Invasive fungal diseases during COVID-19: We should be prepared

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The epidemic of respiratory infection due to the new coronavirus SARS-CoV-2 that emerged by the end of 2019 in China is now pandemic and associated with a huge number of deaths. The mortality rate greatly varies between countries, with an unexplained high rate in some of them. Among various causes of morbidity and mortality in COVID-19 patients, the frequency and impact of co-infections has still been poorly studied, particularly in patients with an acute respiratory distress syndrome (ARDS).

Invasive fungal infections (IFI) during COVID-19 are still rarely reported and may be underdiagnosed

Some gripping epidemiological points must be underlined:

(i) Risk factors. Patients hospitalized in intensive care units (ICU) for COVID-19 share risk factors and underlying diseases reported for IFI, particularly chronic respiratory diseases, corticosteroid therapy, intubation/mechanical ventilation, cytokinic storm etc…

(ii) Incidence. Recent Chinese publications reported at least 10% of co-infection during COVID-19 in patients hospitalized in ICU for ARDS, among them *Aspergillus* infections (1-2). Besides, the incidence of invasive pulmonary aspergillosis (IPA) in ICU patients admitted for severe influenza A and B is high, reaching 19% versus 5% in patients with severe pneumonia other than flu (3).

(iii) Mortality. We still don't know exactly how fungal co-infection impacts on mortality but are aware of the dramatic impact of influenza/IPA co-infection with a mortality reaching 23% in some European centers (4-5). In the study by Schauwvlieghe, the 3-month mortality rate of influenza is 51 % when associated with IPA and 28% without IPA (3).

Besides, the particular pathophysiology of COVID-19 may also account for unprecedented co-morbidity with IFI. First, the high aggressive feature of the SARS-CoV-2 virus to the lung tissue and the large bilateral alveolo-interstitial lesions make the occurrence of IFI very likely, specifically those with a primary pulmonary entry and an airborne route of infection such as IPA, pneumocystosis (PjP) and mucormycosis (6). Second, absolute number of T lymphocytes, CD4+T and CD8+T cells are markedly lower in severe COVID-19 cases than moderate cases, associated with markedly higher levels of IL-2R, IL-6, IL-10, TNF-alpha and some other inflammatory markers (7).

What we still don't know

- Numerous studies will be implemented in ICU patients, particularly in patients with ARDS, because a performant diagnosis for IFI will usually be available. It will be more complicated to evaluate the dynamic of colonization, the risk of chronic and allergic fungal diseases, and at a lower extent the risk of invasive fungal diseases in non-hospitalized patients while chronic respiratory diseases and long-term corticosteroid therapy may be part of risk factors.

- The balance between underlying disease and COVID-19 as attributable risk factors for fungal infection will be difficult to appreciate. That's why large surveys and registries with sufficient description of the patient characteristics are mandatory.
- Will we propose the optimal diagnostic tools to ensure a correct survey? In particular, numerous laboratories have stopped some manipulations of at risk respiratory samples such as direct examination, or galactomannan determination in respiratory samples. Besides, the performances of some blood biomarkers such as galactomannan, beta-D-glucan or DNA detection are well evaluated in neutropenic patients but far less in other conditions.

What we should do

In France, IFI account for a high risk of mortality in patients with co-morbidities from 9.2% to 40% depending on the fungal disease (8). IA is notably diagnosed in neutropenic patients, patients under chemotherapy, particularly for hematological malignancies, prolonged corticosteroid therapy or biotherapy, HSCT allografts or solid organ transplantation, or chronic respiratory diseases. PCP is an opportunistic infection diagnosed in lymphopenic patients, patients co-infected with HIV, and patients suffering from hematological malignancies, solid organ transplantation or chronic respiratory diseases. Invasive mucormycosis is increasingly reported (thanks to the improvement of diagnostic tools) in susceptible patients such as those suffering from diabetes, hematological malignancies, solid organ transplantation or chronic respiratory diseases and superficial injuries in burned patients or after local traumatism. Using local and literature data, the global burden of severe fungal infection is estimated approximately 1,000,000 (1.47%) cases in France each year (9).

We believe that microbiological diagnosis should be promptly adapted to the current unprecedented situation. In accordance with the preliminary data available concerning the occurrence of IFI in COVID-19 patients, the French High Council for Public Health (HSCP - Haut Conseil de la santé publique) recommends to systematically screen for fungal pathogens in patients admitted with pneumoniae (10). Among the 5 first well described French patients, one is co-infected with *Aspergillus flavus* (11).

In this context, vigilance is essential and we consider that a large panel of tools must be proposed to better characterize the epidemiology of IFI during this striking pandemic:

-local implementation of diagnostic tools to optimize the early diagnosis in order to allow a prompt specific antifungal treatment and to optimize the management of the patients. A 2-step process could associate an efficient syndromic molecular approach (qPCR for *Aspergillus*, *Pneumocystis jiroveci*, and mucorales) associated to culture for respiratory samples. In case of positivity of any of these tests, a confirmation step with blood biomarkers will be implemented depending on the positive results, with serum galactomannan and/or serum beta-D-glucan and/or cryptococcal antigenemia and/or blood qPCR for *Aspergillus* or mucorales,

- national multicentric studies that aim to explore the risk of fungal co-infection during COVID-19 with joint consortia of ICU and Mycology specialists. The French Society for Medical Mycology (SFMM) will be supportive for these studies,

- contribution to national (Centre National de Référence Mycoses Invasives et Antifongiques, https://www.pasteur.fr/fr/sante-publique/CNR/les-cnr/mycoses-invasives-antifongiques) and international registries such as the one endorsed by the European Confederation of Medical Mycology (ECMM, https://data.castoredc.com/).

Our collective goal is :

- To provide original and still unknown epidemiological data focused on fungal infections during COVID-19; better evaluate the incidence and the dynamic of fungal infection in the course of COVID-19, particularly during the ICU stay.

- To improve the diagnosis, in proposing an efficient syndromic molecular approach for fungal respiratory infection during ARDS that can be shared with all hospitals receiving COVID-19 patients

- To optimize immediate COVID-19 patient management, with a real-time screening in order to introduce as early as possible a targeted treatment. First-line treatment for aspergillosis, pneumocystosis and mucormycosis are far different and empirical treatments will be avoided as much as possible. Depending on the epidemiological data obtained, preventive strategies such as antifungal chemoprophylaxis and environmental measures could be envisaged with the aim to decrease morbidity and mortality.

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