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Update on the management of SARS-CoV-2 infection

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COVID-19 and fungal infections: Etiopathogenesis and therapeutic implications

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ABSTRACT

Invasive fungal infection often complicates patients with severe viral infection, especially those admitted to critical care units. Severe SARS-CoV-2 infection has been no exception and a significant association with *Aspergillus* spp. has been documented, resulting in high patient mortality. In this summary we describe the clinical presentation, the underlying diseases most commonly linked with this association, radiological manifestations and therapeutic management of CAPA.

Keywords: COVID-19; aspergillosis; CAPA; SARS-CoV-2; co-infection

INTRODUCTION

The relationship between invasive aspergillosis (IA) and viral infection, mainly influenza A, in critically ill patients with acute respiratory distress syndrome (ARDS) is widely known nowadays. Since 1972, when this association was first published [1], this association had hardly been described. However, in 2011, and following the remarkable advancements made in diagnostic techniques for influenza infection—that is, a real-time polymerase chain reaction (PCR) performed on nasopharyngeal throat swabs—and invasive aspergillosis, the role of invasive pulmonary aspergillosis (IPA) complicating severe influenza became more evident.

Indeed, several publications demonstrated a strong association between the two diseases [2,3]. In one particular paper, investigators developed the AspICU algorithm [4] to define IPA in critical care patients with viral infections.

One of the most important publications in this field detailed the relationship between viral infections and *Aspergillus* in 40 patients admitted to intensive care units (ICU) in two tertiary hospitals in Belgium. Investigators described up to 23% of patients with severe influenza infections had further complications due to *Aspergillus* [3,5].

That all stated, when patients with IA were compared with those without infection, mortality rates were much higher (51% vs 28%, respectively) [6]. Clinical forms of IA in these patients present some differences with respect to immunosuppressed people, with more atypical findings [7]. There is a high variability in clinical manifestations, ranging from tracheobronchitis to invasive and angioinvasive disease [5].

COVID-19-ASSOCIATED PULMONARY ASPERGILLOSIS

Therefore, when the COVID-19 pandemic arrived, physicians first expected to observe an increase in the incidence of *Aspergillus* spp. cases in relation to SARS-CoV-2 viral infection. In December 2019, autopsy reports described deceased patients with severe SARS-CoV-2 infection who developed co-infection with *Aspergillus* spp. In the following months, different case series were also reported (Figure 1). For example, Marr et al. [8] reported 20 cases of COVID-19-associated pulmonary aspergillosis (CAPA) occurring at Johns Hopkins University (Baltimore, MD, USA) and Hospital Clinic of Barcelona (Barcelona, Spain) before June 2020. Thanks to this international, multicenter CAPA series, we have acquired some key learnings.

First, radiographic manifestations are difficult to interpret. Chest x-rays may not be clear due to diffuse lung damage to the lung parenchyma caused by the viral infection—associated with inflammatory changes—and possible ARDS. Although cavitation and necrosis occur occasionally, no radiographic reports describe manifestations classically seen in angioinvasive cases [3,7].

Second, most of these patients had underlying diseases,

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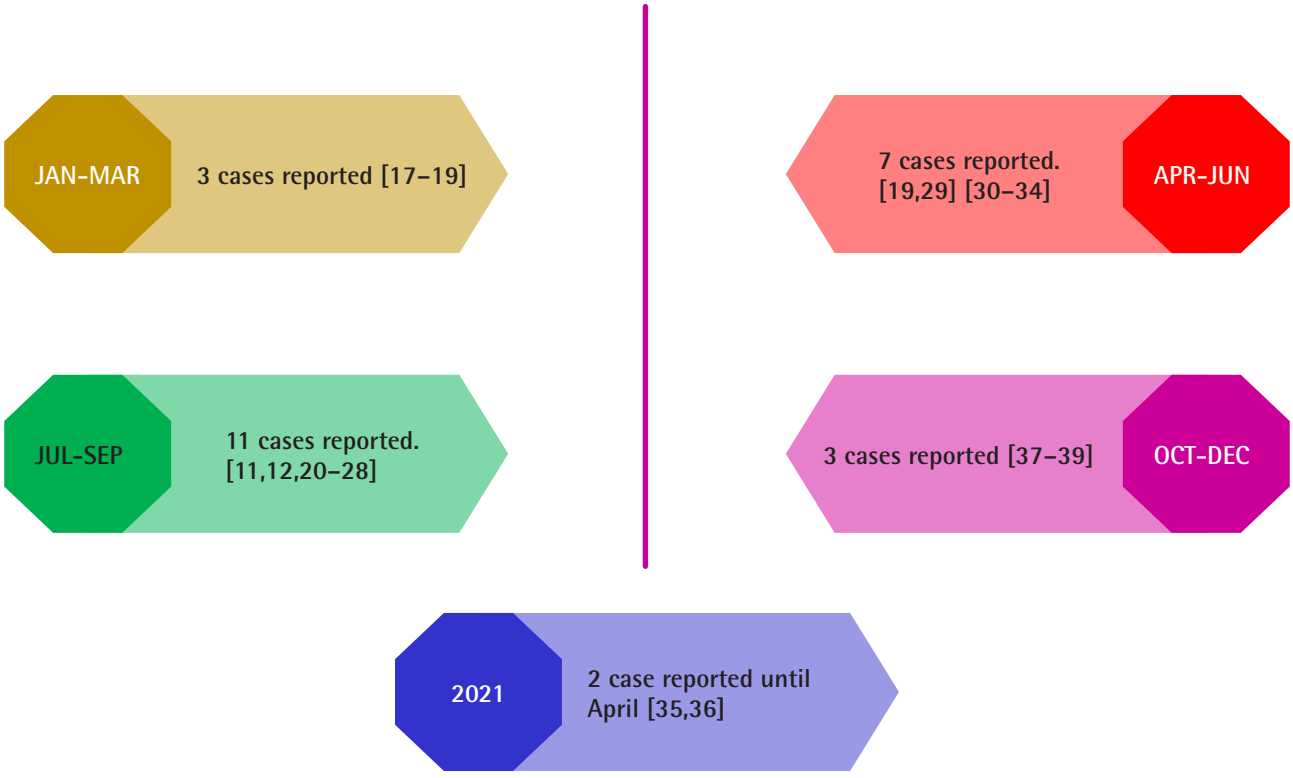

Figure 1 | **Quarterly timeline about cases reported for coronavirus disease–associated pulmonary aspergillosis.**

predominantly prior lung disease that required ICU admission with respiratory support for more than nine days.

Third, performing cultures of respiratory samples, mainly tracheal aspirates, was the most common diagnostic testing approach. In the study by Marr et al. [8], only 25% of serum galactomannan (GM) was positive among patients with CAPA. Conversely, because of invasive diagnostic strategies used in both centers and the lower rate of angioinvasion, 17 of 20 (85%) respiratory cultures tested positive. This observance may be attributable to the fact that these patients were in early stages of the disease. In this series, mortality rates were relatively low.

Furthermore, Salmanton-Garcia et al. [9] reported 186 cases of CAPA across 17 different countries collected from Fungiscope (a global emerging fungal infection registry; https://www.clinicaltrials.gov;National Clinical Trial identifier NCT01731353) and a literature search. In this large series, we found again that 97.8% of patients were admitted to the ICU, and 94.1% required mechanical ventilation. Investigators observed median days until CAPA diagnosis of 10, which was similar to data reported in the multicentric series by Marr et al. [8]. A notable difference between both studies is that up to 60.8% of total CAPA were diagnosed with a positive GM, mainly due to bronchoalveolar lavage (BAL). This data suggests that these patients were in advanced stages of the disease with the presence of angioinvasion. Also, described mortality rates (52.2%) were higher.

Due to the importance of this entity, a group of 22 experts from six continents and 14 countries gathered together to develop guidelines for the management, diagnosis and treatment of CAPA [10]. In this review, they proposed three clinical forms: i) proven aspergillosis when invasive growth of *Aspergillus* was evidenced in histopathological and/or microbiological samples obtained from a sterile tissue; ii) probable aspergillosis when *Aspergillus* spp. evidence was obtained from BAL or blood (culture, GM, or *Aspergillus* PCR); iii) possible aspergillosis when compatible radiological findings were described together with mycological evidence obtained via non-bronchoscopic lavage. In conclusion, should clinical findings elicit suspicion and meet inclusion criteria, it is necessary to initiate diagnostic tests for CAPA, so as to avoid a rapid and undesirable evolution towards more invasive forms.

As high mortality has been reported in cases of CAPA, [11,12] early and adequate therapy is crucial. Traditionally, voriconazole or isavuconazole has AI evidence for the treat-

Table 1	Main advantages of isavuconazole versus voriconazole.
Broad spectrum.	
Linear and predictable pharmacokinetics.	
Not influenced by genetic polymorphisms or by diet.	
Few intervariabilities.	
Does not need therapeutic drug monitoring.	
High volume of distribution; high dose in lung.	
Few interactions with other drugs.	
Few side effects.	
Cyclodextrin-free.	
Can be used in renal failure, dialysis, and hemodialysis.	

ment of IA in main guidelines [13]. However, both drugs are quite different. Table 1 summarizes potential advantages with the use of isavuconazole. Remarkably, isavuconazole has fewer interactions than voriconazole. This fact is of main interest in patients with COVID-19, especially in those who require ICU admission. Baniasadi et al. [14] reported data from a prospective study about drug-drug interactions among patients in ICU, and voriconazole was one of the more frequently involved drugs due to its ability to inhibit CYP3A4 [15]. Secondarily, voriconazole interacts with corticosteroids, some sedative drugs and remdesivir. Isavuconazole is metabolized differently via CYP2C19, CYP2C9, and CYP3A4, which makes the possibility of drug-drug interaction significantly lower. The use of voriconazole must therefore be associated with therapeutic drug monitoring on a weekly basis, given its drug-drug interaction and great interpersonal variability due to genetic polymorphisms of CYP3A4.

Finally, it is important to note that critically ill patients with SARS-CoV-2 infection may suffer from other fungal infections [16]. Like other patients admitted to the ICU, critically ill patients with SARS-CoV-2 can develop candidemia due to prolonged ICU length of hospital stay, invasive medical devices, use of broad-spectrum antibiotics and corticosteroids, etc. More occasionally, though, other fungal infections like *Pneumocystis jirovecci* or mucormycosis have been described.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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