Candidaemia in COVID-19, a link to disease pathology or increased clinical pressures?

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Dear Editor:

With UK reports describing a significant incidence of invasive candidal disease (IC) in critically-ill COVID-19 patients, we were intrigued to see that other countries, heavily affected by the COVID-19 pandemic, were also documenting this secondary complication. [1-5] Mastrangelo and colleagues correctly highlighted that we did not indicate whether the incidence of IC in our primary COVID-19 study was higher than the non-COVID-19 population. [1, 3] Their study confirmed that IC incidence was increased in COVID-19 patients, linked to intensive care management and the use of immunosuppressive agents. Our study only involved critical-care patients, the use of the immunomodulatory therapies was not widely documented and no significant risks for developing IC were identified. [1]

In response to Mastrangelo and colleagues, the incidence of IC in non-COVID-19 and COVID-19 critically-ill patients was compared. Analysis of two non-COVID-19 populations was undertaken, using a pre-COVID-19 population of 157 critically-ill patients admitted over a similar period during 2019 and 48 non-COVID-19 critically-ill patients, admitted alongside COVID-19 patients during the first wave of the pandemic. This comparative analysis would indicate whether COVID-19 directly increases the risk of IC. For proportionate values ninety-five percent confidence intervals and, where required, *P* values (Fishers exact test; *P*: 0·05) were generated.

In the Pre-COVID-19 population 2/157 (1.3%) patients had a documented invasive yeast infection (Table 1), similar to rates typically seen in UK critical-care units (<1%). [6] A further six line infections were documented, generating a combined IC rate of 5.1% (95% CI: 2.6-9.7). During the first wave of COVID-19 in Wales there were 12 (6.6%, 95% CI: 3.8-11.1) documented fungaemias and 12 documented line infections, generating a combined rate of 22/183 (12.0%, 95% CI: 8.1-17.5. NB: two patients with line infections developed candidaemia), significantly greater than rates prior to COVID-19 (Difference: 6.9%, 95% CI: 0.8-13.0; *P*: 0.0336). However, there was no significant difference in the rates of IC during the first wave of COVID-19 for patients with or without PCR-confirmed COVID-19 (Difference: 2.2%, 95% CI: -10.4–11.1; *P*: 0.8006).

Our current understanding of the host's immune dysfunction due to COVID-19 leads to the hypothesis that it is not a major factor in IC. [5] While, hyper-inflammatory disruption of respiratory mucosal membranes does provide the opportunity for commensal *Candida* to become invasive, our data suggests that the increased IC rates during COVID-19 are not directly associated with the disease itself. Other factors, including classical clinical risk factors (e.g. Central lines, antibiotics etc.), sepsis enhanced translocation of gut microbiota, a switch in the composition of microbiota promoting commensal/colonizing *Candida* or altered practice during the pandemic warrant further investigation. [3, 5] The necessity for extracorporeal membrane oxygenation (ECMO) and the use of corticosteroids in COVID-19 have been suggested as specific risk factors, but ECMO was not used in our patients and no significant association with corticosteroids was found. [1, 5]

Managing significant numbers of complex patients while wearing extensive personal protective equipment may have influenced infection prevention and control practice. However, while fungaemia rates were significantly lower prior to COVID-19 (Difference: 5.3%, 95% CI: 1.0-9.9; *P*: 0.0146), rates of line infection (typically an infection control issue) were not significantly different (Difference: 2.7%, 95% CI: -2.4–7.7; *P*: 0.3340). Maintaining a pre-COVID-19 standard of oral care in critical-care patients is difficult due to COVID-19 infection control concerns, subsequent increased oropharyngeal *Candida* colonization combined invasive ventilatory support may have enhanced IC. *Candida albicans* was the predominant (79.4%) species isolated irrespective of COVID-19 status, so the report by Rodriguez and colleagues confirming significant IC in COVID-19 patients caused by predominantly non-*albicans* species, including *Candida auris* highlights geographical variability. [4] Over the past five years only a single patient in Wales had *C. auris* isolated, so its absence from our cohorts is not unexpected and opposite to Colombia, where *C. auris* is endemic in certain regions, leading to healthcare transmission and outbreaks. [7, 8] As *Candida auris* has been predominately identified as a healthcare associated infection this potentially suggests that the increase is related to a change in practice associated with the pandemic and the impact of potentially unnecessary use of azoles in driving the emergence of resistant species. While the mortality rate in the Colombian study

was higher than that documented in Wales, it is unclear if this is associated with a delay in appropriate antifungal therapy, particularly in cases of non-*albicans* candidaemia

It appears that IC is a significant complication of severe COVID-19 infection, but not necessarily directly associated with the disease itself, and it is essential that further research improves our understanding of risk. Active surveillance for IC and knowledge of local epidemiology is critical to minimizing the deleterious effects of this secondary infection.

Potential Conflicts of Interest

PLW reports personal fees from Gilead, Pfizer, F2G, and MSD, and meeting sponsorship from Dynamiker, Bruker, and Launch, outside the submitted work. RD reports expert opinion fees from MSD and an educational grant from Gilead Sciences, outside the submitted work. MB reports personal fees from Gilead and meeting sponsorship from Abbvie, outside the submitted work. All other authors have no potential conflicts.

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Table 1. The rates of yeast infections in critical-care patients prior to and during the first wave of the COVID-19 pandemic in Wales

Population	Documented line infections	Causative Agent	Documented invasive yeast infection	Causative Agent
Pre-COVID-19 ICU 03-05/2019 (n=157, (%, 95% CI))	6 (3.8, 1.8-8.1)	*C. albicans* (n=6)	2[a] (1.3, 0.4-4.5)	*C. albicans* (n=1) *C. glabrata* (n=1)
Non-COVID-19 03-05/2020 (n=48, (%, 95% CI))	3[b] (2.1, 0.4-10.9)	*C. albicans* (n=3)	4[b, c] (8.3, 3.3-19.6)	*C. albicans* (n=4)
COVID-19 03-05/2020 (n=135, (%, 95% CI))	10[d] (7.4, 4.1-13.1)	*C. albicans* (n=7) *C. parapsilopsis* (n=1) *Candida* sp. (n=1) Unidentified Yeast (n=1)	8[d, e] (5.9, 3.0-11.3)	*C. albicans* (n=6) *C. parapsilopsis* (n=1) *Rhodotorula* sp. (n=1) Unidentified Yeast (n=1)

[a] One candidaemia and one *Candida* positive tissue biopsy

[b] Two patients with documented candidaemia also had positive line cultures.

[c] All candidaemia.

[d] One patient with documented candidaemia also had a positive line culture.

[e] Six candidaemia, one *Candida* ascites and one *Rhodotorula* fungaemia, one patient had candidaemia with *C. albicans* and *C. parapsilopsis*