

LETTER

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# *Pneumocystis jirovecii* pneumonia in COVID-19: an overlooked clinical entity—Response to “Pneumocystis pneumonia risk among viral acute respiratory distress syndrome related or not to COVID 19”

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## To the editor,

We read with great interest the article published in *Critical Care* by Razazi et al. reporting no cases of *Pneumocystis jirovecii* pneumonia (PJP) among intubated patients with acute respiratory distress syndrome (ARDS) secondary to COVID-19 (C-ARDS) [1].

The authors compared these results with a historical cohort of non-COVID-19 ARDS (NC-ARDS). They showed a higher incidence of proven PJP and PCR positivity (without a diagnosis of PJP) in respiratory samples in NC-ARDS than in C-ARDS (0.05% and 13% vs 0% and 0%, respectively) [1].

However, patients in study by Razazi et al. are enrolled during the first period of pandemic, when dexamethasone was not strongly recommended and, surprisingly, they found a more profound lymphopenia in NC-ARDS. Moreover, in NC-ARDS group 82% of enrolled patients were immunocompromised compared to 13% of C-ARDS [1].

Conversely, we have published 5 cases of proven PJP in immunocompetent hosts in late phase of COVID-19 disease [2, 3]. According to EORTC/MSGERC diagnostic criteria, we observed that the use of steroids was the most frequent host factor that predispose to PJP [4].

Moreover, Razazi et al. showed that the two proven PJP diagnosis in NC-ARDS cohort had Beta-D Glucan assay (BDG) > 80, while in our experience we documented negative BDG in all the proven cases.

In the end, we think that the absence of PJP cases in C-ARDS cohort may have been influenced by the phase of COVID-19 clinical course and lower dosage of steroids administered, while the higher prevalence of PJP diagnosis and qPCR positivity in NC-ARDS cohort should be led back to the high prevalence of immunocompromised patients enrolled.

Therefore, since either lymphopenia or steroidal treatment are strongly associated with the risk of PJP development, further studies are needed to detect any other risk factor for developing PJP in COVID-19 and to design any potential prophylactic strategies. Nevertheless, it is noteworthy that BDG assay has a high negative predictive value in HIV positive patients for PJP diagnosis, while it is less clear the real power of this test in other settings such as immunocompetent patients and COVID-19.

In conclusion, the pathogenesis of PJP in late COVID-19 and the role of BDG and of PCR in predicting development of PJP must be further investigated, and PJP should be taken into account in differential diagnosis of respiratory relapse in late COVID-19 by obtaining invasive samples (bronchoalveolar lavage), since BDG seems to have a low negative predictive value in this setting.

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## Authors' response

Romain Arrestier, Armand Mekontso-Dessap,  
Francoise Botterel and Keyvan Razazi

### To the Editor,

We thank Buonomo and colleagues for their comment that our finding of a very low risk of *Pneumocystis* pneumonia in COVID-19 patients with acute respiratory distress syndrome (ARDS) stands in contrast to their experience on *Pneumocystis* pneumonia in COVID-19 patients.

We agree that enrolment of patients during the first wave may be a limit of our study because of a lower use of steroid therapy. To explore further this potential bias, we analyzed 239 consecutive COVID-19 patients, hospitalized in our intensive care unit during the following waves from May 26th 2020 to April 11th 2021 (*Anticovid study Clinical trials NCT04433105*). All were treated with steroids, 39 (16.3%) with tocilizumab and 29 (12.1%) were immunocompromised.

Of these, 73 had a *Pneumocystis* examination, including 131 PCR and 107 direct examinations (43 May Grunwald Giemsa stainings and 64 Grocott colorations) which were all negative. Only three patients (4%) had a positive PCR with a cycle threshold range of 35.5–37. All were classified as *Pneumocystis* colonization. Two of them did not have any pre-existing risks factors besides 10 days of steroid for COVID-19 and had a negative  $\beta$ -D-glucan. One patient with liver transplantation and long-term steroid therapy and calcineurin inhibitor treatment had a positive PCR with only one low titer positive  $\beta$ -D-glucan (178 pg/mL); he was classified as *Pneumocystis* colonization because his state improved without trimethoprim-sulfamethoxazole treatment.

The five patients described by Gentile and al [2] were very different from those of our cohort. None of them had ARDS requiring invasive mechanical ventilation, and they were surprisingly all treated with steroids with a very high cumulative dose of steroid (range from 400 to 1150 mg prednisone equivalent) and a longer duration than recommended.

The authors did not specify if they received a trimethoprim-sulfamethoxazole prophylaxis. In our intensive care unit, we systematically prescribed a prophylaxis as suggested if the steroid dose is higher than 0.3 mg/kg/d equivalent prednisone for at least 3 weeks, whatever the disease [5, 6]. This could explain the difference between our observation and those from Gentile and al.

In a recent meta-analysis, a negative BDG test to 'rule out' PJP with 95% certainty (post-test probability of 5%) requires that the pre-test probability be low (< 20%), as in COVID-19 patients [7].

Altogether, these data confirm that even when steroid therapy was the standard of care, *Pneumocystis* pneumonia risk is very low among patients with COVID-19 related ARDS even in immunocompromised patients.

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All the authors have equally contributed.

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#### Ethics approval and consent to participate

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#### Consent for publication

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Authors have no competing interests to disclose.

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