her coinfection was a coincidence (a proof of principle of “Hickam’s dictum” [13]) or that an unbeknownst underlying immune defect predisposed the patient independently to SARS-CoV-2 and *P. jirovecii* infection.

Given the inherent risk of overextending conclusions from a single case, we were conservative in the interpretation of our case and suggested that it may be reasonable to consider additional diagnostic testing for *P. jirovecii* by assaying serum (1,3)-β-D-glucan in patients with COVID-19 if there are additional clinical findings, such as cystic findings on chest computed tomography or elevated lactate dehydrogenase that may support coinfection (1). This approach should be considered particularly in patients with classical *P. jirovecii* risk factors such as HIV, as coinfection with SARS-CoV-2 and *P. jirovecii* has been reported in both well-controlled (14) and severely immunocompromised patients with HIV (15, 16). We commend the authors for their work and for expanding the COVID-19 evidence

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base by systematically testing the hypothesis generated by our initial clinical observation. At a minimum, their data provide reassurance that the risk of *P. jirovecii* coinfection in patients with COVID-19-related lymphocytopenia is likely not high. Further understanding of the clinical features of this novel disease requires a continued collaborative and systematic approach. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Control of Respiratory Drive by Noninvasive Ventilation as an Early Predictor of Success



To the Editor:

Early prediction of failure of noninvasive ventilation (NIV) in patients with *de novo* acute hypoxemic respiratory failure is crucial to prevent patient self-inflicted lung injury and avoid delayed intubation. NIV should cope with the elevated respiratory drive to deliver effective yet still protective ventilation. However, drive increases for many different reasons: lung collapse and shunt lead to hypoxia, high dead space and elevated metabolic demand raise the concentrations of CO₂, lung inflammation and altered mechanics activate chemoreceptors and mechanoreceptors, and anxiety and subjective discomfort act on the neural respiratory drive, amplifying the response to chemical and mechanical stimuli (1). The clinical study by Tonelli and colleagues (2) testing the hypothesis that inspiratory effort estimated by esophageal balloon manometry might be an early predictor of NIV failure and worsening lung injury is a valuable addition to the field. Tonelli and colleagues report that lack of reduction in the swing of esophageal pressure (ΔP_{es}) after 2 hours from start of NIV is an accurate predictor of NIV failure.

According to the study protocol, pressure support (PS) was initially set at 10 cm H₂O and then modified to maintain the expired V_T (V_{Te}) of <9.5 ml/kg predicted body weight (PBW) and the respiratory rate of <30 breaths/min. Of note, as a consequence of these per-protocol adjustments, PS level at 2 hours was significantly lower in the NIV failure group, whereas V_{Te} did not differ (3). As pointed out by Tuffet and colleagues (4), the amount of assistance during NIV influences the respiratory effort, and they

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