Short Review

COVID-19 associated Aspergillosis

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ABSTRACT

Invasive pulmonary aspergillosis (IPA) may complicate severe COVID-19 patients. The incidence, although is not well confirmed, varies (20-35%) and the already recognized host factors for IPA in immunosuppressed patients are not identified in non-immunocompromised patients with COVID-19 associated pulmonary aspergillosis (CAPA). Additionally, clinical characteristics and radiological findings are not specific. Given the probable high burden of the co-infection, a screening diagnostic work-up, including serum and BAL galactomannan measurement, fungal cultures of upper and lower respiratory tract samples are considered mandatory in all mechanically ventilated patients with COVID-19.

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Key words:
- Covid-19 associated pulmonary aspergillosis
- Invasive pulmonary aspergillosis
- Galactomannan

Abbreviations:
IPA: Invasive pulmonary aspergillosis
CAPA: COVID-19 associated pulmonary aspergillosis
BAL: bronchoalveolar lavage

Patients with severe coronavirus disease 2019 (COVID-19) are at increased risk of secondary infections, including invasive fungal infections. Such cases of invasive pulmonary aspergillosis (IPA) complicating COVID-19 disease are reported in the literature. IPA is well described in immunocompromised patients where certain risk factors, mainly neutropenia and steroid treatment, have been identified. Also patients with severe influenza are susceptible to IPA, possibly due to respiratory epithelium damage and local anosoparalysis. Similar pathophysiologic mechanisms, with lung damage due to viral replication and cytokine storm in combination with immune dysregulation, characterize COVID-19 associated pulmonary aspergillosis (CAPA).[1]

The incidence of CAPA is unknown and may be underestimated while the used diagnostic criteria differ among the different studies. Van Arkel et al identified 6/31 **(incidence 19,4%)** COVID-19 patients with presumed IPA, based on the diagnostic criteria included in influenza-associated pulmonary aspergillosis case definition proposed by an expert panel[2,3]. In this study tracheal aspirate and bronchoalveolar lavage (BAL) culture and serum and BAL galactomannan assays have been used to confirm the diagnosis while all patients were treated with antifungals. In another prospective study with 27 mechanically ventilated patients with COVID-19, probable IPA was diagnosed in one (4%) and putative IPA in 8 patients **(incidence 30%)**. The cultures from respiratory specimens (BAL or bronchial aspirate), have been

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collected three days after intubation while serum and BAL galactomannan levels in combination with serum β-D-glucan and quantitative real-time PCR (qPCR) in the serum or pulmonary specimens were used for the diagnosis. However, only two (2/9) patients received antifungal treatment[4]. Rutsaert et al reported that among 20 intubated patients with COVID 19 pneumonia, 7 **(incidence 35%)** were suspected of IPA. In this study the AspICU algorithm was used for the evaluation of the patients[5]. Four patients demonstrated proven IPA based on histopathological examination, one patient had negative histopathological examination but positive assays for galactomannan in BAL and serum, 2 patients had positive culture and/or BAL galactomannan post mortem while 6/7 patients received antifungal treatment with voriconazole or isavuconazole[6]. In a retrospective study, putative IPA was diagnosed in 5/19 **(incidence 26%)** patients with COVID 19 - associated ARDS. For the diagnosis of IPA the modified AspICU algorithm was used also. A positive galactomannan test (≥1) in BAL or tracheal aspiration fluid or in two consecutive serum samples were also regarded as entry criteria. All patients received antifungal treatment[7]. All the published until today studies contain a small number of patients but the key message is that the incidence of CAPA varies between 20-35% and depends on the used diagnostic criteria and the thresholds adopted in order to start antifungal treatment.

In the majority of patients with a definite diagnosis of CAPA the "conventional" host factors are not recognized[3,7]. Most of the patients are immunocompetent, fact that limits the role of European Organization for Research and Treatment of Cancer Mycoses Study Group (EORTC-MSG) consensus criteria for the diagnosis of IPA[4]. Also, the clinical characteristics do not differ among patients with and without CAPA[3]. Additionally, radiological findings are not specific while a CT scan cannot always be performed due to the high risk of transportation. In a case series of 7 patients with suspected IPA and COVID 19 pneumonia, only one CT scan was performed without however being able to differentiate between the lesions, while ground glass opacities are common findings both in COVID 19 pneumonia and IPA[4,6,7]. In a case report, one patient was diagnosed with IPA, 22 days after his admission to ICU for COVID-19. The patient deteriorated clinically and the chest CT showed bilateral ground-glass opacities and excavated lesions, one of which with crescent sign which did not pre-exist in previous CT. The BAL culture was positive for *Aspergillus fumigatus* and the patient was treated with voriconazole[8]. However, CAPA is an early onset complication. The mean time from the intubation to the positive microbiological results for IPA is 8 days, the median time between ICU admission and IPA diagnosis 5 days and between COVID-19 symptom onset and IPA diagnosis 11.5 days.[3,6]

COVID-19-associated aspergillosis seems to be related

TABLE 1. The AspICU algorithm

I. Proven invasive pulmonary aspergillosis
Microscopic analysis on sterile material
- Histopathologic, cytopathologic or direct microscopic examination of a specimen obtained by needle aspiration or sterile biopsy in which hyphae are seen accompanied by evidence of associated tissue damage.
- Culture on sterile material: recovery of *Aspergillus* by culture of a specimen obtained by lung biopsy

II. Putative invasive pulmonary aspergillosis (all four criteria must be met)
1. *Aspergillus*-positive lower respiratory tract specimen culture **(= entry criterion)**
2. Compatible signs and symptoms (one of the following)
- Fever refractory to at least 3 d of appropriate antibiotic therapy
- Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause
- Pleuritic chest pain
- Pleuritic rub
- Dyspnea
- Hemoptysis
- Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support

3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs
4. Either 4a or 4b
4a. Host risk factors (one of the following conditions)
- Neutropenia (absolute neutrophil count <500/mm^3) preceding or at the time of ICU admission
- Underlying hematological or oncological malignancy treated with cytotoxic agents
- Glucocorticoid treatment (prednisone equivalent, >20 mg/d)
- Congenital or acquired immunodeficiency

4b. Semiquantitative Aspergillus-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae

III. Aspergillus respiratory tract colonization
When ≥1 criterion necessary for a diagnosis of putative IPA is not met, the case is classified as Aspergillus colonization.

with a high incidence and increase significantly the mortality of the patients. For this reason the systematic screening for specific IPA markers is mandatory in all mechanically ventilated patients with COVID-19[3,6]. Consecutive measurements of serum and BAL galactomannan through bronchoscopy procedure, fungal cultures of tracheal / bronchial aspirate and BAL cultures are included in the diagnostic work-up. Also, the AspICU algorithm[5] (Table 1) for distinguishing IPA in critically ill patients needs to be applied and tested. Molecular methods can also be used although the role of positive PCR in tracheal aspirate, BAL and serum needs to be further examined in non-neutropenic patients[4,9,10]. However, serum galactomannan levels exhibit low sensitivity in patients with CAPA. In a recently published study, serum galactomannan levels were positive (≥0.5) in 2/5 patients with putative IPA while in another study were raised in only 1/7 ventilated patients with COVID 19 pneumonia and suspected IPA[6,7]. In other studies, serum galactomannan levels were negative in 3/6 patients and in 8/9 patients with CAPA on the third day after intubation. Interestingly, treatment with hydroxychloroquine seems that affects negatively galactomannan levels[3,4,11]. Bronchoscopy is not always feasible in COVID-19 patients due to the high risk for the patient and the physician while debatable informations are related to BAL galactomannan measurement. Recent studies reported that BAL galactomannan levels were positive a) in all patients with definite IPA (diagnosis confirmed with histopathological examination), b) in 3/5 patients with putative IPA (in the rest of the patients was not available) and c) in 2/9 patients with probable and putative IPA three days after intubation[4,6,7]. In an autopsy study, in 6 patients the diagnosis of IPA was not confirmed post mortem although the BAL galactomannan levels were positive ante-mortem[1].

In conclusion, IPA may complicate COVID-19 and increase mortality. The incidence of CAPA is not well known, the diagnosis is difficult because a) the "traditional" risk factors for IPA development are not related to CAPA and b) of the lack of a diagnostic tool able to differentiate colonization from infection. For this reason, the high clinical suspicion, the evaluation of risk factors in conjunction with clinical and laboratory findings and the appropriate screening of critically ill patients may facilitate the timely diagnosis and contribute to the early treatment.

CONFLICT OF INTEREST
None.

ΠΕΡΙΛΗΨΗ

Ασπεργίλλωση σχετιζόμενη με COVID-19 λοίμωξη

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Η σοβαρή COVID -19 λοίμωξη μπορεί να επιπλακεί με διηθητική πνευμονική ασπεργίλλωση. Η επίπτωση, αν και δεν είναι σαφώς καθορισμένη, ποικίλλει (20-35%) ενώ οι γνωστοί παράγοντες κινδύνου για ανάπτυξη ασπεργίλλωσης σε ανοσοκατασταλμένους ασθενείς δεν αναγνωρίζονται στους μη ανοσοκατασταλμένους ασθενείς με COVID-19 λοίμωξη και διηθητική ασπεργίλλωση. Επιπλέον τα κλινικά χαρακτηριστικά και τα ακτινολογικά ευρήματα δεν είναι ειδικά. Λαμβάνοντας υπόψη τη σημαντική νοσηρότητα της συλλοίμωξης, κρίνεται αναγκαίος ο προληπτικός διαγνωστικός έλεγχος για ασπεργίλλωση σε μηχανικά αεριζόμενους ασθενείς με COVID-19 με τη μέτρηση γαλακτομαννάνης στον ορό και στο BAL, και τη λήψη καλλιεργειών για μύκητες του ανώτερου και κατώτερου αναπνευστικού συστήματος.

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