Intensive Care Med
https://doi.org/10.1007/s00134-020-06091-6

CONFERENCE REPORTS AND EXPERT PANEL

Review of influenza-associated pulmonary aspergillosis in ICU patients and proposal for a case definition: an expert opinion

Paul E. Verweij[1,2*], Bart J. A. Rijnders[3], Roger J. M. Brüggemann[2,4], Elie Azoulay[5], Matteo Bassetti[6,7], Stijn Blot[8,9], Thierry Calandra[10], Cornelius J. Clancy[11,12], Oliver A. Cornely[13,14,15], Tom Chiller[16], Pieter Depuydt[17], Daniele Roberto Giacobbe[6,18], Nico A. F. Janssen[2,19], Bart-Jan Kullberg[2,19], Katrien Lagrou[20,21], Cornelia Lass-Flörl[22], Russell E. Lewis[23], Peter Wei-Lun Liu[24,25], Olivier Lortholary[26,27], Johan Maertens[20,28], Ignacio Martin-Loeches[29,30], M. Hong Nguyen[11,12], Thomas F. Patterson[31,32], Thomas R. Rogers[33], Jeroen A. Schouten[34,35], Isabel Spriet[36], Lore Vanderbeke[20,37], Joost Wauters[37] and Frank L. van de Veerdonk[2,19]

Abstract

Purpose: Invasive pulmonary aspergillosis is increasingly reported in patients with influenza admitted to the intensive care unit (ICU). Classification of patients with influenza-associated pulmonary aspergillosis (IAPA) using the current definitions for invasive fungal diseases has proven difficult, and our aim was to develop case definitions for IAPA that can facilitate clinical studies.

Methods: A group of 29 international experts reviewed current insights into the epidemiology, diagnosis and management of IAPA and proposed a case definition of IAPA through a process of informal consensus.

Results: Since IAPA may develop in a wide range of hosts, an entry criterion was proposed and not host factors. The entry criterion was defined as a patient requiring ICU admission for respiratory distress with a positive influenza test temporally related to ICU admission. In addition, proven IAPA required histological evidence of invasive septate hyphae and mycological evidence for *Aspergillus*. Probable IAPA required the detection of galactomannan or positive *Aspergillus* culture in bronchoalveolar lavage (BAL) or serum with pulmonary infiltrates or a positive culture in upper respiratory samples with bronchoscopic evidence for tracheobronchitis or cavitating pulmonary infiltrates of recent onset. The IAPA case definitions may be useful to classify patients with COVID-19-associated pulmonary aspergillosis (CAPA), while awaiting further studies that provide more insight into the interaction between *Aspergillus* and the SARS-CoV-2-infected lung.

*Correspondence: paul.verweij@radboudumc.nl
[1] Department of Medical Microbiology, Radboud University Medical Center, PO box 9101, 6500 HB Nijmegen, The Netherlands
Full author information is available at the end of the article

Disclaimer: The findings and conclusions in this report those of the authors do not necessarily represent the official positions of the Centers for Disease Control and Prevention (CDC).

Springer

Conclusion: A consensus case definition of IAPA is proposed, which will facilitate research into the epidemiology, diagnosis and management of this emerging acute and severe *Aspergillus* disease, and may be of use to study CAPA.

Keywords: Viral pneumonia, Influenza, COVID-19, Invasive aspergillosis, ICU

Introduction

Invasive pulmonary aspergillosis (IPA) is a well-recognized disease affecting immunocompromised individuals with prolonged neutropenia, inherited neutrophil disorders or T cell defects, with the risk depending on the patients' underlying disease and the type and duration of immunosuppressive therapy [1]. Patients at the highest risk of invasive aspergillosis (IA) include those undergoing intensive chemotherapy for acute leukemia (AL) or recipients of allogeneic cell transplantation (alloHCT) who develop severe graft-versus-host disease, for whom antifungal prophylaxis is currently recommended [2, 3]. With changing treatment modalities, new risk groups continue to emerge, such as patients treated with ibrutinib [4, 5].

Although over the past four decades a link between influenza and IPA has been noted in single cases [6], recent cohort studies provide new insights into the epidemiology and clinical presentation of IPA in intensive care unit (ICU) patients with influenza [7–9]. Patients presenting with influenza-associated pulmonary aspergillosis (IAPA) may have classic European Organization for Research and Treatment of Cancer (EORTC)/Mycosis Study Group Education and Research Consortium (MSGERC)-defined host factors [10], but a notable proportion of patients was deemed to be at low risk of IPA, including previously healthy individuals. In addition, the clinical and radiological presentation was often atypical with radiological features that were not considered suggestive of invasive fungal disease. As a consequence, we cannot classify these patients according to existing consensus definitions, i.e., the EORTC/MSGERC definitions and the *AspICU* algorithm for classification of IPA patients in the ICU [10, 11]. We therefore set out to discuss current insights into the epidemiology, pathogenesis, diagnosis and management of IAPA and to propose case definitions that can facilitate homogeneity and comparability in clinical studies.

Participants and methods

The expert panel is comprised of 29 participants from seven European countries, the USA and Taiwan. To ensure heterogenicity, participants were selected from various fields of expertise: medical microbiology (PEV, KL, CL-F, TRR), infectious diseases (BJAR, MB, TC, CJC, OAC, DRG, NAFJ, BJK, OL, MH-N, TFP, FLvdV), intensive care medicine (EA, SB, PD, PW-LL, IM-L, JAS, LV, JW), clinical pharmacology (RJMB, RL, IS), public health (TC) and hematology (OAC, JM). Selected participants furthermore had specific expertise in epidemiology, diagnosis and management of invasive fungal diseases or fungal disease guideline development. The meeting was prepared by PEV, RJMB, JW and FLvdV. Case definitions were developed through a process of informal consensus. Although a systematic literature review was not performed, experts in the field presented overviews regarding epidemiology, pathogenesis, diagnosis and treatment of IAPA, which were followed by a group discussion process designed to allow members of the group to voice their opinions and contribute equally to the decision-making [12]. The goal of the consensus process was to bring the group to general agreement. Presentations and initial discussions took place on a single day meeting in April 2019 in Amsterdam and were continued through electronic exchange of views until consensus was achieved. The chosen framework included host and risk factors, clinical factors and mycological evidence, similar to the framework in the EORTC/MSGERC definitions and the *AspICU* algorithm [10, 11]. A medical writer made notes of the meeting, which were used as input to write the manuscript. A first draft manuscript was prepared by PEV, BJAR, RJMB, JW and FLvdV and circulated for comments from all experts. The experts reviewed and commented on the manuscript. Using these comments, a final version was circulated for approval. The logistics of the meeting were handled by a certified Congress organizer (Congress Care, s'Hertogenbosch, the Netherlands) with financial support of Pfizer (Pfizer B.V., Capelle aan den IJssel, the Netherlands). Congress Care and Pfizer had no influence on the selection of participants, selected topics, discussions, preparation and final approval of the content of the manuscript.

Take-home message

Invasive pulmonary aspergillosis is an emerging co-infection in patients with influenza who are admitted to the ICU. An international team of experts proposed consensus case definitions of influenza-associated pulmonary aspergillosis in order to facilitate clinical studies and the definition may also be useful to study COVID-19-associated pulmonary aspergillosis.

Expert review

Global epidemiology of influenza and IAPA

Although figures vary depending on geographic region, season and vaccination rates, approximately 0.1% of influenza patients require hospital admission with 5–10% of these requiring ICU admission [13, 14]. The mortality in patients admitted for influenza is 4% and 20–25% for those admitted to ICU [14–16]. Bacterial superinfection is common, affecting 10–35% of cases, typically with *Streptococcus pneumoniae* or *Staphylococcus aureus* [16]. However, a recent Dutch–Belgian multicenter study over seven influenza seasons in seven institutes demonstrated influenza as an independent risk factor of IPA (adjusted odds ratio 5.19, 95% confidence interval (CI) 2.63–10.26, $p < 0.001$) [9]. Results also showed that the 90-day mortality rate for ICU patients with IAPA was almost double that of ICU influenza patients without IAPA (51% vs. 28%, adjusted odds ratio 1.87, 95% CI 1.05–3.32). IAPA was initially thought to be associated with influenza A/H1N1pdm09 only [7, 17], but it became clear that IAPA is also associated with other influenza A and influenza B viruses [9]. The median time between influenza diagnosis and IAPA was short, often in the first 5 days [7, 8, 18]. Studies have shown considerable variation in rates of IAPA in different countries, with high rates in the Netherlands, Belgium and Taiwan, but lower rates in other countries [19], and in some we do not know the incidence (e.g., USA) [20–22]. Potential reasons for these regional differences are related to the underlying conditions, concomitant exposure to corticosteroids, environmental factors, including exposure to *Aspergillus*, use of non-culture-based diagnostic tests for *Aspergillus* (e.g., galactomannan (GM)) and differences in awareness of IAPA [23–25]. Autopsy rates are very low, which results in a considerable underdiagnosis in many countries [26]. Other factors that might contribute to regional differences in IAPA rates include influenza vaccination rates, with different policies in different countries, and differences in influenza antiviral treatment strategies with oseltamivir or zanamivir [27]. Annual vaccination reduces influenza-associated complications (hospitalization, ICU admission, severity of illness, superinfection) and improves the outcome in transplant recipients and COPD patients [28, 29].

Pathogenesis of IAPA

In pending studies that explore the pathogenesis of IAPA and host immune defects, it is likely that damage to the epithelium by influenza and defective fungal host responses in the lung due to influenza and/or inflammatory conditions predispose to *Aspergillus* disease, similar as what is seen in bacterial superinfections. Furthermore, autopsy studies have shown the presence of sporulating heads of *Aspergillus* inside the bronchi with invasive growth occurring into the lung tissue. Sporulation could contribute to a high fungal burden and spread of the disease within the lung, thus contributing to the rapid disease progression and extensive lung damage. Other factors that have been implicated in IAPA include the use of corticosteroids and of neuraminidase inhibitors, such as oseltamivir [7, 30]. Ultimately, these insights may aid in identifying patients at risk of IAPA and to design effective antifungal and adjunctive immunomodulatory treatment strategies.

Clinical presentation and diagnosis of IAPA

A retrospective Belgian study of influenza patients admitted to ICU between September 2009 and March 2011 showed that 9 of 40 (23%) patients had IAPA. Four cases (44%) were proven despite not being immunocompromised according to the EORTC/MSGERC consensus definitions [7]. The median time between influenza diagnosis and IAPA was 2 days (range 0–4 days). All IAPA patients had positive BAL GM, and 78% had positive serum GM, despite not being neutropenic. Eighty-nine percent of patients had *Aspergillus* growth in BAL culture (almost exclusively *Aspergillus fumigatus*), and 55% of patients had endobronchial lesions observed during bronchoscopy, possibly indicating invasive tracheobronchitis [7]. Similar performance characteristics of BAL GM and culture were reported in two other cohort studies [8, 9]. BAL sampling is thus an important diagnostic procedure as serum GM can be negative and sputum/tracheal aspirate cultures can remain sterile.

Lesions that are suggestive of invasive mold disease on imaging in neutropenic patients, such as the halo sign, are often absent in critically ill patients. However, in some IAPA patients with autopsy-confirmed *Aspergillus* tracheobronchitis, chest CT demonstrated peribronchial infiltrates. The main diagnostic clue for airway-invasive *Aspergillus* tracheobronchitis is epithelial plaques, pseudomembranes or ulcers that can be visualized via bronchoscopy, as radiological features may be subtle [31]. Worsening of radiographic pulmonary infiltrates in patients with influenza is often attributed to progression of ARDS or bacterial infection, leading to a change of antimicrobial therapy without performing diagnostic procedures [32]. Patients who survived IAPA received antifungal therapy much earlier than those who did not (2 days after diagnosis of influenza among survivors versus 9 days among non-survivors) [8], suggesting that early diagnosis and administration of antifungal therapy may be important. Lateral flow tests have recently become available as an alternative for diagnosing IPA (AspLFD, OLM Diagnostics and the sōna Aspergillus GM, IMMY) showing overall good performance in

hematology patients [33]. The very quick assessment, with results available within 30–45 min, makes this type of test very attractive for the management of IAPA and use in clinical trials. However, lateral flow tests have not yet been validated in the ICU population.

IAPA needs to be considered in patients admitted to the ICU with influenza and where indicated these patients should undergo early BAL for *Aspergillus* antigen testing, culture and microscopy. Patients who test positive require anti-*Aspergillus* therapy, and the BAL fluid sample should be fast-tracked for azole resistance testing by PCR (and culture when positive) in regions with high (> 5%) azole resistance rates [34]. This would enable diagnostic assessment and initiation of adequate antifungal therapy within 24–48 h of ICU admission. Diagnostic workup for IAPA may be repeated in patients deteriorating while on antivirals and/or appropriate antibiotics or when initiating corticosteroid treatment is unavoidable.

Discussion on clinical presentation and diagnosis of IAPA

If a patient is admitted to the ICU and has influenza with pulmonary infiltrates, the diagnosis of IAPA should be considered and further investigation performed as appropriate. Ideally, this would include in order of invasiveness, serum GM testing, fungal cultures of sputum and/or tracheal aspirate, pulmonary CT, bronchoscopy to visualize the large airways and obtain BAL fluid for GM testing and fungal and bacterial cultures. Testing is most appropriate in patients who are on mechanical ventilation, but the diagnostic strategy is less clear in patients not intubated. As up to 50% of patients may present with tracheobronchitis, the presence of plaques and ulceration might be considered for inclusion in the definition of IPA [35]. Policies for taking biopsies of lesions seen on bronchoscopy may vary, mainly because of concerns about the risk of bleeding with biopsy in ICU patients. The use of a flexible brush may also be sufficient to make the diagnosis.

Although a positive serum GM is highly indicative of IA, BAL GM can be positive in patients with *Aspergillus* colonization. It therefore does not absolutely discriminate between colonization and invasive disease. However, it clearly makes it more likely that an invasive disease is present [36].

Use of corticosteroids

Corticosteroids should not be given to influenza patients as their use may be associated with increased risk of IAPA [7, 37–39]. A recent Cochrane review on this topic concluded that the use of corticosteroids in patients with influenza was associated with a worse outcome [40]. However, the evidence was almost exclusively observational. Furthermore, patients are often given steroids in the first few days preceding or after ICU admission for a variety of reasons including COPD exacerbation or complications such as sepsis. With surveys suggesting that approximately half of the physicians are not aware of IAPA [24], many physicians may additionally not be aware of the potential drawbacks of corticosteroids. Whenever the use of corticosteroids is unavoidable, more efforts (bronchoscopy with GM detection in BAL fluid or serum β-D-glucan test) should be made to exclude or diagnose IAPA [41].

Rationale for antifungal prophylaxis for IAPA

In settings with high IAPA rates in ICU patients with influenza pneumonia, an antifungal prophylaxis strategy might be appropriate, particularly as IAPA typically occurs early after ICU admission. However, there is currently no mold-active antifungal agent licensed for prophylaxis of IA in ICU patients. Posaconazole (POS) prophylaxis reduces the prevalence of IA in neutropenic AML patients and those with graft-versus-host disease following alloHCT [2, 3]. Based on this proof-of-principle, it has been hypothesized that POS prophylaxis can reduce IAPA prevalence in ICU patients. Intravenous (IV) administration of POS prophylaxis in the ICU is favored in patients on mechanical ventilation or with a high likelihood of malabsorption of oral formulations. POS IV formulation should be administered through a central catheter due to its acidity (pH 3.2) [42].

Treatment options and challenges for IAPA in the ICU

First-line treatment options for IPA include voriconazole and isavuconazole [35, 43]. Other options include echinocandins in combination with anti-mold azoles, and liposomal amphotericin B (L-AmB) in regions with high rates of azole-resistant *A. fumigatus*, although clinical data with L-AmB in ICU patients are limited [43, 44]. Achieving adequate drug exposure is challenging in ICU patients with multiple factors contributing to pharmacokinetic variability. Unlike L-AmB and the echinocandins, drug interactions are clinically relevant for the azoles and pharmacogenetic factors are important in inter-individual drug exposure variability [45]. The impact of therapeutic drug monitoring (TDM) for voriconazole shows a clear relation between exposure and both efficacy and toxicity. Target plasma trough voriconazole concentrations of $\geq$ 1.5–2 mg/L are associated with near-maximal clinical response in treatment of IA with a wild-type phenotype [46–51], with higher exposures (> 5.5 mg/L) increasing the risk of (neuro)toxicity. Higher trough concentrations (> 2 mg/L) are recommended for treatment of pathogens with elevated MICs (e.g., > 0.25 mg/L) [52]. For isavuconazole, there is no robust target plasma concentration, and the population

average exposure of participants that demonstrated a favorable response (2–4 mg/L) is commonly used [43].

Discussion on antifungal treatment options and challenges for IAPA in the ICU

A specific drug–drug interaction is relevant for patients with IAPA given the fact that co-infections with *S. aureus* are frequently observed; undetectable voriconazole levels have been observed in 11 of 20 patients, who were concomitantly treated with flucloxacillin [53], but the mechanisms of interaction are not yet fully understood. Similar interactions have not been seen with other azoles. Many other drug interactions with azoles and drugs commonly deployed in the ICU can be expected [45].

Aerosolized antifungal treatment may be a useful adjunctive therapy to systemic antifungal therapy for patients with confirmed *Aspergillus* tracheobronchitis, to achieve good endobronchial exposure [35, 54]. However, dense lipophilic plaques in the trachea may be difficult to penetrate and more research is needed into when and how to use aerosolized antifungals as well as their efficacy. The ECCMID/ECMM/ERS *Aspergillus* guideline reviewed the teratogenic and mutagenic potential of antifungals in early pregnancy and recommends that azoles should be avoided, with polyenes being considered the preferred therapy [43, 55]. Thus, for pregnant patients at risk of IAPA a diagnostic approach was preferred above antifungal prophylaxis.

There is little evidence on the impact of ECMO on antifungal drug exposure [56]. For the echinocandins, an impact of ECMO is not expected. Experts felt that, given these uncertainties, TDM of any antifungal used would be advised to ensure sufficient drug exposure.

Consensus case definition for IAPA

The expert panel discussed which case definition of IAPA would be appropriate to use in clinical studies, initially considering various aspects regarding four main areas of focus: entry criteria of the consensus definition, host, clinical features and mycological evidence similar to the currently used EORTC/MSGERC classification.

Entry criterion

In addition to having a positive diagnostic test for influenza, patients would require to have a clinical syndrome compatible with influenza disease as part of the definition. This criterion should be termed the 'entry criterion' and not 'host factor' for clarity. To avoid the risk of missing patients who initially tested negative with a rapid influenza antigen test but subsequently tested positive (by PCR) for influenza when admitted to hospital, a recommendation on a timescale, such as between 1 week before ICU admission and 72–96 h post-admission, was included. The consensus on the entry criterion was: a patient requiring ICU admission for respiratory distress with a positive influenza PCR or antigen test temporally related to ICU admission.

Host factors

Host factors are considered in the EORTC/MSGERC definition and *AspICU* algorithm [10, 11], but the system of taking host factors into account was a necessity because the risk of a false-positive *Aspergillus* test increases substantially when the test is done in patients at low risk of the disease. Clinicians had to take into account the type of host in order to increase the pretest probability of an invasive fungal disease being present. However, for IAPA the key question is whether the disease is present or not, and not whether the patient group has a higher risk than other patient groups for developing the disease. More importantly, the incidence of IAPA in patients admitted to the ICU with influenza may be higher in some centers [9, 21]. No further host factors are needed to increase the pretest probability in this patient population. Although most IAPA cases have at least one underlying condition or steroid use, host factors were not be included in the case definition for IAPA.

Criteria to define proven and probable cases of IAPA

The distinction between proven and probable IAPA is important for clinical trials, while in clinical practice, people should not distinguish between proven and probable disease.

The criteria for proven disease include a patient fulfilling the entry criterion plus histological evidence of invasive fungal elements and mycological evidence for the presence of *Aspergillus* (obtained by *Aspergillus* PCR or culture from tissue). Tracheobronchitis (tracheal and/or bronchial ulcerations or nodules, pseudomembranes or plaques visualized at bronchoscopy), as also described in the EORTC/MSGERC definitions [10], is a separate entity. Although a tissue biopsy would normally be required to prove a case of IAPA, in tracheobronchitis cases hyphal elements suggestive of *Aspergillus* seen on sloughed-off pseudomembrane, and *Aspergillus* identified on culture or PCR, can also be considered proven disease (Table 1).

A patient fulfilling the case definition of probable IAPA is required to fulfill the entry criterion. A positive serum GM (GM index > 0.5) is important evidence for the diagnosis of IAPA, in patients with pulmonary infiltrates on chest X-ray or other imaging modality or bronchoscopic evidence of tracheobronchitis (Table 1). In patients with tracheobronchitis, an infiltrate is not required.

Table 1 Proposed case definition for IAPA in ICU patients

Entry criteria: influenza-like illness + positive influenza PCR or antigen + temporally relationship		
	***Aspergillus* tracheobronchitis**	**IAPA in patients without documented *Aspergillus* tracheobronchitis**
Proven	Biopsy or brush specimen of airway plaque, pseudomembrane or ulcer showing hyphal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue	Lung biopsy showing invasive fungal elements and *Aspergillus* growth on culture or positive *Aspergillus* PCR in tissue
Probable	Airway plaque, pseudomembrane or ulcer and at least one of the following: Serum GM index > 0.5 *or* BAL GM index ≥ 1.0 *or* Positive BAL culture *or* Positive tracheal aspirate culture *or* Positive sputum culture *or* Hyphae consistent with *Aspergillus*	**A**: Pulmonary infiltrate and at least one of the following: Serum GM index > 0.5 *or* BAL GM index ≥ 1.0 *or* Positive BAL culture ***OR*** **B**: Cavitating infiltrate (not attributed to another cause) and at least one of the following: Positive sputum culture *or* Positive tracheal aspirate culture

In patients with endobronchial plaques or pulmonary infiltrates, a positive BAL GM or culture of a tracheal aspirate is considered mycological evidence that supports a probable IAPA diagnosis. In patients with bacterial pneumonia where *Aspergillus* is cultured only from a sputum sample, there may be a risk of overdiagnosis and thus over-treatment. For clinical practice, clinicians should take into account that a positive culture of an upper airway sample may indicate IAPA, but that confirmation with serum or BAL GM or BAL culture should be pursued. However, one problem is that the background incidence varies in different regions, making it difficult to develop generalized guidelines that apply uniformly. The significance of a positive sputum culture thus depends on the background incidence in a specific unit. Although any *Aspergillus*-positive respiratory sample is in itself insufficient to classify patients as probable IAPA, a new pulmonary cavitating infiltrate is indicative of IAPA in patients who meet the entry criterion. Therefore, any *Aspergillus*-positive respiratory sample is sufficient evidence to classify patients as probable IAPA provided that a pulmonary cavitating infiltrate is present (Table 1; Fig. 1).

A BAL GM index cutoff of ≥ 1.0 is recommended as this cutoff value ensures high specificity, without decreasing sensitivity significantly, which is also in line with other definitions and recommendations [10, 57]. *Aspergillus* PCR is not recommended as a primary diagnostic tool because of concerns about its reliability and positive predictive value for the diagnosis of IPA. However, *Aspergillus* PCR is recommended in the proven category because it enables *Aspergillus* identification in tissue samples.

In some patients, discordant results are obtained, for instance a positive sputum culture but negative BAL GM. For most situations, IAPA classification relies on a positive GM test, as a positive sputum culture with a negative GM result would be interpreted as a lower probability of IAPA (unless a pulmonary cavity or tracheobronchitis is present)(Fig. 1).

Conclusion

IAPA has emerged as a severe complication of influenza, especially in ICU patients, and this secondary infection may occur in any patient, including those considered to be at low risk of developing IPA. The global epidemiology of IAPA may be variable, which might be partly due to underdiagnosis [24]. The clinical presentation of IAPA includes invasive *Aspergillus* tracheobronchitis, which requires bronchoscopic visualization of plaques in the airways to make a diagnosis. *Aspergillus* culture and BAL GM are positive in > 80% of IAPA cases, and ordering such tests is recommended in influenza cases in the ICU. The proposed case definition relies on an entry criterion based on an influenza-like illness and the detection of influenza virus. The case definition distinguishes between invasive tracheobronchitis and other pulmonary forms of IAPA, with demonstration of invasive fungal hyphae with positive mycology qualifying as proven infection. Detection of GM or positive *Aspergillus* culture in BAL is the main mycological criteria in probable case definition.

The expert group acknowledges that to date still limited data exist to support a definitive approach regarding

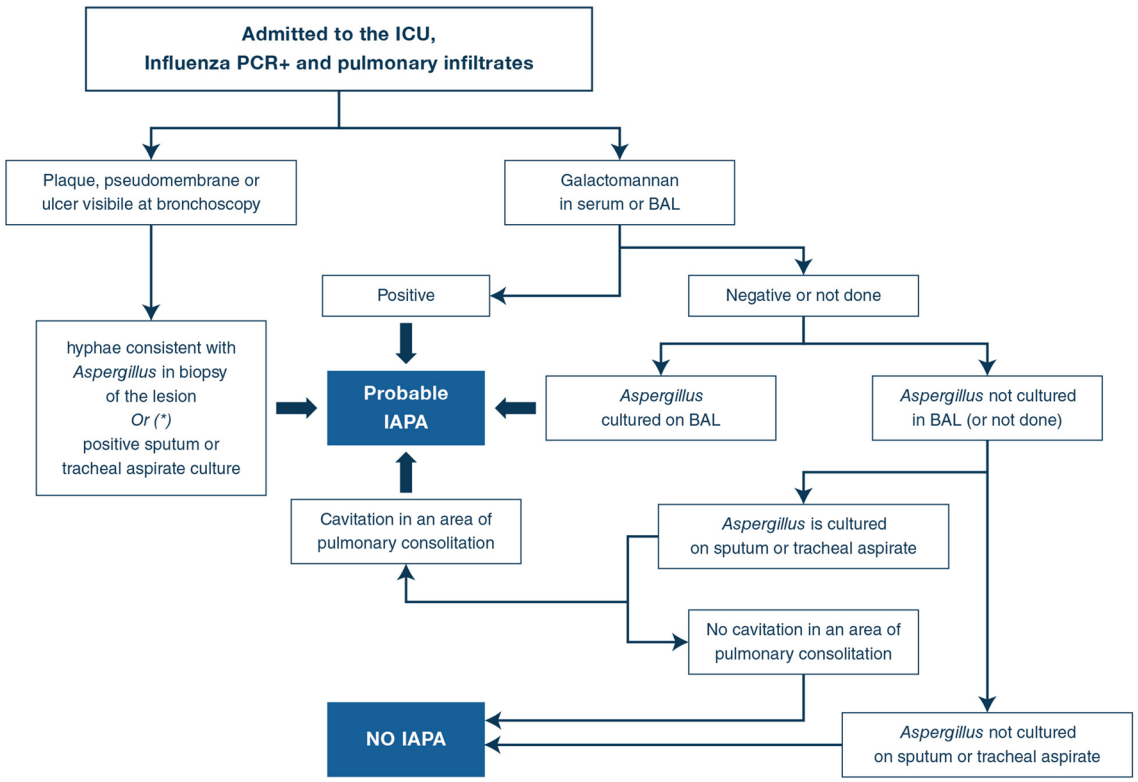

Fig. 1 Flowchart of probable IAPA classification. (*)If hyphae consistent with *Aspergillus* are documented in a biopsy of an airway lesion AND *Aspergillus* is grown from sputum or a tracheal aspirate, the case fulfills the definition of proven IAPA

definitions, diagnosis and treatment of IAPA, but the proposed case definition will facilitate clinical research, will enable valid study comparisons and is essential for surveillance. Awareness of IAPA and early antifungal therapy based on high clinical suspicion and *Aspergillus* diagnostics remains critical to improve the outcome of IAPA.

Can the IAPA definitions be applied to COVID-19-associated pulmonary aspergillosis?

Recent reports of IPA cases in coronavirus disease 2019 (COVID-19) patients in the ICU raise the question of whether these IAPA definitions can be applied to COVID-19-associated pulmonary aspergillosis (CAPA) [58–60]. Although the number of CAPA cases that have been reported is still limited, two recent studies reported putative CAPA cases in 9 of 27 (33%) and 5 of 19 (26%) COVID-19 patients admitted to the ICU [59, 60]. Although the high number of cases suggests a high risk of developing IPA in COVID-19 patients, there are a number of differences regarding the pathogenesis of SARS-CoV-2 infection compared with influenza (Table 2). In influenza patients, there are several factors that are thought to contribute to the risk of IAPA, including the local tissue damage caused by influenza, an immune modulatory effect by suppression of the NADPH oxidase complex and possible effect of treatment with neuraminidase inhibitors, such as oseltamivir. In SARS-CoV-2 infection, another receptor is used by the virus to enter human cells, which are not commonly found in the large airways (Table 2). Thus, the risk of invasive *Aspergillus* tracheobronchitis may be lower in CAPA compared with IAPA. In addition, there is no known direct immune modulatory effect of SARS-CoV-2, which suggests no virus infection-related increased risk of IPA. While IAPA is characterized by rapidly fatal infections with high fungal burden, such course of disease progression has not been reported for CAPA. On the contrary, eight of nine CAPA cases reported from a French cohort did not receive antifungal therapy, with a mortality rate similar to COVID-19 cases without IPA [59]. As, in contrast to IAPA cases, virtually all CAPA cases reported to date are serum GM negative, the question remains if COVID-19 patients develop invasive disease or just become colonized with *Aspergillus*. It is possible that COVID-19 is in itself not a risk factor for IPA, but that the risk is associated with other risk factors related to treatment such

Table 2 Comparison between characteristics of IAPA and CAPA

Factor	IAPA	CAPA
Host/Risk	57% EORTC/MSGERC host factor negative [9]	85% EORTC/MSGERC host factor negative [59, 60]
	IAPA associated with corticosteroid use [7]	IPA developed in SARS-2003-infected patients receiving corticosteroids [61]
		Lymphopenia and chemokine-producing monocyte-derived FCN1 + macrophages causing hyperinflammation [62]
Virus	Cell entry through sialic acids-2,6Gal: epithelial layer in lung including larger airways [63]	Cell entry through ACE2: type 2 pneumocytes and ciliated cells [64]
	Immune modulation by suppression of the NADPH oxidase complex [65]	No evidence for immunomodulatory effect on known antifungal host defense mechanisms, although this has not been extensively studied yet
Fungal infection	Invasive *Aspergillus* tracheobronchitis in up to 55% of patients [7–9]	Invasive *Aspergillus* tracheobronchitis not yet reported [59, 60]
	Median time between ICU admission and IAPA diagnosis 2–3 days [7–9]	Median time between ICU admission and CAPA diagnosis 6 days [59]
Aspergillus diagnostics	BAL GM positive in > 88% [7–9]	BAL GM commonly positive, diagnostic performance currently unknown [59, 60]
	Serum GM positive in 65% [7–9]	Serum GM positive in 3 of 14 (21%) COVID-19 patients [59, 60]
Secondary infections	In 80 of 342 (23.4%) ICU patients, most frequent pathogens *S. pneumoniae*, *Pseudomonas aeruginosa* and *S. aureus* [66]	In four of 13 (31%) ICU patients, pathogens not specified [67]
ICU mortality	45% in IAPA compared with 20% in influenza without IAPA ($p < 0.0001$) [9]	33% in CAPA cases compared with 17% in COVID-19 without CAPA ($p = 0.4$) [59] (although mortality rates due to COVID-19 without CAPA vary enormous between countries and we have no clear data yet on the true mortality in ICU of COVID-19)

as administration of corticosteroids or underlying host factors. Nevertheless, the high rate of *Aspergillus* recovered from COVID-19 patients suggests that there might be conditions that favor growth of the fungus in the lung. We think that the proposed IAPA case definitions may be considered for classification of CAPA patients, while awaiting further histopathological studies that provide more insight into the interaction between *Aspergillus* and the SARS-CoV-2-infected lung.

Author details
[1] Department of Medical Microbiology, Radboud University Medical Center, PO box 9101, 6500 HB Nijmegen, The Netherlands. [2] Centre of Expertise in Mycology Radboudumc/CWZ, Radboudumc Center for Infectious Diseases (RCI), Nijmegen, The Netherlands. [3] Department of Internal Medicine and Infectious Diseases, Erasmus MC, University Medical Center, Rotterdam, 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, DISSAL, 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] Division of Infectious Diseases, University of Pittsburgh, Pittsburgh, PA, USA. [12] Infectious Diseases Section, VA Pittsburgh Healthcare System, Pittsburgh, USA. [13] Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Cologne, Germany. [14] Department of Internal Medicine, ECMM Center of Excellence for Medical Mycology, German Centre for Infection Research, Partner Site Bonn-Cologne (DZIF), University of Cologne, Cologne, Germany. [15] Clinical Trials Centre Cologne (ZKS Köln), University of Cologne, Cologne, Germany. [16] Centers for Disease Control and Prevention, Atlanta, GA 30329, USA. [17] Department of Critical Care Medicine, Ghent University Hospital, Ghent, Belgium. [18] Department of Health Sciences, University of Genoa, Genoa, Italy. [19] Department of Medicine, Radboud University Medical Center, Nijmegen, The Netherlands. [20] Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium. [21] Department of Laboratory Medicine and National Reference Centre for Mycosis, University Hospitals Leuven, Leuven, Belgium. [22] Division of Hygiene and Medical Microbiology, Medical University of Innsbruck, Innsbruck, Austria. [23] Infectious Diseases Hospital, S'Orsola-Malpighi, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy. [24] Department of Emergency and Critical Care Medicine, Fu Jen Catholic University Hospital, Fu Jen Catholic University, New Taipei, Taiwan. [25] School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei, Taiwan. [26] Necker - Pasteur Center for Infectious Diseases and Tropical Medicine, Necker-Enfants Malades Hospital, AP-HP, Paris University, Paris, France. [27] Molecular Mycology Unit National Reference Center for Invasive Mycoses and Antifungals, CNRS, UMR 2000, Institut Pasteur, Paris, France. [28] Department of Hematology, University Hospitals Leuven, Leuven, Belgium. [29] Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St. James's Hospital, Dublin, Ireland. [30] Hospital Clinic, IDIBAPS, Universidad de Barcelona, Ciberes, Barcelona, Spain. [31] Department of Medicine, Division of Infectious Diseases, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA. [32] South Texas Veterans Health Care Center, San Antonio, TX, USA. [33] Department of Clinical Microbiology, Trinity College Dublin, St. James's Hospital, Dublin, Ireland. [34] Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands. [35] Scientific Center for Quality of Healthcare (IQ Healthcare), Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, The Netherlands. [36] Pharmacy Department, University Hospitals Leuven, Leuven, Belgium. [37] Department of General Internal Medicine, Medical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium.

Author contributions
An expert meeting was organized by PEV, RJMB, JW and FLvdV and held in Amsterdam on April 16, 2019. Present at the expert meeting were PEV, BJAR, RJMB, SB, CJC, OAC, DRG, NAFJ, BJK, KL, JM, MHN, TFP, TRR and FLvdV. A first draft manuscript was prepared by PEV, BJAR, RJMB, JW and FLvdV and circulated for comments from all experts. All experts reviewed and commented on the manuscript. Using these comments, a final version was circulated for approval.

Funding
The meeting was supported by Pfizer. Pfizer had no role in the topics discussed nor were they involved in drafting of the consensus document.

Compliance with ethical standards

Conflicts of interest
PE Verweij reported grants from Gilead Sciences, MSD, Pfizer and F2G, and non-financial support from OLM and IMMY, outside the submitted work. BJA Rijnders was the 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, Jansen-Cilag, BMS; and an advisory board member for BMS, Abbvie, MSD, Gilead, Jansen-Cilag; he received travel support from BMS, Abbvie, MSD, Gilead, Jansen-Cilag. RJM Brüggemann served as a consultant to Astellas Pharma, Inc., F2G, Amplyx, Gilead Sciences, Merck Sharp & Dohme Corp., and Pfizer, Inc., and has received unrestricted and research grants from Astellas Pharma, Inc., Gilead Sciences, Merck Sharp & Dohme Corp., and Pfizer, Inc. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. E Azoulay has received fees for lectures from Pfizer, Gilead, MSD, Alexion and Baxter. His institution received research support from Fisher&Payckle, Jazz pharma and Gilead. M Bassetti has received funding for scientific advisory boards, travel and speaker honoraria from Angelini, Astellas, AstraZeneca, Basilea, Bayer, BioMèrieux, Cidara, Correvio, Cubist, Menarini, Molteni, MSD, Nabriva, Paratek, Pfizer, Roche, Shionogi, Tetraphase, Thermo Fisher and The Medicine Company. S Blot received research funding from Pfizer and MSD, travel support from Pfizer, MSD and Gilead, and is an invited speaker for Pfizer and Gilead. T Calandra reported advisory board membership from Astellas, Basilea, Cidara, MSD, Sobi, ThermoFisher and GE Healthcare and data monitoring board membership from Novartis, all outside the submitted work. Fees are paid to its institution. CJ Clancy has been awarded investigator-initiated research grants from Astellas, Merck, Melinta and Cidara for projects unrelated to this project, served on advisory boards or consulted for Astellas, Merck, the Medicines Company, Cidara, Scynexis, Shionogi, Qpex and Needham & Company, and spoken at symposia sponsored by Merck and T2Biosystems. OA Cornely 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, Allecra Therapeutics, Amplyx, Astellas, Basilea, Biosys UK Limited, Cidara, Da Volterra, Entasis, F2G, Gilead, Grupo Biotoscana, Janssen Pharmaceuticals, Matinas, Medicines Company, MedPace, Melinta Therapeutics, Menarini Ricerche, Merck/MSD, Octapharma, Paratek Pharmaceuticals, Pfizer, PSI, Rempex, Scynexis, Seres Therapeutics, Tetraphase, Vical. T Chiller reported no conflicts of interest. P Depuydt reported no conflicts of interest. DR Giacobbe reported honoraria from Stepstone Pharma GmbH and an unconditional grant from MSD Italia. NAF Janssen reported no conflicts of interest. BJ Kullberg has been a scientific advisor for Amplyx, Cidara and Scynexis. K Lagrou received consultancy fees from MSD, SMB Laboratoires Brussels and Gilead, travel support from Pfizer and MSD and speaker fees from Gilead, MSD, FUJIFILM WAKO. C Lass-Florl received research funding from Pfizer, Gilead and Egger, travel support from Pfizer, MSD, and Gilead, and is an invited speaker for Pfizer and Gilead. RE Lewis has received research support from Merck and has served as an invited speaker for Gilead, Cidara. 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. O Lortholary has served as an invited speaker for Gilead, MSD, Pfizer, Astellas Pharma, and is a consultant for Gilead, Novartis and F2G. J Maertens reported personal fees and non-financial support from Basilea Pharmaceuticals, Bio-Rad Laboratories, Cidara, F2G Ltd., Gilead Sciences, Merck, Astellas, Scynexis, and Pfizer Inc. and grants from Gilead Sciences, IMMY and OLM. I Martin-Loeches reported no conflicts of interest. MH Nguyen has been awarded investigator-initiated research grants from Astellas, Merck, Melinta and Cidara for projects unrelated to this study and served on advisory boards for Astellas, Merck, the Medicines Company, Scynexis and Shionogi. TF Patterson reported grants from Cidara to UT Health San Antonio; personal fees from Basilea, Gilead, Mayne, Merck, Pfizer, Scynexis, Sfunga, Toyama and United Medical outside the submitted work. TR Rogers has received grants from Gilead Sciences, lecture honoraria from Gilead Sciences and Pfizer Healthcare Ireland, and advisory board membership with Menarini Pharma. JA Schouten has received unrestricted educational and research grants from MSD and has been an advisor to Pfizer. All contracts were through Radboudumc, and all payments were invoiced by Radboudumc. I Spriet has received unrestricted research grants, speaker fees and travel grants from MSD, Pfizer, Gilead and Cidara. She has served in the advisory board for Cidara. L Vanderbeke is supported by the Flanders Research Foundation (FWO Vlaanderen) through a doctoral fellowship. J Wauters reported grants from Gilead Sciences, MSD and Pfizer, and non-financial support from MSD, outside the submitted work. FL van de Veerdonk has served as an invited speaker for Gilead.

Publisher's Note

Received: 28 February 2020 Accepted: 7 May 2020
Published online: 22 June 2020

References
1. Kosmidis C, Denning DW (2015) The clinical spectrum of pulmonary aspergillosis. Thorax 70:270–277. https://doi.org/10.1136/thoraxjnl-2014-206291
2. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, Helfgott D, Holowiecki J, Stockelberg D, Goh YT, Petrini M, Hardalo C, Suresh R, Angulo-Gonzalez D (2007) Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. N Engl J Med 356:348–59. PMID: 17251531
3. Ullmann AJ, Lipton JH, Vesole DH, Chandrasekar P, Langston A, Tarantolo SR, Greinix H, Morais de Azevedo W, Reddy V, Boparai N, Pedicone L, Patino H, Durrant S (2007) Posaconazole or fluconazole for prophylaxis in severe graft-versus-host disease. N Engl J Med 356:335–347. PMID: 17251530
4. Ghez D, Calleja A, Protin C, Baron M, Ledoux MP, Damaj G, Dupont M, Dreyfus B, Ferrant E, Herbaux C, Laribi K, Le Calloch R, Malphettes M, Paul F, Souchet L, Truchan-Graczyk M, Delavigne K, Dartigeas C, Ysebaert L, French Innovative LeukemiaOrganization, (FILO) CLL group (2018) Early-onset invasive aspergillosis and other fungal diseases in patients treated with ibrutinib. Blood 131:1955–1959. https://doi.org/10.1182/blood-2017-11-818286
5. Maschmeyer G, De Greef J, Mellinghoff SC, Nosari A, Thiebaut-Bertrand A, Bergeron A, Franquet T, Blijlevens NMA, Maertens JA, on behalf of the European Conference on Infections in Leukemia (ECIL)(2019) Infections associated with immunotherapeutic and molecular targeted agents in hematology and oncology. In: A position paper by the European conference on infections in Leukemia (ECIL). Leukemia 33:844–862. https://doi.org/10.1038/s41375-019-0388-x
6. Fischer JJ, Walker DH (1979) Invasive pulmonary aspergillosis associated with influenza. JAMA 241:1493–1494

7. Wauters J, Baar I, Meersseman P, Meersseman W, Dams K, De Paep R, Lagrou K, Wilmer A, Jorens P, Hermans G (2012) Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. Intensive Care Med 38:1761–1768. https://doi.org/10.1007/s00134-012-2673-2
8. van de Veerdonk FL, Kolwijck E, Lestrade PP, Hodiamont CJ, Rijnders BJ, van Paassen J, Haas PJ, OliveiraDosSantos C, Kampinga GA, Bergmans DC, van Dijk K, de Haan AF, van Dissel J, van Hoeven HG, Verweij PE (2017) Influenza-associated aspergillosis in critically ill patients. Am J Respir Crit Care Med 196:524–527. https://doi.org/10.1164/rccm.201612-2540LE
9. Schauwvlieghe AFAD, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, Lagrou K, Verweij PE, Van de Veerdonk FL, Gommers D, Spronk P, Bergmans DCJJ, Hoedemaekers A, Andrinopoulou ER, van den Berg CHSB, Juffermans NP, Hodiamont CJ, Vonk AG, Depuydt P, Boelens J, Wauters J, Dutch-Belgian Mycosis Study Group (2018) Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 6:782–792. https://doi.org/10.1016/S2213-2600(18)30274-1
10. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, Clancy CJ, Wingard JR, Lockhart SR, Groll AH, Sorrell TC, Bassetti M, Akan H, Alexander BD, Andes D, Azoulay E, Bialek R, Bradsher RW, Bretagne S, Calandra T, Caliendo AM, Castagnola E, Cruciani M, Cuenca-Estrella M, Decker CF, Desai SR, Fisher B, Harrison T, Heussel CP, Jensen HE, Kibbler CC, Kontoyiannis DP, Kullberg BJ, Lagrou K, Lamoth F, Lehrnbecher T, Loeffler J, Lortholary O, Maertens J, Marchetti O, Marr KA, Masur H, Meis JF, Morrisey CO, Nucci M, Ostrosky-Zeichner L, Pagano L, Patterson TF, Perfect JR, Racil Z, Roilides E, Ruhnke M, Prokop CS, Shoham S, Slavin MA, Stevens DA, Thompson GR, Vazquez JA, Viscoli C, Walsh TJ, Warris A, Wheat LJ, White PL, Zaoutis TE, Pappas PG (2019) 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 Dec 5. pii: ciz1008. https://doi.org/10.1093/cid/ciz1008. [Epub ahead of print]
11. Blot S, Taccone F, Van Abeele A, Bulpa P, Meersseman W, Brusselaers N, Dimopoulos G, Paiva JA, Misset B, Rello J, Vandewoude K, Vogelaers D, AspICU Study Investigators (2012) A clinical algorithm to diagnose invasive pulmonary aspergillosis in ICU patients. Am J Respir Crit Care Med 186:56–64. https://doi.org/10.1164/rccm.201111-1978OC
12. Black N, Murphy M, Lamping D, McKee M, Sanderson C, Askham J, Marteau T (1999) Consensus development methods: a review of best practice in creating clinical guidelines. J Health Serv Res Policy. 4:236–248
13. Kalil AC, Thomas PG (2019) Influenza virus-related critical illness: pathophysiology and epidemiology. Crit Care 23:258. https://doi.org/10.1186/s13054-019-2539-x
14. GBD (2017) Influenza Collaborators (2019) Mortality, morbidity, and hospitalizations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. Lancet Respir Med 7:69–89. https://doi.org/10.1016/S2213-2600(18)30496-X
15. Beumer MC, Koch RM, van Beuningen D, OudeLashof AM, van de Veerdonk FL, Kolwijck E, van der Hoeven JG, Bergmans DC, Hoedemaekers CWE (2019) Influenza virus and factors that are associated with ICU admission, pulmonary co-infections and ICU mortality. J Crit Care 50:59–65. https://doi.org/10.1016/j.jcrc.2018.11.013
16. Martin-Loeches I, Lemiale V, Geoghegan P, McMahon MA, Pickkers P, Soares M, Perner A, Meyhoff TS, Bukan RB, Rello J, Bauer PR, van de Louw A, Taccone FS, Salluh J, Hemelaar P, Schellongowski P, Rusinova K, Terzi N, Mehta S, Antonelli M, Kouatchet A, Klepstad P, Valkonen M, Landburg PP, Barratt-Due A, Bruneel F, Pène F, Metaxa V, Moreau AS, Souppart V, Burghi G, Girault C, Silva UVA, Montini L, Barbier F, Nielsen LB, Gaborit B, Mokart D, Chevret S, Azoulay E, Efraim Investigators and the Nine-I Study Group (2019) Influenza and associated co-infections in critically ill immunosuppressed patients. Crit Care 23:152. https://doi.org/10.1186/s13054-019-2425-6
17. Vehreschild JJ, Brockelmann PJ, Bangard C, Verheyen J, Vehreschild MJGT, Michels G, Wisplinghoff H, Cornely OA (2012) Pandemic 2009 influenza A(H1N1) virus infection coinciding with invasive pulmonary aspergillosis in neutropenic patients. Epidemiol Infect 140:1848–1852. https://doi.org/10.1017/S0950268811002603
18. Ku YH, Chan KS, Yang CC, Tan CK, Chuang YC, Yu WL (2017) Higher mortality of severe influenza patients with probable aspergillosis than those with and without other coinfections. J Formos Med Assoc 116:660–670. https://doi.org/10.1016/j.jfma.2017.06.002
19. Schwartz IS, Friedman DZP, Zapernick L, Dingle TC, Lee N, Sligl W, Zelyas N, Smith SW (2020) High rates of influenza-associated invasive pulmonary aspergillosis may not be universal: a retrospective cohort study from Alberta, Canada. Clin Infect Dis. https://doi.org/10.1093/cid/ciaa007
20. Uyeki TM, Ison MG, Wolfe CR, Pavia AT et al (2020) Reply to Verweij et al. Clin Infect Dis 70:350–351. https://doi.org/10.1093/cid/ciz568
21. Vanderbeke L, Spriet I, Breynaert C, Rijnders BJA, Verweij PE, Wauters J (2018) Invasive pulmonary aspergillosis complicating severe influenza: epidemiology, diagnosis and treatment. Curr Opin Infect Dis 31:471–480. https://doi.org/10.1097/QCO.0000000000000504
22. Rothberg MB, Haessler SD (2010) Complications of seasonal and pandemic influenza. Crit Care Med 38(4 Suppl):e91–e97. https://doi.org/10.1097/CCM.0b013e3181c92eeb
23. Verweij PE, Brüggemann RJM, Wauters J, Rijnders BJA, Chiller T, van de Veerdonk F (2020) Influenza coinfection: be(a)ware of invasive aspergillosis. Clin Infect Dis 70:349–350. https://doi.org/10.1093/cid/ciz391
24. Thevissen K, Jacobs C, Holtappels M, Toda M, Verweij PE, Wauters J (2020) International survey on influenza-associated pulmonary aspergillosis (IAPA) in intensive care units: responses suggest low awareness and potential under-diagnosis outside Europe. Crit Care 24:84. https://doi.org/10.1186/s13054-020-2808-8
25. Rijnders BJA, Schauwvlieghe AFAD, Wauters J (2020) Influenza-associated pulmonary aspergillosis: a local or global lethal combination? Clin Infect Dis. https://doi.org/10.1093/cid/ciaa010
26. Tejerina EE, Abril E, Padilla R, Rodríguez Ruíz C, Ballen A, Frutos-Vivar F, Lorente JÁ, Esteban A (2019) Invasive aspergillosis in critically ill patients: an autopsy study. Mycoses 62:673–679. https://doi.org/10.1111/myc.12927
27. Bassetti M, Castaldo N, Carnelutti A (2019) Neuraminidase inhibitors as a strategy for influenza treatment: pros, cons and future perspectives. Expert Opin Pharmacother 20:1711–1718. https://doi.org/10.1080/14656566.2019.1626824
28. Kumar D, Ferreira VH, Blumberg E, Silveira F, Cordero E, Perez-Romero P, Aydillo T, Danziger-Isakov L, Limaye AP, Carratala J, Munoz P, Montejo M, Lopez-Medrano F, Farinas MC, Gavalda J, Moreno A, Levi M, Fortun J, Torre-Cisneros J, Englund JA, Natori Y, Husain S, Reid G, Sharma TS, Humar A (2018) A 5-year prospective multicenter evaluation of influenza infection in transplant recipients. Clin Infect Dis 67:1322–1329. https://doi.org/10.1093/cid/ciy294
29. Mulpuru S, Li L, Ye L, Hatchette T, Andrew MK, Ambrose A, Boivin G, Bowie W, Chit A, Dos Santos G, ElSherif M, Green K, Haguinet F, Halperin SA, Ibarguchi B, Johnstone J, Katz K, Langley JM, LeBlanc J, Loeb M, MacKinnon-Cameron D, McCarthy A, McElhaney JE, McGeer A, Powis J, Richardson D, Semret M, Shinde V, Smyth D, Trottier S, Valiquette L, Webster D, McNeil SA, Serious Outcomes Surveillance (SOS) Network of the Canadian Immunization Research Network (CIRN) (2019) Effectiveness of influenza vaccination on hospitalizations and risk factors for severe outcomes in hospitalized patients with COPD. Chest 155:69–78. https://doi.org/10.1016/j.chest.2018.10.044
30. Dewi IMW, Cunha C, Gkountzinopoulou ME, Jaeger M, Gresnigt MS, Duarte-Oliveira C, Vanderbeke L, Resendiz A, Brüggemann R, Verweij PE, Lagrou K, Vande Velde G, de Mast Q, Joosten LAB, Netea MG, van der Ven AJAM, Wauters J, Carvalho A, van de Veerdonk FL. Neuraminidase and SIGLEC15 modulate the host defense against pulmonary aspergillosis. (submitted)
31. Koehler P, Bassetti M, Kochanek M, Shimabukuro-Vornhagen A, Cornely OA (2019) Intensive care management of influenza-associated pulmonary aspergillosis. Clin Microbiol Infect. https://doi.org/10.1016/j.cmi.2019.04.031
32. Pietsch U, Müller-Höcker C, Enzler-Tschudy A, Filipovic M (2016) Severe ARDS in a critically ill influenza patient with invasive pulmonary aspergillosis. Intensive Care Med 42:1632–1633. https://doi.org/10.1007/s00134-016-4379-3
33. Mercier T, Dunbar A, de Kort E, Schauwvlieghe A, Reynders M, Guldentops E, Blijlevens NMA, Vonk AG, Rijnders B, Verweij PE, Lagrou K, Maertens J (2019) Lateral flow assays for diagnosing invasive pulmonary aspergillosis in adult hematology patients: a comparative multicenter study. Med Mycol. https://doi.org/10.1093/mmy/myz079

34. Lestrade PPA, Meis JF, Melchers WJG, Verweij PE (2019) Triazole resistance in *Aspergillus fumigatus*: recent insights and challenges for patient management. Clin Microbiol Infect 25:799–806. https://doi.org/10.1016/j.cmi.2018.11.027
35. Patterson TF, Thompson GR 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, Kontoyiannis DP, Marr KA, Morrison VA, Nguyen MH, Segal BH, Steinbach WJ, Stevens DA, Walsh TJ, Wingard JR, Young JA, Bennett JE (2016) Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 63:e1–e60. https://doi.org/10.1093/cid/ciw326
36. Meersseman W, Lagrou K, Maertens J, Wilmer A, Hermans G, Vanderschueren S, Spriet I, Verbeken E, Van Wijngaerden E (2008) Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. Am J Respir Crit Care Med 177:27–34. PMID: 17885264
37. Martin-Loeches I, Lisboa T, Rhodes A, Moreno RP, Silva E, Sprung C, Chiche JD, Barahona D, Villabon M, Balasini C, Pearse RM, Matos R, Rello J, ESICM H1N1 Registry Contributors (2011) Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection. Intensive Care Med 37:272–283. https://doi.org/10.1007/s00134-010-2078-z
38. Lamoth F, Calandra T (2018) Let's add invasive aspergillosis to the list of influenza complications. Lancet Respir Med. 6:733–735. https://doi.org/10.1016/S2213-2600(18)30332-1
39. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, Gravenstein S, Hayden FG, Harper SA, Hirshon JM, Ison MG, Johnston BL, Knight SL, McGeer A, Riley LE, Wolfe CR, Alexander PE, Pavia AT (2018) Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. Clin Infect Dis 68:895–902. https://doi.org/10.1093/cid/ciy874
40. Lansbury LE, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS (2020) Corticosteroids as adjunctive therapy in the treatment of influenza: an updated Cochrane systematic review and meta-analysis. Crit Care Med 48:e98–e106. https://doi.org/10.1097/CCM.0000000000004093
41. Pastores SM, Annane D, Rochwerg B, Corticosteroid Guideline Task Force of SCCM and ESICM (2018) Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (Part II): society of Critical Care Medicine (SCCM) and European Society of Intensive Care Medicine (ESICM) 2017. Intensive Care Med 44:474–477. https://doi.org/10.1007/s00134-017-4951-5
42. https://www.medicines.org.uk/emc/product/3435/smpc
43. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, Lass-Flörl C, Lewis RE, Munoz P, Verweij PE, Warris A, Ader F, Akova M, Arendrup MC, Barnes RA, Beigelman-Aubry C, Blot S, Bouza E, Brüggemann RJM, Buchheidt D, Cadranel J, Castagnola E, Chakrabarti A, Cuenca-Estrella M, Dimopoulos G, Fortun J, Gangneux JP, Garbino J, Heinz WJ, Herbrecht R, Heussel CP, Kibbler CC, Klimko N, Kullberg BJ, Lange C, Lehrnbecher T, Löffler J, Lortholary O, Maertens J, Marchetti O, Meis JF, Pagano L, Ribaud P, Richardson M, Roilides E, Ruhnke M, Sanguinetti M, Sheppard DC, Sinkó J, Skiada A, Vehreschild MJGT, Viscoli C, Cornely OA (2018) Diagnosis and management of *Aspergillus* diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect 24(Suppl 1):e1–e38. https://doi.org/10.1016/j.cmi.2018.01.002
44. Verweij PE, Ananda-Rajah M, Andes D, Arendrup MC, Brüggemann RJ, Chowdhary A, Cornely OA, Denning DW, Groll AH, Izumikawa K, Kullberg BJ, Lagrou K, Maertens J, Meis JF, Newton P, Page I, Seyedmousavi S, Sheppard DC, Viscoli C, Warris A, Donnelly JP (2015) International expert opinion on the management of infection caused by azole-resistant *Aspergillus fumigatus*. Drug Resist Updat 21–22:30–40. https://doi.org/10.1016/j.drup.2015.08.001
45. Brüggemann RJ, Alffenaar JW, Blijlevens NM, Billaud EM, Kosterink JG, Verweij PE, Burger DM (2009) Clinical relevance of the pharmacokinetic interactions of azole antifungal drugs with other coadministered agents. Clin Infect Dis 48:1441–1458. https://doi.org/10.1086/598327
46. Pascual A, Csajka C, Buclin T, Bolay S, Bille J, Calandra T, Marchetti O (2012) Challenging recommended oral and intravenous voriconazole doses for improved efficacy and safety: population pharmacokinetics-based analysis of adult patients with invasive fungal infections. Clin Infect Dis 55:381–390. https://doi.org/10.1093/cid/cis437
47. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O (2008) Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis 46:201–211. https://doi.org/10.1086/524669
48. Park WB, Kim NH, Kim KH, Lee SH, Nam WS, Yoon SH, Song KH, Choe PG, Kim NJ, Jang IJ, Oh MD, Yu KS (2012) The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. Clin Infect Dis 55:1080–1087. PMID: 22761409
49. Troke PF, Hockey HP, Hope WW (2011) Observational study of the clinical efficacy of voriconazole and its relationship to plasma concentrations in patients. Antimicrob Agents Chemother 55:4782–4788. https://doi.org/10.1128/AAC.01083-10
50. Trifilio S, Pennick G, Pi J, Zook J, Golf M, Kaniecki K, Singhal S, Williams S, Winter J, Tallman M, Gordon L, Frankfurt O, Evens A, Mehta J (2007) Monitoring plasma voriconazole levels may be necessary to avoid subtherapeutic levels in hematopoietic stem cell transplant recipients. Cancer 109:1532–1535. PMID: 17351937
51. Dolton MJ, Ray JE, Chen SC, Ng K, Pont LG, McLachlan AJ (2012) Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother 56:4793–4799. https://doi.org/10.1128/AAC.00626-12
52. Siopi M, Mavridou E, Mouton JW, Verweij PE, Zerva L, Meletiadis J (2014) Susceptibility breakpoints and target values for therapeutic drug monitoring of voriconazole and *Aspergillus fumigatus* in an in vitro pharmacokinetic/pharmacodynamic model. J Antimicrob Chemother 69:1611–1619. https://doi.org/10.1093/jac/dku484
53. Muilwijk EW, Dekkers BGJ, Henriet SSV, Verweij PE, Witjes B, Lashof AMLO, Groeneveld GH, van der Hoeven J, Alffenaar JWC, Russel FGM, van de Veerdonk F, Brüggemann RJM (2017) Flucloxacillin results in suboptimal plasma voriconazole concentrations. Antimicrob Agents Chemother 61(9):e00915-17. https://doi.org/10.1128/aac.00915-17
54. Boots RJ, Paterson DL, Allworth AM, Faoagali JL (1999) Successful treatment of post-influenza necrotizing bronchial aspergillosis with liposomal amphotericin, inhaled amphotericin gamma interferon and GM-CSF. Thorax 54:1047–1049
55. Cottreau JM, Barr VO (2016) A review of antiviral and antifungal use and safety during pregnancy. Pharmacother 36:668–678. https://doi.org/10.1002/phar.1764
56. Rodriguez-Goncer I, Thomas S, Foden P, Richardson MD, Ashworth A, Barker J, Geraghty CG, Muldoon EG, Felton TW (2018) Invasive pulmonary aspergillosis is associated with adverse clinical outcomes in critically ill patients receiving veno-venous extracorporeal membrane oxygenation. Eur J Clin Microbiol Infect Dis 37:1251–1257. https://doi.org/10.1007/s10096-018-3241-7
57. Hage CA, Carmona EM, Epelbaum O, Evans SE, Gabe LM, Haydour Q, Knox KS, Kolls JK, Murad MH, Wengenack NL, Limper AH (2019) Microbiological laboratory testing in the diagnosis of fungal infections in pulmonary and critical care practice. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med 200:535–550. https://doi.org/10.1164/rccm.201906-1185ST
58. Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S, Gaymard A, Bouscambert-Duchamp M, Donati F, Le Hingrat Q, Enouf V, Houhou-Fidouh N, Valette M, Mailles A, Lucet JC, Mentre F, Duval X, Descamps D, Malvy D, Timsit JF, Lina B, van-der-Werf S, Yazdanpanah Y (2020) Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis S1473–3099(20):30200. https://doi.org/10.1016/S1473-3099(20)30200-0
59. Alanio A, Dellière S, Fodil S, Bretagne S, Mégarbane B (2020) High prevalence of putative invasive pulmonary aspergillosis in critically ill COVID-19 patients. https://papers.ssrn.com/abstract=3575581
60. Koehler P, Cornely OA, Böttiger BW, Dusse F, Eichenauer DA, Fuchs F, Hallek M, Jung N, Klein F, Persigehl T, Rybniker J, Kochanek M, Böll B, Shimabukuro-Vornhagen A (2020) COVID-19 associated pulmonary aspergillosis. Mycoses. https://doi.org/10.1111/myc.13096
61. Wang H, Ding Y, Li X, Yang L, Zhang W, Kang W (2003) Fatal aspergillosis in a patient with SARS who was treated with corticosteroids. N Engl J Med 349:507–508. PMID: 12890854
62. Liao M, Liu Y, Yuan J (2020) The landscape of lung bronchoalveolar immune cells in COVID-19 revealed by single-cell RNA sequencing. MedRxiv

63. Shinya K, Ebina M, Yamada S, Ono M, Kasai N, Kawaoka Y (2006) Avian flu: influenza virus receptors in the human airway. Nature 440:435–436. PMID: 16554799
64. van de Veerdonk FL, Netea MG, van Deuren M, van der Meer JW, de Mast Q, Brüggemann RJ, van der Hoeven H (2020) Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. Elife 9:55. https://doi.org/10.7554/eLife.57555
65. Sun K, Metzger DW (2014) Influenza infection suppresses NADPH oxidase-dependent phagocytic bacterial clearance and enhances susceptibility to secondary methicillin-resistant Staphylococcus aureus infection. J Immunol 192:3301–3307. https://doi.org/10.4049/jimmunol.1303049
66. Martin-Loeches I, Schultz JM, Vincent J-L, Alvarez-Lerma F, Bos LD, Solé-Violán J, Torres A, Rodriguez A, Sole-Violan J, Torres A, Rodriguez A (2017) Increased incidence of co-infection in critically ill patients with influenza. Intensive Care Med 43:48–58. https://doi.org/10.1007/s00134-016-4578-y
67. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5