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Coronavirus Disease 2019-Associated Pulmonary Aspergillosis

Young Hoon Hwang and Wan Beom Park†

Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Korea

As the coronavirus disease 2019 (COVID-19) pandemic continues, a new disease, COVID-19-associated pulmonary aspergillosis (CAPA), is on the rise. CAPA is a secondary fungal infection in patients with critical COVID-19 receiving mechanical ventilation in intensive care units (ICUs). Although the incidence rate of CAPA is estimated to be 10.2% in ICU patients, CAPA appears to be associated with an increase in overall mortality. CAPA is like classical invasive pulmonary aspergillosis (IPA) but has an ambiguous clinical manifestation and occurs without typical host factors. It is also like influenza-associated pulmonary aspergillosis but differs in clinical characteristics. For research and clinical practice, the European Confederation for Medical Mycology and the International Society for Human and Animal Mycology proposed novel case definition criteria for CAPA. Although CAPA management is not much different from typical IPA, areas of uncertainty remain that require further investigation.

Key Words: COVID-19, Pulmonary aspergillosis, SARS-CoV-2

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), eliciting a diverse spectrum of respiratory illnesses. The infection causes flu-like symptoms in most cases. However, some high-risk patients develop acute diseases characterized by acute respiratory failure. In a study conducted at the beginning of the pandemic, the mortality rate of critical COVID-19 cases was 49.0%, significantly higher than the overall mortality rate of COVID-19 patients (2.3%)[1].

With the development of vaccines and advances in treatment strategies, the mortality rate of COVID-19 has decreased[2]. However, the mortality rate remains high in the high-risk group of patients who may progress to acute respiratory distress syndrome. Among critical COVID-19 patients, secondary infection is a severe complication. A recent meta-analysis showed that the prevalence of coinfection and superinfection in COVID-19 patients was 19% and 24%, respectively, and both are associated with increased mortality[3]. Bacteria are the common cause of secondary infection in COVID-19 patients, but the superinfection of fungi has also been reported in 8% of patients[3]. In previous studies on critical influenza infection, invasive pulmonary aspergillosis (IPA) is reportedly a fatal secondary infection in patients receiving mechanical ventilation[4]. Similarly, IPA in critical COVID-19 patients, named COVID-19-associated pulmonary aspergillosis (CAPA), has received increasing attention, especially in intensive care units (ICUs)[5-8].

CAPA has different clinical characteristics from classical IPA[9]. The significant difference is the absence of long-term immunocompromised host status in CAPA patients described in the

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†Corresponding: Wan Beom Park, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul, 03080, Korea.
Phone: +82-2-2072-3596, Fax: +82-2-762-9662, e-mail: wbpark1@snu.ac.kr

diagnostic criteria of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium (EORTC/MSGERC)[10]. In addition, simultaneous pulmonary involvement of COVID-19 makes it difficult to diagnose CAPA[9]. In the early disease stage, it is hard to tell if clinical deterioration is due to an ongoing disease course of COVID-19 or superinfection of *Aspergillus*. Although cavitary lesions and well-described nodules are still useful diagnostic signs of IPA in ICU patients, atypical signs of COVID-19 can mimic imaging signs of aspergillosis and vice versa[8,11]. Tracheobronchitis form of invasive aspergillosis without lung parenchymal lesion is also a diagnostic challenge[9,12], and diagnostic delay in CAPA makes its management difficult. In this review, we discuss the clinical characteristics of CAPA and the recent approach for its diagnosis and management.

PATHOPHYSIOLOGY OF CAPA

Aspergillus is an ubiquitous fungal organism, and IPA is an opportunistic infection that mainly occurs in immunocompromised hosts[13]. However, a series of cases of invasive *Aspergillus* infection without a classical host factor has been reported among patients with severe influenza in ICUs[14]. Experts named this influenza-associated pulmonary aspergillosis (IAPA). Early studies on CAPA were inferred from IAPA research due to pathophysiological similarities between CAPA and IAPA. There were 30~78% of IAPA patients[12] and 86% of CAPA patients[12] who presented without typical host factors. Virus-related anatomical factors, such as airway damage due to lytic infection and immunologic factors related to the host response to infection, are crucial for the pathogenesis of both IAPA and CAPA[12].

As reported for SARS-CoV-1 in the 2003 pandemic, SARS-CoV-2 binds to the angiotensin-converting enzyme-II receptor through a spike protein and thus invades airway epithelial cells and type II pneumocytes[15,16], thereby leading to cell damage. An autopsy study of COVID-19 patients reported plaques in the large airway and mucosal ulceration with inflammatory cell infiltration[17]. This deterioration of barrier function makes hosts prone to secondary infection. Furthermore, danger-associated molecular patterns from damaged tissue induce a hyperinflammatory response and accelerate lung damage[18].

Hyperinflammation is one of the main pathogeneses of respiratory failure in critical COVID-19 patients. While hyperinflammation due to a sustained innate immune response persists in COVID-19 patients, defects in the number and function of adaptive immune cells are also seen[16]. This imbalance in innate and adaptive immunity causes immune dysregulation, providing a possible explanation for the predisposition of COVID-19 patients to secondary infection.

Anatomical and immunologic alterations caused by SARS-CoV-2 make patients prone to CAPA. However, not all patients with aspergillosis present with invasive fungal infection. In a review article, experts suggested the angioinvasion threshold model and placed CAPA on the spectra of colonization, tissue invasion, angioinvasion, and disseminated fungal infection[12]. The degree of invasion of *Aspergillus* in COVID-19 patients and the angioinvasion threshold are determined by complex interplay between the virus, host, and fungus, a concept shared with IAPA. However, IAPA is associated with more severe and earlier airway damage by viruses before aspergillosis than CAPA. Moreover, the influenza virus invades monocytes and macrophages, resulting in the impairment of NADPH oxidase, which contributes to interrupting fungal invasion. In addition, an anti-influenza drug, a neuraminidase inhibitor, impairs the fungicidal ability of myeloid cells[19]. Due to these influenza virus infection characteristics, IAPA patients are more prone to develop early angioinvasive diseases than CAPA patients. In other words, diagnostic time is delayed for CAPA patients than for IAPA patients[12]. Active use of immunotherapeutic agents, such as corticosteroids and anti-interleukin (IL)-6 drugs, in COVID-19 patients may affect the disease course of secondary *Aspergillus* infection. There is a need for this concept to be further researched.

EPIDEMIOLOGY AND RISK FACTORS FOR CAPA

The incidence rate of CAPA is 3~33%. However, according to a systematic review and meta-analysis published in September 2021, which included 28 studies and 3,148 patients until April 2021, the pooled estimate of its incidence was 10.2% (95% confidence interval [CI], 8.0~12.5%)[20]. Studies conducted in the early stages of the pandemic in Europe, most of which were case series, reported a relatively high incidence of CAPA (20~35%). Recent studies, which included more cases than earlier ones, reported a lower incidence of CAPA (approximately 3%)[20].

One reason for the variation in CAPA incidence is inconsistent diagnostic criteria for case definition. Studies included in the meta-analysis[20] adopted at least five different entry criteria, including the EORTC/MSGERC definition[10] commonly used for IPA diagnosis in immunocompromised hosts, *Asp*ICU algorithm[21], an alternative algorithm adopted for the ICU

population for discriminating colonized patients from patients with IPA, and its modified version (modified-*Asp*ICU algorithm)[14]. In addition, they adopted the IAPA case definition[4] and 2020 European Confederation of Medical Mycology/International Society for Human and Animal Mycology (ECMM/ISHAM) consensus criteria[9], the first consensus criteria for CAPA diagnosis. Other experts argued that this inconsistency in diagnostic criteria affects the estimation of CAPA incidence[22]. For example, according to a literature review of 17 articles published from May 2020 to December 2020, the estimated incidence of CAPA reported by the authors was 10.9%. However, the incidence of proven or probable CAPA was only 6.1% when the ECMM/ISHAM consensus criteria were consistently applied to the same articles.

Another major limitation of epidemiological studies of CAPA is that it is difficult to distinguish between fungal colonization and invasive infections. In a prospective multicenter cohort study from four ICUs in Italy, laboratory-confirmed COVID-19 patients with acute respiratory distress syndrome were assigned to routine bronchoscopy for screening fungal infection at days 0 and 7 of ICU admission[6]. The *Asp*ICU algorithm and IAPA case definition were adopted for CAPA diagnosis. In total, 27.8% of patients showed galactomannan positivity (index > 1) in bronchoalveolar lavage (BAL) specimens and were diagnosed with probable CAPA. However, 59 of 108 subjects had both BAL and serum galactomannan results, and among patients diagnosed with probable CAPA, only one showed serum galactomannan positivity. The higher incidence of CAPA in the routine screening group and their low serum galactomannan positivity reflects angioinvasion, and many of these patients present with colonization or subclinical invasive disease.

The mortality of CAPA also varies between studies. According to meta-analysis[20], the pooled estimate of CAPA mortality was 54.9% (95% CI, 45.6~64.2%). This is far higher than the overall 90-day mortality of COVID-19 patients in ICUs of 31%, as reported in a multicenter, prospective cohort study in Europe[2]. A large, multicenter, prospective cohort study by the ECMM enrolled 592 patients from 20 centers in 9 countries from March 2020 to May 2021[23]. The median prevalence of CAPA per center was 10.7% (range, 1.7~26.8%), and the 90-day survival of patients with CAPA (29%; 95% CI, 19~39%) was significantly lower than that of patients without CAPA (57%; 95% CI, 52~62%; $p < 0.001$).

The classical risk factors for IPA listed in the EORTC/MSGERC definition apply to CAPA. Pulmonary mold infection was more common in COVID-19 patients with an EORTC/MSCGERC host factor (20% *vs.* 2.4%, $p = 0.007$)[24]. However, according to a published case series, only a few patients have a traditional host factor for IPA, as defined by EORTC/MSGERC[11]. Recent studies revealed that potential risk factors are old age[23], use of corticosteroids[6,7,25], underlying pulmonary disease[25,26], use of azithromycin (cumulative dose ≥ 1,500 mg)[7], and anti-IL-6 therapy[23]. In the case of corticosteroids, long-term use (≥16 mg/day prednisolone equivalent dose for at least 15 days)[6] and use of a high or high cumulative dose (≥100 mg dexamethasone equivalent dose)[7,25,26] were suggested to be risk factors. However, the use of steroids was not associated with CAPA when the dose was unspecified[6,23].

CAPA DIAGNOSIS

There was no consensus regarding the case definition of CAPA until the ECMM/ISHAM criteria were published in December 2020. The EORTC/MSGERC definition[10] could not be applied to most patients due to the absence of host factors or atypical radiologic findings. Regarding invasive aspergillosis in ICU patients, the *Asp*ICU algorithm[21] was designed to distinguish IPA (proven or putative) from *Aspergillus* colonization in patients whose lower respiratory specimens are positive for *Aspergillus* culture. The modified-*Asp*ICU criteria[14] define putative IPA if all clinical, radiological, and mycological criteria are satisfied. The modified-*Asp*ICU algorithm adopts a cutoff value for galactomannan in serum (optical index ≥0.5) or BAL fluid (optical index ≥1) as mycological criterion, which is not emphasized in the *Asp*ICU algorithm.

In 2020, an international team of experts proposed the case definition of IAPA for clinical studies[4]. They suggested that the case definition could be applied to CAPA diagnosis. The entry criterion of the case definition was ICU admission for respiratory distress with confirmed influenza (or COVID-19). The case definition categorizes invasive aspergillosis into two groups: *Aspergillus* tracheobronchitis and IAPA without documented tracheobronchitis. Tracheobronchial manifestation with airway damage caused by virus seemed to be one of the main pathophysiologic features, which is distinct from typical IPA; therefore, the case definition could encompass more atypical aspergillosis cases in influenza patients. Cases could be defined as proven or probable according to the degree of evidence of infection. Like other diagnostic criteria, patients with mycological evidence of invasive aspergillosis from appropriate biopsy specimens were defined as proven cases. Probable cases are defined by clinical and mycological factors, including a positive result for respiratory specimen culture and an elevated galactomannan index in serum (≥0.5) or BAL (≥1) specimens.

ECMM/ISHAM[9] proposed the first consensus criteria for

CAPA in December 2020. The entry criteria were COVID-19 patients needing intensive care and a temporal relationship between SARS-CoV-2 infection and ICU admission. CAPA was classified as tracheobronchitis or other pulmonary forms

Table 1. 2020 ECMM/ISHAM consensus criteria for diagnosis of CAPA

Case definition		Host factor	Clinical factor	Mycological evidence
Tracheo-bronchitis	Proven	Patients with COVID-19 needing treatment in an ICU and with a temporal relationship (entry criterion)	–	At least one of the following (≥1 findings): 1. Histological or direct microscopic detection of fungal hyphae plus invasive growth with tissue damage 2. Sterile aspiration or biopsy from pulmonary site - Recovery of *Aspergillus* in culture - Microscopy, histology, or PCR showing the infectious disease process
	Probable	Patients with COVID-19 needing treatment in an ICU and with a temporal relationship (entry criterion)	Bronchoscopic findings: tracheobronchial ulceration, nodule, pseudomembrane, plaque, or eschar	At least one of the following (≥1 findings): 1. BAL: microscopic detection of fungal elements indicating mold 2. BAL: culture (+) or PCR (+) 3. BAL GM or LFA index ≥1.0 4. Serum GM or LFA index >0.5
Other pulmonary forms*	Proven	Patients with COVID-19 needing treatment in an ICU and with a temporal relationship (entry criterion)	–	At least one of the following (≥1 findings): 1. Histological or direct microscopic detection of fungal hyphae plus invasive growth with tissue damage 2. Sterile aspiration or biopsy from pulmonary site - Recovery of *Aspergillus* in culture - Microscopy, histology, or PCR showing the infectious disease process
	Probable	Patients with COVID-19 needing treatment in an ICU and with a temporal relationship (entry criterion)	Radiologic findings: pulmonary infiltrate or cavitating infiltrate (not attributed to another cause)	At least one of the following (≥1 findings): 1. BAL: microscopic detection of fungal elements indicating mold 2. BAL: culture (+) 3. BAL: GM or LFA index ≥1.0 4. Serum GM or LFA index >0.5 5. Blood†: two or more PCR (+) 6. BAL: single PCR (+) (threshold <36 cycles) 7. Single blood† PCR (+) plus single BAL PCR (+) (any threshold)
	Possible	Patients with COVID-19 needing treatment in an ICU and with a temporal relationship (entry criterion)	Radiologic findings: pulmonary infiltrate or cavitating infiltrate (not attributed to another cause)	At least one of the following (≥1 findings): 1. NBL: microscopic detection of fungal elements indicating mold 2. NBL: culture (+) 3. NBL: single GM index >4.5 4. NBL: two or more GM index >1.2 5. Single NBL GM index >1.2 plus another NBL mycology test (+) (PCR or LFA)

Abbreviations: BAL, bronchoalveolar lavage; CAPA, COVID-19-associated pulmonary aspergillosis; COVID-19, coronavirus disease-19, ECMM/ISHAM, European Confederation for Medical Mycology and the International Society for Human and Animal Mycology; GM, galactomannan; ICU, intensive care unit; LFA, lateral flow assay; NBL, non-bronchoscopic lavage; PCR, polymerase chain reaction

*In patients with chronic obstructive pulmonary disease or chronic respiratory disease, PCR or culture results should be confirmed by GM testing to rule out colonization or chronic infection.

†Plasma, serum, or whole blood

with proven, probable, or possible diagnosis. The diagnosis of tracheobronchitis requires direct bronchoscopic evidence of tracheobronchial ulceration, nodules, pseudomembranes, plaques, or eschars as clinical factors. The diagnosis of other pulmonary forms requires clinical suspicion when a patient has a refractory fever, pleural rub, chest pain, or hemoptysis, which could be ambiguous in the ICU setting. In addition, the diagnosis of other pulmonary forms requires suspected imaging findings with pulmonary or cavitating infiltrates. Typical radiologic findings of IPA, such as the halo sign, the air-crescent sign, cavitating lung lesions, and well-defined intrapulmonary nodules, are also useful for CAPA diagnosis. However, it is difficult to diagnose or rule CAPA out by imaging because radiologic findings of COVID-19 in the late phase can be atypical and mimic or hide signs of CAPA[9]. Therefore, mycological evidence is required to diagnose probable or possible (only for the pulmonary form) CAPA in conjunction with host and clinical factors (Table 1).

In the ECMM/ISHAM criteria[9], direct evidence of tissue invasion by *Aspergillus* in sterile aspiration or biopsy specimens is required for proven diagnosis; therefore, mycological evidence in BAL specimens play a critical role for probable diagnosis. Direct fungal detection by microscopy or culture of BAL specimens, galactomannan assay, and *Aspergillus* PCR of BAL or blood samples provide mycological evidence for probable diagnosis. Regarding galactomannan assay, not only a conventional enzyme immunoassay but also a lateral flow assay, which provides a rapid point-of-care test, can contribute to CAPA diagnosis[9,27]. In addition, nonbronchoscopic lavage, a blind lavage technique with a closed suction system in an intubated patient, is a new sampling method for possible diagnosis of other pulmonary CAPA forms[9,28].

According to the ECMM/ISHAM criteria, a possible diagnosis has been proposed to select subjects for early empirical treatment. However, there is insufficient evidence, and the threshold values of galactomannan in nonbronchoscopic lavage specimens have only been verified in few studies[25]. The Society for Advanced Bronchoscopy guideline suggests that evaluation of coinfection in COVID-19 patients can be an indication for bronchoscopy[29], and there is a report that bronchoscopy can be safely performed using personal protective equipment[30]. Therefore, it is best to perform bronchoscopy, if possible; otherwise, further validation is required for nonbronchoscopic lavage.

CAPA MANAGEMENT

There is no evidence that CAPA treatment should differ from that of pulmonary aspergillosis in patients without COVID-19. Although it is difficult to distinguish between colonization and invasive disease, some studies suggest that patients with CAPA have excess mortality[20,23]. Therefore, experts recommend antifungal treatment in patients with CAPA[9,11].

The ECMM/ISHAM guideline and international taskforce report on CAPA recommend voriconazole or isavuconazole as the first-line antifungal medication for treating CAPA[9,11]. Although voriconazole has been the conventional drug of choice for treating IPA since 2002[31], a new drug, isavuconazole, is receiving attention due to its comparable outcome with fewer toxicities[32]. However, voriconazole has a narrow therapeutic window, and its potential side effects, including hepatotoxicity, neurotoxicity, and risk of QT-interval prolongation, require therapeutic drug monitoring[33]. In addition to their toxicity profile, drug-drug interactions of triazole antifungals are problematic in the ICU setting[9]. Voriconazole is metabolized via CYP2C19, CYP2C9, and CYP3A4. Isavuconazole, which is metabolized via CYP3A4, tends to have less pronounced drug-drug interactions than voriconazole. In addition, posaconazole could be a first-line option since a randomized, controlled trial in 2021 supported the noninferiority of posaconazole to voriconazole as a first-line treatment of invasive aspergillosis[34].

Liposomal amphotericin B is a second-line treatment option recommended for CAPA[9,11]. It can also be considered a first-line drug when the level of azole resistance exceeds 10%. A combination of echinocandins and voriconazole or isavuconazole can be an option for suspected azole-resistant cases, along with a concomitant test for azole resistance. However, echinocandins monotherapy is not recommended. Some experts propose that addition of nebulized liposomal amphotericin B helps to control fungal growth in patients with invasive *Aspergillus* tracheobronchitis[12]. Although there is a case report[35] of successful treatment of post-influenza pseudomembranous necrotizing bronchial aspergillosis with nebulized liposomal amphotericin, benefit of antifungal nebulizer in CAPA patients is uncertain due to lack of evidence.

Two observational studies have evaluated the efficacy of antifungal prophylaxis in ICU to prevent CAPA[36,37]. In one study[36], mold-active antifungal prophylaxis, mainly through intravenous posaconazole, resulted in significant CAPA reduction. One patient was diagnosed with CAPA among 75 patients in the prophylaxis group, while 9 were recorded among 57 patients in the nonprophylaxis group. However, there was no survival benefit of antifungal prophylaxis. In another study[37], patients who received prophylactic therapy twice-weekly inhaled liposomal amphotericin B, showing

a lower incidence of CAPA (9%; 3 of 32) than the non-prophylaxis group (16%; 11 of 18). Although these two studies suggest the potential role of antifungal prophylaxis, there is no randomized, controlled trial that has proven the benefit of antifungal prophylaxis for CAPA. Therefore, there is no recommendation on antifungal prophylaxis in critical COVID-19 patients due to insufficient evidence for clinical use and absence of licensed prophylactic drugs[9,11].

CONCLUSION

CAPA is a type of secondary infection in critical COVID-19 patients in ICUs. In contrast to IPA, CAPA occurs without a classical host factor and has a more ambiguous clinical and radiologic presentation. Airway damage and immune dysregulation caused by SARS-CoV-2 are presumed to be important pathophysiologic factors. CAPA is estimated to occur in 10% or less of COVID-19 patients admitted to ICUs and has a death risk. Suggested risk factors include the EORTC /MSGERC host factors, old age, high-dose or long-term steroid use, underlying lung disease, azithromycin use, and anti-IL-6 treatment, although this requires further verification. The ECMM/ISHAM consensus criteria published in December 2020 are widely used for diagnosis. Like IAPA, CAPA can present with the tracheobronchitis form. If indicated and feasible, bronchoscopic evaluation should be considered for diagnostic evaluation. In many ways, CAPA treatment follows the recommendations for treating IPA. Antifungal therapy is recommended if CAPA diagnosis is proven or probable. Voriconazole and isavuconazole are first-line antifungal drugs, and isavuconazole may be advantageous in the ICU setting. The effect and indication of nebulized antifungal drug are not obvious. There is no recommendation on the use of prophylactic antifungal agents; therefore, further research is needed.

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CONFLICT OF INTEREST

Wan Beom Park is an associate editor of the Journal of Mycology and Infection; however, he was not involved in this article's peer reviewer selection, evaluation, and decision process. All other authors have no competing interests.

ORCID

Young Hoon Hwang: 0000-0003-2653-0221
Wan Beom Park: 0000-0003-0022-9625

REFERENCES

1. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239-1242
2. COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4,244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med 2021; 47:60-73
3. Musuuza JS, Watson L, Parmasad V, Putman-Buehler N, Christensen L, Safdar N. Prevalence and outcomes of co-infection and superinfection with SARS-CoV-2 and other pathogens: a systematic review and meta-analysis. PLoS One 2021;16:e0251170
4. Verweij PE, Rijnders BJA, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, et al. Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion. Intensive Care Med 2020;46:1524-1535
5. Seo HM, Park JH, Oh SU, Park SK, Kim JS. COVID-19-associated pulmonary aspergillosis: a new entity. J Mycol Infect 2021;26:23-27
6. Bartoletti M, Pascale R, Cricca M, Rinaldi M, Maccaro A, Bussini L, et al. Epidemiology of invasive pulmonary aspergillosis among intubated patients with COVID-19: a prospective study. Clin Infect Dis 2021;73:e3606-e3614
7. Dellière S, Dudoignon E, Fodil S, Voicu S, Collet M, Oillic PA, et al. Risk factors associated with COVID-19-associated pulmonary aspergillosis in ICU patients: a French multicentric retrospective cohort. Clin Microbiol Infect 2020; 27:790.e1-e5
8. Permpalung N, Chiang TP, Massie AB, Zhang SX, Avery RK, Nematollahi S, et al. Coronavirus disease 2019-associated pulmonary aspergillosis in mechanically ventilated patients. Clin Infect Dis 2022;74:83-91
9. Koehler P, Bassetti M, Chakrabarti A, Chen SCA, Colombo AL, Hoenigl M, et al. Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMM/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis 2021;21:e149-e162

10. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer and the Mycoses Study Group Education and Research Consortium. Clin Infect Dis 2020;71:1367-1376
11. Verweij PE, Brüggemann RJM, Azoulay E, Bassetti M, Blot S, Buil JB, et al. Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis. Intensive Care Med 2021;47:819-834
12. Van de Veerdonk FL, Brüggemann RJM, Vos S, De Hertogh G, Wauters J, Reijers MHE, et al. COVID-19-associated *Aspergillus* tracheobronchitis: the interplay between viral tropism, host defence, and fungal invasion. Lancet Respir Med 2021;9:795-802
13. Thompson GR, 3rd, Young JH. *Aspergillus* infections. N Engl J Med 2021;385:1496-1509
14. Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 2018;6:782-792
15. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005;11:875-879
16. Arastehfar A, Carvalho A, van de Veerdonk FL, Jenks JD, Koehler P, Krause R, et al. COVID-19 associated pulmonary aspergillosis (CAPA)-from immunology to treatment. J Fungi (Basel) 2020;6:91
17. Borczuk AC, Salvatore SP, Seshan SV, Patel SS, Bussel JB, Mostyka M, et al. COVID-19 pulmonary pathology: a multi-institutional autopsy cohort from Italy and New York City. Mod Pathol 2020;33:2156-2168
18. Tolle LB, Standiford TJ. Danger-associated molecular patterns (DAMPs) in acute lung injury. J Pathol 2013;229:145-156
19. Dewi IMW, Cunha C, Jaeger M, Gresnigt MS, Gkountzinopoulou ME, Garishah FM, et al. Neuraminidase and SIGLEC15 modulate the host defense against pulmonary aspergillosis. Cell Rep Med 2021;2:100289
20. Mitaka H, Kuno T, Takagi H, Patrawalla P. Incidence and mortality of COVID-19-associated pulmonary aspergillosis: a systematic review and meta-analysis. Mycoses 2021;64:993-1001
21. Blot SI, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselaers N, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 2012;186:56-64
22. Fekkar A, Neofytos D, Nguyen MH, Clancy CJ, Kontoyiannis DP, Lamoth F. COVID-19-associated pulmonary aspergillosis (CAPA): how big a problem is it? Clin Microbiol Infect 2021;27:1376-1378
23. Prattes J, Wauters J, Giacobbe DR, Salmanton-García J, Maertens J, Bourgeois M, et al. Risk factors and outcome of pulmonary aspergillosis in critically ill coronavirus disease 2019 patients-a multinational observational study by the European Confederation of Medical Mycology. Clin Microbiol Infect 2021;doi:10.1016/j.cmi.2021.08.014
24. Fekkar A, Lampros A, Mayaux J, Poignon C, Demeret S, Constantin JM, et al. Occurrence of invasive pulmonary fungal infections in patients with severe COVID-19 admitted to the ICU. Am J Respir Crit Care Med 2021;203:307-317
25. White PL, Dhillon R, Cordey A, Hughes H, Faggian F, Soni S, et al. A national strategy to diagnose coronavirus disease 2019-associated invasive fungal disease in the intensive care unit. Clin Infect Dis 2021;73:e1634-e1644
26. Janssen NAF, Nyga R, Vanderbeke L, Jacobs C, Ergün M, Buil JB, et al. Multinational observational cohort study of COVID-19-associated pulmonary aspergillosis. Emerg Infect Dis 2021;27:2892-2898
27. Pan Z, Fu M, Zhang J, Zhou H, Fu Y, Zhou J. Diagnostic accuracy of a novel lateral-flow device in invasive aspergillosis: a meta-analysis. J Med Microbiol 2015;64:702-707
28. Van Biesen S, Kwa D, Bosman RJ, Juffermans NP. Detection of invasive pulmonary aspergillosis in COVID-19 with non-directed bronchoalveolar lavage. Am J Respir Crit Care Med 2020;202:1171-1173
29. Pritchett MA, Oberg CL, Belanger A, De Cardenas J, Cheng G, Nacheli GC, et al. Society for advanced bronchoscopy consensus statement and guidelines for bronchoscopy and airway management amid the COVID-19 pandemic. J Thorac Dis 2020;12:1781-1798
30. Lormans P, Blot S, Amerlinck S, Devriendt Y, Dumoulin A. COVID-19 acquisition risk among ICU nursing staff with patient-driven use of aerosol-generating respiratory procedures and optimal use of personal protective equipment. Intensive Crit Care Nurs 2021;63:102993
31. Herbrecht R, Denning DW, Patterson TF, Bennett JE, Greene RE, Oestmann JW, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Eng J Med 2002;347:408-415
32. Maertens JA, Raad, II, Marr KA, Patterson TF, Kontoyiannis DP, Cornely OA, et al. Isavuconazole versus voriconazole

for primary treatment of invasive mould disease caused by *Aspergillus* and other filamentous fungi (SECURE): a phase 3, randomised-controlled, non-inferiority trial. Lancet 2016;387:760-769
33. Park WB, Kim NH, Kim KH, Lee SH, Nam WS, Yoon SH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis 2012;55: 1080-1087
34. Maertens JA, Rahav G, Lee DG, Ponce-de-León A, Ramírez Sánchez IC, Klimko N, et al. Posaconazole versus voriconazole for primary treatment of invasive aspergillosis: a phase 3, randomised, controlled, non-inferiority trial. Lancet 2021;397:499-509
35. Boots RJ, Paterson DL, Allworth AM, Faoagali JL. Successful treatment of post-influenza pseudomembranous necrotising bronchial aspergillosis with liposomal amphotericin, inhaled amphotericin B, gamma interferon and GM-CSF. Thorax 1999;54:1047-1049
36. Hatzl S, Reisinger AC, Posch F, Prattes J, Stradner M, Pilz S, et al. Antifungal prophylaxis for prevention of COVID-19-associated pulmonary aspergillosis in critically ill patients: an observational study. Crit Care 2021;25: 335
37. Van Ackerbroeck S, Rutsaert L, Roelant E, Dillen K, Wauters J, Van Regenmortel N. Inhaled liposomal amphotericin-B as a prophylactic treatment for COVID-19-associated pulmonary aspergillosis/*Aspergillus* tracheobronchitis. Crit Care 2021;25:298