CONFERENCE REPORTS AND EXPERT PANEL

Taskforce report on the diagnosis and clinical management of COVID-19 associated pulmonary aspergillosis

Paul E. Verweij1,2,3*, Roger J. M. Brüggemann2,4, Elie Azoulay5, Matteo Bassetti6,7, Stijn Blot8,9, Jochem B. Buil1,2, Thierry Calandra10,11, Tom Chiller11,12, Cornelius J. Clancy12,13, Oliver A. Cornely13,14,15, Pieter Depuydt16, Philipp Koehler13,14, Katrien Lagrou17,18, Dylan de Lange19, Cornelia Lass-Flörl20,21, Russell E. Lewis21,22, Olivier Lortholary22,23, Peter-Wei Lun Liu24,25, Johan Maertens26, M. Hong Nguyen12, Thomas F. Patterson27,28, Bart J. A. Rijnders29,30, Alejandro Rodriguez30,31, Thomas R. Rogers31,32, Jeroen A. Schouten32,33, Joost Wauters34, Frank L. van de Veerdonk35, and Ignacio Martin-Loeches36,37,38*

© 2021 The Author(s)

Abstract

Purpose: Invasive pulmonary aspergillosis (IPA) is increasingly reported in patients with severe coronavirus disease 2019 (COVID-19) admitted to the intensive care unit (ICU). Diagnosis and management of COVID-19 associated pulmonary aspergillosis (CAPA) are challenging and our aim was to develop practical guidance.

Methods: A group of 28 international experts reviewed current insights in the epidemiology, diagnosis and management of CAPA and developed recommendations using GRADE methodology.

Results: The prevalence of CAPA varied between 0 and 33%, which may be partly due to variable case definitions, but likely represents true variation. Bronchoscopy and bronchoalveolar lavage (BAL) remain the cornerstone of CAPA diagnosis, allowing for diagnosis of invasive Aspergillus tracheobronchitis and collection of the best validated specimen for Aspergillus diagnostics. Most patients diagnosed with CAPA lack traditional host factors, but pre-existing structural lung disease and immunomodulating therapy may predispose to CAPA risk. Computed tomography seems to be of limited value to rule CAPA in or out, and serum biomarkers are negative in 85% of patients. As the mortality of CAPA is around 50%, antifungal therapy is recommended for BAL positive patients, but the decision to treat depends on the patients’ clinical condition and the institutional incidence of CAPA. We recommend against routinely stopping concomitant corticosteroid or IL-6 blocking therapy in CAPA patients.

Conclusion: CAPA is a complex disease involving a continuum of respiratory colonization, tissue invasion and angioinvasive disease. Knowledge gaps including true epidemiology, optimal diagnostic work-up, management strategies and role of host-directed therapy require further study.

Keywords: Viral pneumonia, SARS-CoV-2, COVID-19, Invasive aspergillosis, ICU

*Correspondence: paul.verweij@radboudumc.nl; drmartinloeches@gmail.com
1 Department of Medical Microbiology, Radboudumc Center for Infectious Diseases (RCI), Radboud University Medical Center, PO box 9101, 6500 HB Nijmegen, The Netherlands
38 Department of Clinical Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St. James’s Hospital, Dublin, Ireland
Full author information is available at the end of the article
Introduction

Soon after the start of the coronavirus disease 2019 (COVID-19) pandemic, reports of suspected invasive pulmonary aspergillosis (IPA) complicating COVID-19 appeared both from clinical and post-mortem findings [1, 2]. Over the past years, IPA secondary to seasonal influenza was recognized as an emerging clinical entity in patients admitted to the intensive care unit (ICU) with respiratory failure [3]. Cases of influenza associated pulmonary aspergillosis (IAPA) were reported in up to 19% of influenza patients in the ICU [3]. The mortality rate was 51% compared to 28% in influenza patients without IAPA [3]. COVID-19 associated pulmonary aspergillosis (CAPA) has been reported to have a similar mortality rate of 52% [4]. However, there are clear differences between IAPA and CAPA, including different patients’ typology and comorbidities, viral lytic effects and tissue tropism, host immune response as well as performance of *Aspergillus* diagnostic tests. Furthermore, the frequent detection of *Aspergillus* species or galactomannan (GM) in airway samples from critically ill COVID-19 patients, limited evidence of histopathological confirmation of CAPA at autopsy and reports of patients with CAPA who survived without receiving antifungal therapy, has challenged existing thoughts on the best diagnostic and therapeutic strategies. A group of experts set out to write practical and evidence-based guidance based on seven key questions (Table 1).

Methods

The taskforce consisted of 28 participants from eight European countries, the United States and Taiwan. Participants were selected based on internationally recognized experience, academic leadership, and field of expertise, including medical microbiology/infection control (PEV, KL, JBB, CL-F, TTR), infectious diseases (BJAR, MB, TCa, CJC, OAC, OL, MH-N, TFP, FLvdV), intensive care medicine (EA, SB, PD, DdL, PK, PW-LL, AR, JAS, LV, JW, IM-L), clinical pharmacology (RJMB, RL), public health (TCh) and hematology (OAC, PK, JM). Selected participants furthermore had specific expertise in epidemiology, diagnosis and management of invasive fungal diseases or fungal disease guideline development, and most participants had previously contributed to the IAPA case definition [5]. The key questions were discussed and regarded well-focused and relevant by all panel members. As the literature regarding CAPA is very limited, the PICo framework for qualitative research questions was followed, involving population characteristics, disease of interest, and context [6]. For each key question we developed short evidence summaries after searching PubMed, Embase and when available, the medRxiv pre-print server and pre-print publications. The search strategy included the following MESH terms (coronavirus or COVID-19 or SARS-CoV-2) and (*Aspergillus* or aspergillosis* or CAPA*). The evidence was subsequently discussed during an online group meeting and quality of evidence for clinically relevant outcomes was graded from high to very low following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [7], involving categories of outcome, summary of evidence using evidence tables, and assessment of quality of evidence. The panel formulated recommendations after structured discussions based on the collected evidence. When evidence could not be obtained, recommendations were provided on the basis of opinions and experiences (good practice statements, GPS). Based on this process, we formulated 13 recommendations on the management of patients with a proven COVID-19 and *Aspergillus* colonization or possible, probable or proven CAPA.

Take-home message

COVID-19 associated pulmonary aspergillosis (CAPA) is associated with excess mortality and requires bronchoscopy and BAL to diagnose. Antifungal therapy is recommended in CAPA, while discon- tinuation or tapering of concomitant corticosteroid therapy could be considered in patients who do not respond.

| Table 1  Key questions |
|------------------------|
| 1. What is the case definition of COVID-19 associated pulmonary aspergillosis? |
| 2. What is the optimal approach towards diagnosing or refuting CAPA in patients with COVID-19? |
| 3. What is the reported prevalence of *Aspergillus* pneumonia in patients with COVID-19? |
| 4. What are the host/-risk factors that are associated with COVID-19 associated pulmonary aspergillosis (CAPA)? |
| 5. Is antifungal therapy indicated in patients suspected of CAPA? |
| 6. How should invasive *Aspergillus* tracheobronchitis be managed in CAPA patients? |
| 7. What is the role of immunomodulating agents in the management of CAPA in ICU patients? |
Key questions

What is the case definition of COVID-19 associated pulmonary aspergillosis?

Evidence summary

A rapidly increasing number of papers on CAPA (125 publications by April 1st) are being reported in the literature. One problem is the lack of a consensus CAPA operational case definition, as various definitions have been used to classify CAPA. The invasive fungal disease case definition of the European Organization for Research and Treatment of Cancer (EORTC)/Mycosis Study Group Education and Research Consortium (MSG ERC) is rarely applicable because it only applies to patients with specific host factors, which are typically absent in patients suspected of having CAPA [8]. Several studies have used the algorithm that was proposed by Blot et al. to distinguish between putative IPA and Aspergillus colonization in the ICU [9].

As this classification is based on a positive culture, sometimes revised definitions were used, which also include the biomarker GM in serum or BAL [10]. Other studies have used the criteria which were used by Schauwvlieghe et al. [3] to classify patients with IAPA or the IAPA case definition proposed by an expert panel [5]. The expert panel indicated that the IAPA case definition may also be applied to classify CAPA cases, but at that time there was limited scientific evidence and clinical experience [5]. In December 2020 a consensus CAPA case definition was published by the European Confederation for Medical Mycology (ECMM) and the International Society for Human and Animal Mycology (ISHAM) [11], categorizing patients by the European Confederation for Medical Mycology (ECMM) consensus definitions permit classification of most CAPA patients, including those who have undergone non-bronchoscopic procedures, such as non-bronchoscopic bronchial lavage (NBL) to obtain mycological evidence [11]. CAPA patients diagnosed through NBL are classified as possible cases, reflecting the uncertainty regarding the diagnostic performance of this (blind) procedure to diagnose IPA, and the lack of validation of Aspergillus tests on this sample type. It is important to note that the possible category in the CAPA definitions differs fundamentally from that used in the EORTC/MSG ERC definitions as the latter lacks mycological evidence for IPA, but is defined by “typical” radiological lesions [8, 11].

What is the optimal approach towards diagnosing or refuting CAPA in patients with COVID-19?

| Recommendations                                                                 | Strength of recommendation | Quality of evidence |
|---------------------------------------------------------------------------------|-----------------------------|---------------------|
| A CAPA diagnostic work-up is recommended in mechanically ventilated COVID-19 patients with unexplained respiratory deterioration or a positive Aspergillus culture from the respiratory tract | Strong                      | Low                 |
| Standard CT imaging is not recommended to refute or diagnose CAPA                | Weak                        | Very low            |
| Screening of critically ill COVID-19 patients for serum GM or BDG is not recommended | Strong                      | Low                 |
| Detection of Aspergillus in sputum and tracheal aspirate is considered insufficient evidence to support CAPA diagnosis, but warrants further diagnostics through bronchoscopy and BAL | Strong                      | Low                 |
| We recommend maximum efforts to perform a bronchoscopy for inspection of the airways and bronchoalveolar lavage (BAL) to diagnose CAPA in patients with proven or high likelihood of COVID-19 in the ICU | Strong                      | Low                 |
| There is no recommendation against or in favor of using lateral flow devices-based assays for diagnosing CAPA | Weak                        | Very low            |

Evidence summary

Mycology

Bronchoscopy with BAL has become the most important tool to diagnose IPA. BAL samples have been validated for microscopy (using optical brighteners such as Blankophor P or calcofluor white), which provides rapid results and helps to interpret culture results. Furthermore, Aspergillus culture, detection of GM and Aspergillus DNA PCR tests for species identification and detection ofazole resistance markers have been reasonably well validated on BAL fluid. Detection of Aspergillus antigen may take place through ELISA test or with use of a lateral flow device (LFD) point-of-care tests that allows the rapid detection of Aspergillus antigen. Alternatively, GM
Respiratory samples from 113 (60.8%) patients, including BAL samples from 63 (33.9%) patients and NBL from 22 (11.8%) patients [4]. Furthermore, GM was detected in serum or plasma from 29 (15.6%) CAPA patients. The performance of LFD tests has been studied in ICU patients [30], showing a good overall test performance (sensitivity 0.88–0.94, specificity 0.81, and the area under the ROC curve 0.90–0.94) [30]. AspLFD (OLM Diagnostics) was used in 8 CAPA cases using one TA and seven BAL samples [27]. The AspLFD was positive in six patients but did not correspond with GM detection in four. Another study compared the performance of the Sona Aspergillus Galactomannan Lateral Flow Assay (IMMY) with that of the Platelia Aspergillus in TA obtained from CAPA patients [31]. However, as bronchoscopy was not performed in this study, a reliable classification of CAPA patients was not possible.

Serum biomarkers show a low sensitivity ranging from 0 to 40% for GM and 0–50% for BDG (Table 2). Overall, serum BDG shows a higher sensitivity than serum GM, but is a panfungal marker and thus not specific for CAPA. Furthermore, some studies indicate only a modest contribution of BDG to the diagnosis of invasive fungal disease in critically ill patients due to low sensitivity and positive predictive value [32]. Circulating GM is associated with angioinvasion, and the low number of CAPA patients with positive serum GM may be due to absence of angioinvasion in most patients. Nevertheless, one recent autopsy series reported Aspergillus angioinvasion in lung tissue in three patients, but the results of circulating biomarker detection in these patients was not reported [2].

**Imaging**

CT has been the most important imaging tool in COVID-19 patients. Typical appearance of COVID-19 includes peripheral, bilateral, ground-glass opacities with or without consolidation or visible intralobular lines (i.e. crazy paving) in early stages; multifocal ground-glass opacities of rounded morphology with or without consolidation or crazy paving at peak stage; reverse halo sign as well as other findings of organizing pneumonia at late stages are observed as well [33]. Many signs of COVID-19 pneumonia can mimic CAPA, and vice versa, and lesions suggestive of CAPA may be hidden. Radiological findings that were previously shown to be sufficiently specific to diagnose IPA in immunocompromised patients are the halo sign, air-crescent sign, cavitating lung lesions and well-defined intrapulmonary nodule(s). In ICU patients with influenza, cavitating lung lesions and well-described nodule(s) are also considered a useful diagnostic sign. In a recent case series of 20 patients with probable CAPA from North-America, nine (45%) presented with cavitating lung lesions [29]. Whether or not, any of these criteria can help in distinguishing Aspergillus colonization from infection in COVID-19 patients is as yet uncertain. Indeed, an intrinsic part of severe COVID-19 is intravascular thrombosis due to endotheliopathy, which can result in infarction and cavitating lesions as well as the halo sign [5, 11]. Therefore, even though CT can reliably ascribe intravascular lesions to venous thrombosis, the role of imaging as a reliable criterion for diagnosing CAPA is probably limited. Importantly, CT may contribute to identifying other reasons for respiratory deterioration. Nevertheless, for critically ill COVID-19 patients, new nodules with cavitation or halo sign, or consolidations have been recommended to trigger a diagnostic work-up for CAPA [34]. Histopathological data of a sufficient number of patients with these radiological findings present in the days preceding death are needed to improve our understanding of the radiology of CAPA.

**What is the reported prevalence of Aspergillus pneumonia in patients with COVID-19?**

**Evidence summary**

With the limitations described above regarding the published definitions of CAPA in mind, the reported frequencies of...
Table 2  Overview of performance of diagnostic tests in CAPA

| Country | # of CAPA cases | BAL (positive/performd) | Aspergillus species | TA/BA (positive/performd) | Serum (positive/performd) | References |
|---------|-----------------|-------------------------|--------------------|--------------------------|--------------------------|------------|
| France  | 9               | Culture 5/7 GM 2/7 PCR 3/7 | A. fumigatus (7) | Culture 2/2 GM – PCR 2/2 | GM 1/9 BDG 4/8 | [15]       |
| Germany | 5               | Culture 1/3 GM 3/3 PCR 3/3 | A. fumigatus (4) | Culture 2/3 GM ND PCR 1/2 | GM 2/5 BDG – | [16]       |
| Netherlands | 6       | Culture 2/3 GM 3/3 PCR – | A. fumigatus (5) | Culture 3/3 GM – PCR – | GM 0/3 BDG – | [17]       |
| Belgium | 6               | Culture 5/6 GM 5/6 PCR – | A. fumigatus (5), A. flavus (1) | Culture – GM – PCR – | GM 1/5 BDG – | [18]       |
| Italy   | 30              | Culture 19/30 GM 30/30 PCR 20/30 | A. fumigatus (16), A. niger (3), A. flavus (1) | Culture – GM – PCR – | GM 1/30 BDG – | [19]       |
| UK      | 19              | Only NBL performed; Denominator not reported | A. fumigatus (9), A. versicolor (1) | Denominator not reported | Denominator not reported | [20]       |
| Belgium | 4               | Culture 4/4a GM 4/4 PCR 2/2 | Not specified | GM – BDG – | | [21]       |
| Switzerland | 3   | Culture – GM – PCR – | A. fumigatus (3) | Culture 3/3 GM – PCR 1/7 | GM 1/7 BDG 1/7 | [22]       |
| France  | 19              | Culture 7/9 GM 7/9 PCR – | A. fumigatus (14), A. calidoustus (1), A. niger (1) | Culture 9/10 GM – PCR – | GM 1/12 BDG – | [23]       |
| Pakistan | 5               | Not specified | A. fumigatus (1), A. flavus (4), A. niger (1) | Not specified | GM 0/5 BDG 1/5 | [24]       |
| USA     | 4               | Not specified | A. fumigatus (4) | Not specified | GM 1/3 BDG – | [25]       |
| France  | 7               | Culture not specified/S GM 3/5 PCR 2/5 | A. fumigatus (5) | Not specified | GM 1/7 BDG 2/7 | [26]       |
| Netherlands | 8     | Culture 7/7 GM 2/6 PCR 4/5 | A. fumigatus (7) | Culture 1/1 GM 1/1 PCR 1/1 | GM 0/1 | [27]       |
| Netherlands | 11   | Culture 5/40 GM 11/37 PCR 11/40 | A. fumigatus (3) | Culture 3/47 GM not performed PCR 23/30 | GM 0/11 | [28]       |
| USA     | 20              | Culture 2/20 GM 2/20 PCR not specified | Not specified | Not specified | GM 8/20 BDG 6/20 | [29]       |

BAL: bronchoalveolar lavage; GM: galactomannan; BDG: beta-D-glucan; PCR: polymerase chain reaction

* BAL and BA were not distinguished

CAPA can be found in Table 3. Overall, 15 CAPA case series in the ICU reported 158 CAPA cases among 1702 COVID-19 patients (9.3%, range between 0 and 33%). Only in four cases CAPA was proven, while the majority had a probable or putative diagnosis. Cohort studies report that most ICU patients who were diagnosed with CAPA were mechanically ventilated, although this may be explained by the fact that diagnostic procedures like BAL are rarely performed in non-ventilated patients with COVID-19. Furthermore, most patients developed CAPA on average between day 4 and 11 after ICU admission. However, as many studies relied on a diagnostic work-up in deteriorating patients or in those with positive upper respiratory cultures, the true prevalence and timing of CAPA remains undefined. The study of Bartoletti is the only study that involved routine bronchoscopy on day 0 and 7 of ICU admission indicated that a high number of
patients (14 of 108) was BAL GM positive (GM index > 1) at ICU admission [19].

What are the host-risk factors that are associated with COVID-19 associated pulmonary aspergillosis (CAPA)?

Evidence summary
Case series published to date show that only a minority of patients have traditional EORTC/MSGERC host factors (Table S1). Five patients (3%) were reported with a hematological malignancy, two (1.3%) with other malignancies and five (3%) with solid organ transplantation. One study identified the presence of an EORTC/MSGERC host factor as significant risk for invasive fungal infection [26]. Four cohort studies have identified risk factors for CAPA. Long-term steroid treatment (at dosages higher than or equivalent to prednisone 16 mg/day for at least 15 days) was found to be significantly more frequent in patients with CAPA compared to those without CAPA [19]. The use of high-dose corticosteroids (dose not defined) and the presence of chronic lung disease were associated with multiple positive Aspergillus tests in another study [19]. A third cohort found that corticosteroids administered at any dose for > 3 weeks was a risk factor for invasive fungal infection, and a fourth study showed a significantly higher proportion of patients receiving hydrocortisone during admission in the patients with CAPA compared to patients without CAPA (50% versus 12.8%; p < 0.001) [26, 29]. Finally, a fifth study did not find a statistically significant association of high-dose corticosteroid therapy with CAPA risk (11.5% versus 28.6%; p = 0.08), but observed cumulative dose ≥ 100 mg to be higher among CAPA patients [35].

All but a few of the reports on CAPA come from a setting where corticosteroid therapy was not yet the standard of care but rather the exception.
the RECOVERY trial, corticosteroid therapy has become the standard of care for all patients admitted with severe COVID-19 [41]. Therefore, the data regarding the impact as well as the magnitude of the impact of corticosteroid use on the incidence of CAPA should be considered preliminary. The question remains if a certain cumulative dose and if a 10-day regimen of dexamethasone, as was used in the RECOVERY trial and has become the standard of care, poses the patient at increased risk for CAPA.

### Is antifungal therapy indicated in patients suspected of CAPA?

| Recommendations | Strength of recommendation | Quality of evidence |
|-----------------|---------------------------|---------------------|
| **Antifungal therapy is indicated in patients with CAPA** | Strong | Low |
| **We recommend to follow national or international guidelines on antifungal therapy of invasive aspergillosis** | Strong | Low |
| **We recommend to consider empirical therapy for CAPA in patients in whom a BAL has been performed and BAL GM/PCR results are pending** | Weak | Very low |
| **In patients with a negative BAL GM, discontinuation of empirical antifungal therapy is recommended** | Weak | Very low |
| **Therapeutic drug monitoring (TDM) is recommended in critically ill CAPA patients receiving triazole therapy** | Strong | Low |

### Evidence summary

Despite the difficulty in distinguishing between *Aspergillus* colonization and invasive disease, studies have shown excess mortality in *Aspergillus* positive COVID-19 patients in the ICU, but the difference was not always statistically significant (Table 4). In the study of Bartoletti et al., of the 30 CAPA patients, 16 received antifungal therapy of whom 13 received voriconazole [19]. Fourteen patients did not receive antifungal therapy due to post-mortem diagnosis (7 patients) or due to clinical decision (7 patients). Survival of patients treated with voriconazole was 54% (7 of 13), and for those not receiving voriconazole 41% (7 of 17) (p = 0.39) [19]. A relationship between initial BAL GM index and 30-day survival was noted. The odds of death within 30 days of ICU admission increased 1.41-fold (1.10–1.81; p = 0.007) for each point increase in the initial BAL GM index [19]. In the study of White et al., all-cause mortality rates ranged from 46.7% (95% CI 24.8–69.9) in CAPA patients receiving appropriate antifungal therapy to 100% (95% CI 51.1–100) in patients not receiving appropriate antifungal therapy [20]. Van Biesen et al. found a mortality of 22.2% in patients with CAPA based on NBL and 15.1% in patients without CAPA [42]. In the study of Dupont, 3 of 9 (33%) of antifungal-treated patients compared to 5 of 10 (50%) untreated patients died at day 42 [23].

Patients diagnosed with CAPA have been reported to survive without receiving antifungal therapy. As indicated above, 7 of 17 (41%) CAPA patients who were not treated with voriconazole survived in the case series reported by Bartoletti et al. [19] Alanio and colleagues described 7 patients with putative (6) or probable (1) CAPA who did not receive antifungal therapy, of whom 5 survived [15]. Survival may be due to various factors, including absence of invasive disease (i.e. colonization). Indeed, in one study tissue biopsies showed no evidence for CAPA, despite most patients being classified as probable cases [43]. These observations might imply that in some critically ill COVID-19 patients positive *Aspergillus* tests reflect colonization rather than invasive disease. Importantly, the prognostic impact of *Aspergillus* colonization in severe COVID-19 pneumonia is yet to be established. Furthermore, baseline mortality of severe COVID-19 may vary between studies as new treatment modalities continue...

### Table 4 All-cause mortality in COVID-19 patients with CAPA compared with controls

| Country          | Case definition                          | # of CAPA patients | Mortality in CAPA | Mortality in controls | References |
|------------------|------------------------------------------|--------------------|-------------------|-----------------------|------------|
| France           | EORTC/MSGERC (if immunocompromised) [7] and IAPA [5] | 9                  | 44%               | 39% (p = 0.99)        | [15]       |
| France<sup>a</sup> | Modified IAPA [8, 9] and EORTC/MSGERC [7] | 21                 | 71.4%             | 36.8% (p < 0.01)      | [35]       |
| Italy            | IAPA [5]                                   | 30                 | 44% (day 30)      | 19% (day 30) (p = 0.002)<sup>b</sup> | [19]       |
| United Kingdom   | AspICU [8]                                 | 19                 | 74%               | 26% (p < 0.001)       |            |
| Netherlands      | 2020 ECMM/ISHAM [10]                      | 19                 | 63.6%             | 23.1% (p = 0.013)     | [28]       |
| USA              | 2020 ECMM/ISHAM [10]                      | 20                 | 50%               | 41.5%                 | [29]       |

<sup>a</sup> Includes cohort of Alanio et al. [15]

<sup>b</sup> Diagnosis of CAPA was associated with 30-day mortality from ICU admission (OR 3.53; 95% CI 1.29–9.67; p = 0.014), even after adjustment for age (OR 0.99; 95% CI 0.94–1.06; p = 0.99), need for renal replacement therapy (OR 3.02; 95% CI 1.11–8.19; p = 0.015), and SOFA score at ICU admission (OR 1.38; 95% CI 1.07–1.73; p = 0.004) with a logistic regression model [19].
to evolve. The United States Food and Drug Administration (FDA) recently approved remdesivir and baricitinib for treatment of COVID-19, but their role in critically ill patients remains unclear. Further discussions of treatment of COVID-19 were beyond the scope of the taskforce.

Azole resistance
Five cases of azole-resistant CAPA have been reported [27, 38, 39, 44]. In four cases the TR34/L98H resistance mutation was detected and in one case a TR46/Y121F/T289A mutation, which are associated with environmental resistance selection. There are currently no indications that the risk for azole-resistant infection differs from that in other ICU patients. In regions with levels of azole resistance exceeding 10%, it was recommended to cover resistance in initial antifungal therapy by adding an echinocandin to voriconazole or isavuconazole or by treating with liposomal amphotericin B [45]. When azole resistance is detected liposomal amphotericin B is recommended [11, 45], while the use of deoxycholate-amphotericin B in the ICU-setting is discouraged [45].

There are no studies that investigate the optimal choice and duration of antifungal therapy of CAPA. We therefore refer to international or national invasive mycoses guidelines for primary treatment choices [45, 46]. Most guidelines recommend voriconazole or isavuconazole as a first line treatment option. Recently, posaconazole was shown to be non-inferior to voriconazole for the treat -
a first line treatment option. Recently, posaconazole was

Pharmacologic considerations
Monitoring of exposure to ensure adequate exposure by means of therapeutic drug monitoring (TDM) and is an important component in triazole treatment of patients with CAPA. Critical illness with (multi) organ failure predisposes patients to a high degree of variability in drug exposure. This is further complicated by factors such as drug-drug interactions, alterations in protein binding, use of vasopressor agents impacting organ perfusion and the frequent use of renal replacement techniques as well as extracorporeal membrane oxygenation (ECMO).

Pharmacokinetic interactions are most likely the biggest source of pharmacokinetic variability in exposure. Clinicians should make a thorough assessment of these interactions and consult a pharmacologist where needed to aid in this matter. A useful resource to recommend is the website on COVID drug interactions that includes reference to the antifungal drugs. (available at [https://www.covid19-druginteractions.org/]).

In addition to pharmacokinetic interactions, pharmacodynamic interactions may be relevant. Pharmacodynamic interactions occur when the pharmacological effect of the victim drug is altered by coadministration of the antifungal drug. Clinically relevant side effects are often off-target effects. Examples are interactions between (lipid) formulations of amphotericin B and nephrotoxic drugs resulting in loss of kidney function, potassium wasting agents and liposomal amphotericin B as well as posaconazole, and many others. Patients with pre-existing QT-prolongation as well as those with severe electrolyte disturbances may be more prone to ventricular arrhythmias when treated with tria -

How should invasive Aspergillus tracheobronchitis be managed in CAPA patients?

| Recommendation | Strength of recommendation | Quality of evidence |
|----------------|-----------------------------|---------------------|
| Patients with visible plaques in trachea and bronchi should undergo mucosal biopsy or brush to diagnose IATB | Strong | Low |

Evidence summary
IATB was found to be a frequent and highly lethal manifestation of IAPA [60]. Autopsy studies indicate that focal white patches may be present in the trachea and large bronchi of 92% of COVID-19 patients [61]. This is likely to be due to viral tropism as the epithelium of the conducting airways was shown to support the replication of SARS-CoV-2 and to express ACE-2 receptor [62]. Local epithelial damage may provide a portal of entry for Aspergillus to cause invasive airway disease. Pseudomembranous plaques or ulcers were visible in 6 of 30 (20%) patients with CAPA [19], and bronchial ulcers reported in two of 8 Aspergillus positive COVID-19 patients, but the patients in the latter study were not classified according to published definitions [63]. These data indicate that the frequency of IATB in CAPA is probably lower than observed in IAPA [5]. However, the diagnosis of IATB is made through visualization of plaques in the airways, and since the use of bronchoscopy has been restricted, tracheobronchitis cases may be underreported.
The mortality associated with IATB is unknown in CAPA but was reported to be as high as 90% in IAPA patients [60]. Systemic antifungal therapy alone might not be sufficient to effectively treat this disease manifestation due to intraluminal growth of the fungus. Inhaled (liposomal) amphotericin B has been recommended by the IDSA as adjunctive therapy in these cases [46]. To date only one IAPA patient with IATB was reported to be treated with nebulized liposomal amphotericin B in addition to systemic antifungal therapy [64].

What is the role of immunomodulating agents in the management of CAPA in ICU patients?

| Recommendations | Strength of recommendation | Quality of evidence |
|-----------------|---------------------------|---------------------|
| We recommend not to stop concomitant dexamethasone or corticosteroid therapy in CAPA patients | Weak | Very low |

**Evidence summary**

Corticosteroids in influenza and other coronavirus respiratory syndromes have shown no benefit or possible harm [65, 66]. Early consensus was against corticosteroids in COVID-19 [67]. During the pandemic the RECOVERY trial, a meta-analysis of steroid trials by the WHO, and the REMAP-CAP trial have changed practice by showing benefit of corticosteroids in COVID-19 patients in the ICU [41, 68, 69]. RECOVERY reported that in over 6000 patients the administration of 6 mg dexamethasone for ten days was associated with significantly reduced 28-day mortality [41]. This result was most pronounced among patients requiring mechanical ventilation (rate ratio 0.65, 95% CI 0.48–0.88, \( p = 0.0003 \)) and immediately changed clinical practice. The question arose whether there would be additive effects of other immunomodulatory drugs in addition of corticosteroids. Recently, REMAP-CAP showed that in an ICU population blocking the IL-6 pathway with tocilizumab or sarilumab could further reduce mortality and organ free support days in the ICU when started within 24 h of admission to the ICU [70]. Median organ support-free days were 10 (interquartile range [IQR] — 1, 16), 11 (IQR 0, 16) and 0 (IQR — 1, 15) for tocilizumab, sarilumab and control, respectively. Hospital mortality was 28% (98/350) for tocilizumab, 22.2% (10/45) for sarilumab and 35.8% (142/397) for control. More recently, an improved overall survival in patients receiving tocilizumab in addition of dexamethasone was confirmed in the RECOVERY trial as well [71]. Again, similar to corticosteroids there were no reports of increased adverse events, including secondary infections during treatment [41, 65, 68, 70]. However, no CAPA-related diagnostic strategy were implemented in these trials and at 0.1%, the
extremely low incidence of infection as the cause of death in the tocilizumab arm of the RECOVERY trial suggests that the registration of this adverse event may have been suboptimal.

Immune-modulation has thus become a cornerstone of treatment of COVID-19 in the ICU, and current practice will include combinations of corticosteroids and blocking IL-6 in some critically ill patients. Although there is no evidence for increased frequency of IPA among patients receiving immunotherapy compared to no immunotherapy, the difficulty of diagnosing CAPA and the fact that registrations of fungal infection complications are not optimal do not allow us to fully understand the impact of immune-modulatory agents on CAPA rates. Future randomized clinical trials should include specific registration of secondary infections such as CAPA to assess the impact of immunomodulation on this patient population. The risk factors identified for CAPA thus far do include corticosteroids and the population with the highest CAPA incidence was a study where over 70% of patients had received tocilizumab [19]. The cytokine IL-6 which signals via STAT3 is crucial for T helper (Th)17 development and Th17 responses are important for protective anti-Aspergillus host responses [72–74]. Clinicians should be aware that CAPA as a complication of COVID-19 in ICU might increase with these new immunosuppressive strategies since they also suppress crucial antifungal host defense pathways. However, dampening the immune response has been shown to benefit critically ill COVID-19 and may subsequently reduce the risk for IPA by limiting damage to the epithelium, endothelium and the tissue. Therefore, when CAPA is diagnosed we do not have data which support stopping or continuing dexamethasone or other immune modulatory agents in the context of risk for CAPA, however these immunomodulatory treatments do reduce the overall mortality in the population at risk for CAPA.

Pathophysiology of CAPA
It is becoming apparent that CAPA is a complex disease, which involves a continuum of Aspergillus respiratory tract colonization, tissue invasion and angioinvasion. The limited histopathological data on CAPA available so far show both tissue invasion and angioinvasion [3, 75], but the low number of patients with circulating GM may indicate that angioinvasion is less frequent than observed in IAPA [75]. Angioinvasion is the hallmark pathologic feature of IPA and is associated with circulating GM. Recently, an angioinvasion threshold model was presented in which a combination of determinants was suggested to contribute to Aspergillus reaching the angioinvasion threshold. These determinants include predisposing factors, such as EORTC/MSGERC host factors and comorbidities, lytic effects on host cells caused by SARS-CoV-2, immune dysregulation, including both hyperinflammation and immune paralysis, and concomitant therapy, such as corticosteroids. These factors together determine if and when Aspergillus infection progresses to cause angioinvasive growth. While this threshold is reached early on in patients with IAPA (corresponding with serum GM positivity in 65–90% of IAPA patients) [4, 60], infrequent serum GM positivity in CAPA patients (between 0 and 50%) indicates that angioinvasion is less frequent. One study showed that mortality in serum GM positive CAPA patients was > 80% compared to 37% in GM negative CAPA patients, which suggests that this marker can be used to stage CAPA infection personal communication, paper submitted for peer-reviewing. There is, however, a need for a marker that is specific for tissue invasion and can discriminate from Aspergillus respiratory tract colonization.

Discussion
Bronchoscopy with BAL remains the cornerstone of CAPA diagnosis. Bronchoscopy allows visual inspection of the airways and thus enables the diagnosis of IATB. In addition to diagnosing CAPA and other respiratory infections, BAL may also be useful to exclude CAPA in patients that require corticosteroid therapy, for instance for the treatment of COP or the prevention of pulmonary fibrosis. In comparison with previous recommendations [11, 34], the use of bronchoscopy has been shown to be a safe procedure in critically ill COVID-19 patients [76], and thus simplifies the management algorithm.

Positive BA/TA Aspergillus culture or any unexplained respiratory deterioration in critically ill COVID-19 patients are considered triggers to perform a bronchoscopy and BAL (management algorithm). The implications of positive Aspergillus test results for starting antifungal therapy will depend on the institutional incidence of CAPA and the clinical condition of the patient.

The need to administer corticosteroids for the treatment of COVID-19 and the associated risk for CAPA, present a dilemma in the management of critically ill COVID-19 patients. Although the decision to continue corticosteroids in critically ill patients who develop CAPA needs to be assessed on an individual patient basis, we believe that dexamethasone therapy should be continued for the recommended time frame, if possible. Stopping dexamethasone could be considered, e.g. when there is no clear hyperinflammation anymore, when it has been given for 10 days, and/or when there is angioinvasive CAPA or secondary bacterial infections such as S. aureus pneumonia. This also applies to patients who are treated with high-dose corticosteroid therapy for pulmonary fibroproliferation during ICU stay and develop CAPA. Discontinuation or tapering of corticosteroids could be considered in patients who do not respond to antifungal therapy or with
underlying EORTC/MSGERC host factors, although this is not supported by clinical data.

Although excess mortality in critically ill COVID-19 patients with CAPA justifies pro-active diagnostic assessment and antifungal therapy, many questions remained unanswered (Table 6). These questions need to be addressed in future trials to further fine-tune integrated and targeted CAPA management.

### Table 6 Research agenda in CAPA

| Epidemiology | Determined the true epidemiology of CAPA  
Frequency of IATB in CAPA  
Identification of host/risk factors |
|--------------|--------------------------------------------------------------------------------|
| Diagnosis    | Markers that discriminate between *Aspergillus* respiratory tract colonization and tissue invasion  
Validation of *Aspergillus* biomarkers in NBL and BA/TA  
Determine the immune status of the host (e.g. FACS) |
| Strategy     | Role for antifungal prophylaxis  
Management of COVID-19 patients with positive upper respiratory tract culture |
| Antifungal agents | Benefit of nebulized antifungals in IATB  
Role of liposomal amphotericin B in the ICU-setting  
Effect of sequestration and drug interactions of antifungals on exposure (i.e. ECMO; CRRT) |
| Therapy      | Implications of antiviral and host-directed therapy for CAPA risk and outcome  
Host directed therapy: dampening or boosting immune response or both, dependent on host immune status |

### Practical recommendations

**When to consider CAPA?**

1. CAPA occurs predominantly in patients on mechanical ventilation for more than 5 days.
2. Host/Risk factor include: high dose or long administration of corticosteroids, an EORTC/MSGERC host/risk factor, and structural lung disease.
3. A diagnostic work-up for CAPA is recommended in clinically deteriorating patients with no other explanation or with cavitory and/or nodular lesions on CT scan. Typical lesions, such as halo sign and hypodense consolidations, may be absent in CAPA. Bronchoscopic inspection of airways is warranted.

**How to diagnose CAPA?**

1. Bronchoscopy with BAL is recommended to diagnose CAPA including IATB, and not to rely on endotracheal aspirates and sputum.
2. Microbiological investigations of BAL include microscopy, culture, galactomannan (GM), and/or *Aspergillus* PCR. A positive culture, PCR or GM (index ≥ 1) is considered consistent with CAPA. We recommend azole resistance testing when *Aspergillus* is detected in regions with known *Aspergillus* resistance.
3. We recommend mucosal biopsy when plaques are visible in trachea and/or bronchi.
4. Serum GM or beta-D-glucan (BDG) are not recommended for patient monitoring due to low sensitivity, but when positive are indicative of advanced CAPA infection. For serum BDG additional evidence of CAPA is required as this marker is not specific for *Aspergillus*.
5. In patients with cavitory lung lesions, we recommend excluding necrotizing pneumonia due to a bacterial pathogen (*Streptococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*).

**How to treat CAPA?**

1. Antifungal prophylaxis is not recommended in mechanically ventilated COVID-19 patients.
2. Consider empirical antifungal treatment in patients with visible plaques in trachea and/or bronchi, or while awaiting results of diagnostic BAL tests in patients with rapidly deteriorating clinical condition.
3. We recommend antifungal therapy in patients with confirmed IATB, positive BAL *Aspergillus* culture, GM and/or *Aspergillus* PCR
4. We recommend following (inter)national treatment guidelines for choice of antifungal therapy, involving voriconazole as a first line treatment, and isavuconazole or posaconazole as alternatives due to less evidence in critically ill patients.
5. We recommend TDM for patients receiving voriconazole therapy.
6. We recommend stopping empirical antifungal treatment if BAL GM and culture are negative.
Management algorithm

**Proposed clinical guidance for the management of CAPA**

**Factors that increase CAPA probability:**
- Immunosuppressive medication
- Positive Aspergillus culture from respiratory tract
- Radiology showing cavitating or well-described nodular lung lesion on CT
- Serum GM+

**Unexplained clinical deterioration despite SOC therapy**

**Bronchoscopy:**
- Inspection of large airways
- BAL for microscopy, fungal + bacterial culture + GM + Asp. PCR

**Serum GM**

**Mucosal plaque or ulcer**
- Superficial biopsy
  - When contra-indicated: brush cytology

**One or more tests positive:**
- Microscopy
- BAL GM
- Aspergillus PCR
- Aspergillus culture
- Serum GM

**Fungal hyphae +**

**Fungal hyphae −**

**BALGM −, Aspergillus PCR −, Aspergillus culture −**

**IATB or CAPA excluded**

**Discontinue pre-emptive antifungal therapy**

**CAPA**

**Antifungal therapy**

**(a)** SOC = Standard of care. The SOC of COVID-19 is likely to change in the future but for now it includes thromboembolic prophylaxis, therapy with dexamethasone, and anti-IL-6 when available, exclusion of pulmonary embolism with CT. Other causes of clinical respiratory deterioration may also need to be have been excluded: pneumothorax, atelectasis, progressive pulmonary fibrosis.

**(b)** Serum GM is generally negative but increases the probability of CAPA if positive in combination with positive BAL GM. Positive serum GM might be associated with poor outcome.

**(c)** Multiple positive Aspergillus test results increase the probability of CAPA and reduces the likelihood of a false-positive result.

**(d)** May require temporarily stopping anticoagulation 24 hrs before the procedure.

**(e)** Azole resistance testing is recommended in regions with known azole resistance or in patients failing azole therapy.

**(f)** Formally, only when septate hyphae size 2.5 to 4.5 μm in diameter are seen AND the presence of Aspergillus DNA is documented as well, the infection is classified as proven CAPA. However, the presence of hyphae compatible with Aspergillus suffices to start antifungal therapy.

**(g)** IATB, invasive Aspergillus tracheobronchitis; CAPA, COVID-19 associated pulmonary aspergillosis.
Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s10013-021-06449-4.

Author details
1 Department of Medical Microbiology, Radboudumc Center for Infectious Diseases (RCI), Radboud University Medical Center, PO box 9101, 6500 HB Nijmegen, The Netherlands. 2 Radboudumc-CW2 Center of Expertise for Mycology, Radboudumc Center for Infectious Diseases (RCI), Nijmegen, The Netherlands. 3 Center for Infectious Disease Research, Diagnostics and Laboratory Surveillance, National Institute for Public Health and the Environment, Bilthoven, The Netherlands. 4 Department of Pharmacy and Radboud Institute of Health Sciences, Radboud University Medical Centre, Nijmegen, The Netherlands. 5 Medical Intensive Care Unit, Saint-Louis Hospital, APHP, Paris, France. 6 Clinica Malattie Infettive, Ospedale Policlinico San Martino-IRCCS, Genoa, Italy. 7 Department of Health Sciences, DSSAL, University of Genoa, Genoa, Italy. 8 Department of Internal Medicine and Paediatrics, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium. 9 Burns, Trauma, and Critical Care Research Centre, Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia. 10 Infectious Diseases Service, Department of Medicine, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland. 11 Centers for Disease Control and Prevention, Atlanta, GA 30329, USA. 12 Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, USA. 13 Cologne Excellence Cluster On Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany. 14 Department I of Internal Medicine, ECMCM Center of Excellence for Medical Mycology, German Center for Infection Research, Partner Site Bonn-Cologne (DZIF), University of Cologne, Cologne, Germany. 15 Clinical Trials Centre Cologne (ZK Köln), University of Cologne, Cologne, Germany. 16 Department of Critical Care Medicine, Ghent University Hospital, Ghent, Belgium. 17 Department of Microbiology, Immunology and Transplantation, IU Leuven, Leuven, Belgium. 18 Department of Laboratory Medicine, National Reference Centre for Mycosis, University Hospitals Leuven, Leuven, Belgium. 19 Department of Intensive Care Medicine, University Medical Center, Utrecht, Utrecht, The Netherlands. 20 Department of Hygiene and Medical Microbiology, Medical University of Innsbruck, Innsbruck, Austria. 21 Department of Medical and Surgical Sciences, Infectious Diseases Hospital, IRCSS S’Orsola-Malpighi, University of Bologna, Bologna, Italy. 22 Neckler-Pasteur Center for Infectious Diseases and Tropical Medicine, Neckler-Enfants Malades Hospital, AP-HP, Paris University, Paris, France. 23 Institut Pasteur, Molecular Mycology Unit, National Reference Center for Invasive Mycoses and Antifungals, CNRS UMR 2000, Paris, France. 24 Department of Emergency and Critical Care Medicine, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei City, Taiwan. 25 School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan. 26 Department of Hematology, University Hospitals Leuven, Leuven, Belgium. 27 Department of Medicine, Division of Infectious Diseases, Texas Health Science Center at San Antonio, San Antonio, TX, USA. 28 South Texas Veterans Health Care System, San Antonio, TX, USA. 29 Department of Internal Medicine and Infectious Diseases, Erasmus MC, University Medical Center, Rotterdam, The Netherlands. 30 Critical Care Department, Joan XXIII University Hospital, Tarragona, Spain. 31 Department of Clinical Microbiology, Trinity College Dublin, St. James’s Hospital, Dublin, Ireland. 32 Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands. 33 Scientific Center for Quality of Healthcare (RCI Healthcare), Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands. 34 Department of General Internal Medicine, Medical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium. 35 Department of Medicine, Radboud University Medical Center, Nijmegen, The Netherlands. 36 Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St. James’s Hospital, Dublin, Ireland. 37 Hospital Clinic, IDIBAPS, Universitat de Barcelona, Ciberes, Barcelona, Spain. 38 Department of Clinical Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St. James’s Hospital, Dublin, Ireland.

Author contributions
IM-L initiated the idea and coordinated the work with PEV. PEV, JBB, RUMR, and F2G performed the literature search. PEV, JBB, RUMR, and F2G constructed the flow chart. All authors participated in critical review and revisions, and grading of the recommendations. All authors approved the final manuscript.

Funding
No funding was involved in the guideline development.

Declarations
Conflicts of interest
PE Verweij reported grants from Gilead Sciences, MSD, Pfizer, Mundipharma, Thermostimulator, and F2G, and non-financial support from OLM and IMMY, outside the submitted work. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. RJM Brüggemann served as consultant to Astellas Pharma Inc., F2G, Amplex, Gilead Sciences, Merck & Dohme Corp., and Pfizer, Inc., and has received unrestricted and research grants from Astellas Pharma Inc., Gilead Sciences, Merck & Dohme Corp., and Pfizer, Inc. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. E Azouel has received fees for lectures from Pfizer, Gilead, MSD, Alexion and Baxter. His institution received research support from Fishen/Payckie, Jazz pharma and Gilead. M Basetti has received funding for scientific advisory boards; travel and speaker honoraria from Angelini, Astellas, Bayer, BioMerieux, Idana, Corevo, Menarini, MSD, Nabirfa, Pfizer, Roche and Shionogi. S Blot received research funding from Pfizer and MSD, travel support from Pfizer, MSD, and Gilead, and invited speaker for Pfizer and Gilead. J-B Bull T Calandra reported advisory board membership from Astellas, Basilca, Idana, MSD, Sobi, Thermostimulator, and GE Healthcare and data monitoring board membership from Novartis, all outside the submitted work. Fees are paid to its institution. T Chiller reported no conflicts of interest. CJ Ciancy has been awarded investigator-initiated research grants from Astellas, Merck, Melinta, and Idana for projects unrelated to this project, served on advisory boards or consulted for Astellas, Merck, the Medicines Company, Idana, Sccyrix, Shionogri, Opeps and Needham & Company, and spoken at symposia sponsored by Merck and T2Bio-systems. OA Connelly is supported by the German Federal Ministry of Research and Education and the European Commission, and has received research grants from, is an advisor to, or received lecture honoraria from Actelion, Allegra Therapectics, Amplexy, Astellas, Basilea, Biosys UK Limited, Idana, Da Volterra, Entasis, F2G, Gilead, Grupo Biotoscana, Janssen Pharmaceuticals, Matinas, Medicines Company, MedPace, Melinta Therapeutics, Menarini Ricorche, Merck/MSD, Octapharma, Paareeke Pharmaceuticals, Pferz, PSL, Rempex, Sccyrix, Seres Therapectics, Tetraphase, Vical. P Depuydt reported no conflicts of interest. P Koehler is supported by the German Federal Ministry of Research and Education and the State of North Rhine-Westphalia, Germany and has received non-financial scientific grants from Miltkeny Biotec GmbH, Bengisch Gladbach, Germany, and the Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany, and received lecture honoraria from and/or is advisor to Akademie fur Infektionsmedizin e.V., Ambu GmbH, Astellas Pharma, European Confederation of Medical Mycology, Gilead Sciences, GPR Academy Rueselstheim, MSD Sharp & Dohme GmbH, Noxon N.V., and University Hospital, LMU Munich outside the submitted work. K Lagrou received consultancy fees from MSD, SBW Laboratories Brussels and Gilead Sciences, travel support from Pfizer, grant from Thermo Fisher Scientific and speaker fees from Gilead Sciences, Pfizer, and FUJIFILM Wako. D de Lange C Lass-Flörl received research funding from Pfizer, Gilead and Egger, travel support from Pfizer, MSD, and Gilead, and has served as invited speaker for MSD, Pfizer, Gilead, Basilea and Angelini. RE Lewis has received research support from Merck, and has served as an invited speaker for Gilead, Idana. O Lorholay has served as an invited speaker for Gilead, MSD, Pfizer, Astellas Pharma, and is a consultant for Gilead, Novartis and F2G. P Wei-Lun Liu has received research grants from MSD, Pfizer, and has served as an invited speaker for Gilead, MSD, Pfizer, Astellas Pharma, and is an advisor to Pfizer. Gilead. J Maertens reported personal fees and non-financial support from Basilea Pharmaceuticals, Bio-Rad Laboratories, Idana, Gilead Ltd, Gilead Sciences, Merck, Astellas, Sccyrix, and Pfizer Inc. and grants from Gilead Sciences, IMMY and OLM. MH Nguyen receives research grants from the National Institute of Health, Astellas, Pulmocide, Sccyrix and Mayne, and participates in clinical trials funded by the Mycosis Study Group and F2G. TF Patterson received research grants or clinical trial support to UT Health San Antonio from Idana and F2G and is an NIH ACTT and ACTIV investigator; is a consultant for Appiil, Basilea, F2G, Gilead, Mayne, Merck, Pfizer, Sccyrix, and SFunga. B Rjinders was investigator for studies supported by Gilead Sciences, Janssen-Cilag, MSD, Pfizer, ViiV; has received research grants from Gilead and MSD; was an invited speaker for Gilead, MSD, Pfizer, Janssen-Cilag; and is an advisory board member for BMS, Abbvie, MSD, Gilead, Janssen-Cilag; he received travel support from BMS, Abbvie, MSD, Gilead, Janssen-Cilag. A Rodriguez reported research grant from Gilead Sciences and fees for lectures from Pfizer, Gilead,
ThermoFisher, Biomereix and MSD. J Schouten reported grants from MSD and Pfizer, outside the submitted work. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. J Wauters reports grants, personal fees and other from MSD, Gilead Sciences, Pfizer, outside the submitted work. F van de Veerdonk reports grants from Gilead Sciences, grants from Sobi, outside the submitted work. I Martin-Loeches reported grants from Gilead, MSD and Pfizer, outside the submitted work.

Open Access
This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 2 April 2021   Accepted: 28 May 2021

Published online: 23 June 2021

References
1. Skok K, Vändr K, Settafy L, Kessler HH, Aberle S, Bargfrieder U, Trauner M, Lax SF. (2021) COVID-19 autopsies: procedure, technical aspects and cause of fatal course. Experiences from a single-center. Pathol Res Pract 217:153305. https://doi.org/10.1016/j.prp.2021.153305
2. Evert K, Dienemann T, Brochhausen C, Lunz D, Lubnow M, Ritza M, Keil F, Trummer M, Scheiter A, Salberberger B, Reischl U, Boor P, Gessner A, Janisch J, Calvisi DF, Evert M, Schmidt B, Simon M (2021) Autopsy findings after long-term treatment of COVID-19 patients with microbiological correlation. Virchows Arch. https://doi.org/10.1007/s00428-020-03014-0
3. Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen DCJJ, Hoedemaekers A, Andrinopoulou ER, van den Berg CHSB, Juffermans NP, Lagrou K, Verweij PE, Van de Veerdonk FL, Gommers D, Spronk PE, Bergmans M, Ostrosky-Zeichner L, Pagano L, Patterson TF, Perfect JR, Ruhnke M, Prokop CS, Shoham S, Slavin MA, Stevens DA, Thompson GR, Vazquez JA, Viscoli C, Walsh TJ, Warnis A, Wheat PL, Zaoutis TE, Pappas PG (2020) 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 71:1367–1376. https://doi.org/10.1093/cid/ciz1038
4. Blox S, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselselaar N, Dimopoulos G, Paiva JA, Misset B, Rello J, Vandewoude K, Vogelaers D, AspCU Study Investigators (2012) A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med 186:55–64. https://doi.org/10.1164/rccm.201111-1970OC
5. Schroeder M, Simon M, Katchanov J, Wijaya C, Rohde H, Christner M, Lapranna M, Wichmann D, Fuhrmann V, Kluge S (2016) Does galactomannan testing increase diagnostic accuracy for IPA in the ICU? A prospective observational study. Crit Care 20:139. https://doi.org/10.1186/s13054-016-1326-1
6. Koehler P, Passetti M, Chakrabarti A, Chen SCA, Comolli AM, Hoening M, Klimko N, Lass-Florl C, Odalele RO, Vinghi DC, Zhu LP, Boll B, Bruggemann R, Gangneux JP, Perfect JR, Patterson TF, Persingh T, Meis JF, Ostrosky-Zeichner L, White PL, Verweij PE, Corney OA, European Confederation of Medical Mycology; International Society for Human Animal Mycology; Asia Fungal Weling, for advanced bronchoscopy consensus statement and guidelines for bronchoscopy and airway management amid the COVID-19 pandemic. J Thorac Dis 12:1781–1798. https://doi.org/10.21037/jtd.2020.04.32
7. Koehler P, Cornely OA, Böttiger BW, Dusse F, Bretagne S, Calandra T, Clancy CJ, Cornely OA, European Confederation of Medical Mycology; Infectious Disease Canada (2020) Defining and managing COVID-19-associated pulmonary aspergillosis: the 2020 ECMWF/ISHAM consensus criteria for research and clinical guidance. Lancet Infect Dis. https://doi.org/10.1016/S1473-3099(20)30847-1
8. Koehler P, Cornely OA, Kochanek M (2021) Bronchoscopy safety precautions for diagnosing COVID-19-associated pulmonary aspergillosis: A simulation study. Mycoses 64:55–59. https://doi.org/10.1111/myc.13183
9. Lomans P, Blot S, Aemflyck D, Devriendt Y, Dumoulin A (2021) 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 Care Med 47:1099–1099. https://doi.org/10.1007/s00134-016-4294-z
10. Koehler P, Cornely OA, Kochanek M (2021) Bronchoscopy safety precautions for diagnosing COVID-19-associated pulmonary aspergillosis: A simulation study. Mycoses 64:55–59. https://doi.org/10.1111/myc.13183
11. Koehler P, Cornely OA, Kochanek M (2021) Bronchoscopy safety precautions for diagnosing COVID-19-associated pulmonary aspergillosis: A simulation study. Mycoses 64:55–59. https://doi.org/10.1111/myc.13183
