



Invasive pulmonary aspergillosis complicating severe influenza: epidemiology, diagnosis and treatment

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Purpose of review

Bacterial super-infection of critically ill influenza patients is well known, but in recent years, more and more reports describe invasive aspergillosis as a frequent complication as well. This review summarizes the available literature on the association of invasive pulmonary aspergillosis (IPA) with severe influenza [influenza-associated aspergillosis (IAA)], including epidemiology, diagnostic approaches and treatment options.

Recent findings

Though IPA typically develops in immunodeficient patients, non-classically immunocompromised patients such as critically ill influenza patients are at high-risk for IPA as well. The morbidity and mortality of IPA in these patients is high, and in the majority of them, the onset occurs early after ICU admission. At present, standard of care (SOC) consists of close follow-up of these critically ill influenza patients with high diagnostic awareness for IPA. As soon as there is clinical, mycological or radiological suspicion for IAA, antifungal azole-based therapy (e.g. voriconazole) is initiated, in combination with therapeutic drug monitoring (TDM). Antifungal treatment regimens should reflect local epidemiology of azole-resistant *Aspergillus* species and should be adjusted to clinical evolution. TDM is necessary as azoles like voriconazole are characterized by nonlinear pharmacokinetics, especially in critically ill patients.

Summary

In light of the frequency, morbidity and mortality associated with influenza-associated aspergillosis in the ICU, a high awareness of the diagnosis and prompt initiation of antifungal therapy is required. Further studies are needed to evaluate the incidence of IAA in a prospective multicentric manner, to elucidate contributing host-derived factors to the pathogenesis of this super-infection, to further delineate the population at risk, and to identify the preferred diagnostic and management strategy, and also the role of prophylaxis.

Keywords

antifungals, aspergillosis, *Aspergillus fumigatus*, ICU, influenza

INTRODUCTION

Worldwide, 3–5 million people develop severe influenza infection every year, leading to 50 000–100 000 deaths annually in the European Union and USA. Of the hospitalized patients, 5–10% needs ICU admission. These patients initially present with typical influenza symptoms, but develop rapidly evolving respiratory deterioration, potentially leading to acute respiratory distress syndrome (ARDS) associated with high mortality [1,2]. Bacterial super-infection, mainly with *Streptococcus pneumoniae* and *Staphylococcus aureus*, is a well known complication of severe influenza, and its pathophysiology has been widely studied [3]. In recent years, however, an increasing number of publications on influenza-associated aspergillosis are reported, and the largest

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KEY POINTS

- IAA is a frequent and severe super-infection in the ICU.
- IAA may occur in any patient and shows a rapid disease progression with a high mortality.
- A broader awareness of this complication and prompt antifungal treatment initiation are crucial.
- Detailed knowledge about the underlying pathophysiological mechanisms and better risk assessment scores are urgently needed.

retrospective case study on the subject was recently published [4[■]]. This review will focus on epidemiological data from published cases of influenza-associated aspergillosis (IAA) up to June 2018, and also on new insights related to the diagnosis and treatment of this infection in the ICU-admitted patient. A brief note on the pathogenesis and suggested topics for further research are presented as well. References were identified using PubMed and Embase searches (January 1950–June 2018) of both English and foreign language literature using the search terms ‘influenza’ and ‘aspergillus’, ‘aspergillosis’ or ‘invasive aspergillosis’. References of identified case reports and case series (<http://links.lww.com/COID/A27>) were reviewed to identify additional articles for inclusion.

EPIDEMIOLOGY

There is a remarkable increase in published cases over time: the first report of probable IAA dates back

to 1952, with up to six case reports per decade thereafter. A sharp increase in reported cases occurred after the 2009 H1N1 influenza pandemic (Fig. 1). Whether this is associated with an increasing trend of *Aspergillus* super-infection or with improved diagnostics remains unclear, though the latter is much more likely. Up to June 2018, 128 IAA cases have been published, which are summarized in Table 1 [5–50,51[■],52[■],53–54]. Most cases had at least one underlying medical condition, yet 28% were reported as previously healthy. The most frequently observed underlying conditions were the use of one or more immunosuppressive drugs for a variety of underlying diseases ($n=32$, 25%), haematological malignancy ($n=19$, 15%) and diabetes ($n=19$, 15%). Only 9% ($n=11$) of patients were reported to take corticosteroids therapy before influenza diagnosis, whereas 48% ($n=61$) were treated with corticosteroid during hospitalization. Antiviral and antifungal therapy was administered in the majority of cases (69 and 89%, respectively). Most IAA cases were found in patients with influenza A infection ($n=111$, 87%), predominantly associated with H1N1 virus. IAA diagnosis was frequently made early after ICU admission [median of 5 days after admission; interquartile range (IQR) 2–11.5]. Diagnosis of IAA was largely based on culture ($n=89$, 70%). Galactomannan antigen was reported positive in serum in half of the patients ($n=60$, 47%) and in bronchoalveolar lavage (BAL) fluid in one-third of the patients ($n=39$, 31%). Bronchoscopy revealed fungal tracheobronchitis in 19 patients (15%). These results need to be interpreted with caution, because not all diagnostic techniques were available in every medical centre, and case definitions differed. Therefore, these numbers in no way

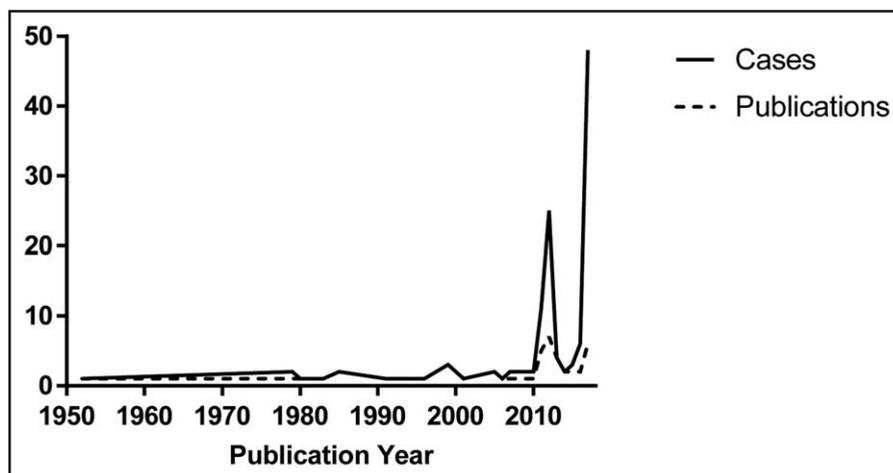


FIGURE 1. Overview of IAA cases and publications in literature over time (1952–2017 period) [5–50,51[■],52[■],53,54]. IAA, influenza-associated aspergillosis.

Table 1. Summary of 128 cases of influenza-associated aspergillosis (literature review of cases and case series [5–50,51^a,52^a,53,54])

Characteristic	Number (%) or median (IQR range)
Demographics	
Age	59 (IQR 51–63)
Male	79 (62%)
Risk factors	
Cirrhosis	6 (5%)
COPD	10 (8%)
Corticosteroids before hospitalisation	11 (9%)
Diabetes mellitus	19 (15%)
Haematological malignancy	19 (15%)
Haematological transplant	5 (4%)
Immunosuppression	32 (25%)
Neutropenia	12 (9%)
Previously healthy	36 (28%)
Solid organ malignancy	11 (9%)
Solid organ transplant	10 (8%)
Aspergillosis classification	
Proven	40 (31%)
EORTC probable	31 (24%)
AspICU putative	31 (24%)
Unclassifiable	47 (37%)
Influenza type	
Influenza A	111 (87%)
A, H1N1	65 (59%) ^a
A, H3	5 (4%) ^a
A, not specified	41 (37%) ^a
Influenza B	12 (9%)
Not specified	5 (4%)
Aspergillosis diagnostics ^b	
BAL culture positive	46 (36%)
1–3-β-D-glucan positive	5 (4%)
Computed tomography	37 (29%)
EORTC defined lesions	13 (35%) ^c
Atypical lesions	24 (65%) ^c
Galactomannan BAL positive	39 (31%)
Galactomannan serum positive	60 (47%)
Lung biopsy	20 (17%)
Necropsy	23 (18%)
PCR positive	4 (3%)
Sputum culture positive	43 (34%)
Tracheobronchitis	19 (15%)
Time from influenza diagnosis to <i>Aspergillus</i> diagnosis (days) ^d	5 (IQR: 2–11.5)
Therapy	
Antiviral treatment	88 (69%)
Not specified	1 (1%) ^e
Oseltamivir only	82 (93%) ^e
Oseltamivir and peramivir	3 (3%) ^e

Table 1 (Continued)

Characteristic	Number (%) or median (IQR range)
Oseltamivir and zanamivir	2 (2%) ^e
Antifungal treatment	114 (89%)
Corticosteroids during hospitalisation	61 (48%)
Outcome	
Mechanical ventilation	100 (78%)
ECMO	14 (11%)
Mortality	73 (57%)
Time to death (days) ^f	21 (IQR 13–26.5)

BAL, bronchoalveolar lavage; COPD, chronic obstructive pulmonary disease; CT, computed tomography; ECMO, extracorporeal membrane oxygenation; EORTC, European organisation for research and treatment of cancer; IQR, interquartile range.

^aPercentages relative to total number of influenza A cases reported.

^bSince multiple diagnostic techniques were employed in a majority of reported cases, the total percentage in the diagnosis category adds up to more than a 100%. All subcategories are listed relative to the total number of 128 cases, even though not every technique was employed in every case.

^cPercentages relative to total number of CT scans reported.

^dTime from influenza diagnosis to aspergillosis diagnosis only reported in 70 reports.

^ePercentages relative to total number of antiviral use.

^fTime from admission to death only reported in 44 reports.

reflect the sensitivity or specificity of these tests. IAA was proven through pathological examination in 40 patients (31%), of which 19 (48%) were proven only at autopsy. Most patients required mechanical ventilation ($n=100$, 78%), and overall mortality was 57% ($n=73$). Though there may be regional differences in prevalence, reports have occurred in all world continents, except South America and Antarctica (Table 2).

Additionally, four recent large retrospective studies in ICU patients need to be mentioned. In the first of these four studies, Martin-Loeches *et al.* studied the occurrence of super-infection in 2901 critically ill influenza patients from a large number of ICUs in Spain between 2009 and 2015. In this dataset, 16.6% ($n=482$) had a super-infection, and of those, *Aspergillus* was found in 7.2% ($n=35$) in the 2 days after ICU admission [55]. The second study is a retrospective cohort of 134 patients on extracorporeal membrane oxygenation (ECMO) in a tertiary care centre in the United Kingdom during 2012–2016. Ten of them had evidence of an invasive *Aspergillus* infection, and influenza A was an independent risk factor for IPA [hazard ratio 11.4, 95% confidence interval (CI) 1.97–65.86] [56]. In the third study, Cavayas *et al.* studied the risk factors for fungal infection in an international database of 2129 ECMO patients. Here again, influenza was an independent risk factor for IPA in ECMO patients [odds ratio (OR) 2.48] [57^{***}]. Finally, in a study on 432 patients with influenza admitted to seven ICUs in the Netherlands and Belgium over a period of 7 years, 19% ($n=83$) were

diagnosed with invasive aspergillosis. Of the 315 influenza patients without a typical host factor that would put them at risk for invasive aspergillosis, the incidence remained high at 14%. A comparison of influenza patients with severe non-influenza pneumonia patients allowed the identification of influenza as an independent risk factor for IPA [adjusted OR (aOR) 5.2, 95% CI 2.6–10.3]. Moreover, IAA was diagnosed very early after ICU admission (median of 3 days after admission), which highlights the need for a structured and prompt diagnostic approach [4^{**}].

DIAGNOSIS

Microbiological detection of influenza can be performed on nasopharyngeal or lower respiratory tract samples. Nucleic acid testing is both rapid and highly sensitive, making it the preferential detection method in most hospitals. Viral culture has similar sensitivity, yet is time and labour-intensive. Direct antibody testing, though clearly less sensitive, is rapid and does not require specialized skills [58]. Sampling of the lower respiratory tract (LRT) has a higher diagnostic yield, and positivity in LRT is associated with worse outcome in critically ill influenza patients [59].

Diagnosing IPA is less straightforward. Histological identification of acute-angle branching septated hyphae invading lung tissue is needed to prove a diagnosis of IPA. Lung biopsy is, however, rarely performed in critically ill patients because of the risk of respiratory complications and bleeding.

Table 2. Overview of published IAA cases from case reports and case series in the period 1952–June 2018, listed per country [5–50,51^a,52^a,53,54]

Continent	Country	Publications (n = 50)	Year of publication	IAA cases per country
Africa				n = 1
	South Africa	1	1985	1
Asia				n = 36
	Japan	6	1992, 1999, 2001, 2005–2007	7
	Korea	5	2012–2014	5
	Taiwan	4	2013, 2017	24
Australia				n = 1
	Australia	1	1999	1
Europe				n = 68
	Belgium	2	2012, 2017	10
	France	3	1999, 2011, 2012	7
	Germany	2	2012, 2013	6
	Ireland	1	2018	2
	Italy	1	2011	1
	Poland	1	2011	1
	Spain	3	1996, 2011, 2012	8
	Switzerland	2	1985, 2016	2
	The Netherlands	3	2012, 2015, 2017	26
	United Kingdom	5	1952, 1980, 1982, 1983, 1991	5
North America				n = 22
	United States of America	10	1979, 2005, 2010–2012, 2015–2018	22

A recent national survey in the Netherlands showed a hospital mortality of 61% in 23 ICU patients with IAA. Patients who survived had received antifungal therapy at a median of 2 days after influenza diagnosis, compared with 9 days in patients who had died, indicating that early diagnosis and treatment are critical [51^a]. Awareness of invasive aspergillosis as a potential cause of secondary infection is important as IAA occurs in non-typical host groups, and characteristic computed tomography (CT) images such as ‘halo-sign’ might be absent. Therefore, any respiratory specimen harbouring *Aspergillus* species in culture or a positive Galactomannan antigen should not be disregarded in ICU patients with severe influenza. A bronchoscopy with BAL appears the preferred diagnostic approach as the performance of Galactomannan antigen detection and culture showed good sensitivity in IAA, that is, 94 and 78%, respectively [51^a]. As up to 15% of patients may develop *Aspergillus* tracheobronchitis, the presence of plaques in the trachea or bronchi should be noted during bronchoscopy, which is recommended by the Infectious Diseases Society of America (IDSA)

[60]. As radiological manifestations of tracheobronchitis are subtle or may be absent, visualization of plaques is regarded the best way to diagnose this condition [61].

In addition to Galactomannan antigen detection in BAL, serum Galactomannan antigen was also positive in 64–71% of IAA patients, which is a high sensitivity, considering that most patients were non-neutropenic [4^{aa},51^a]. A positive serum Galactomannan antigen increases the probability of IAA and helps to distinguish invasive infection from respiratory colonization. Any positive serum Galactomannan antigen in a patient with severe influenza therefore should prompt immediate antifungal treatment, even if pre-existing risk factors are absent. The logistics of Galactomannan antigen detection, however, might cause diagnostic delay as in many centres Galactomannan antigen testing is performed only once or twice a week. Recently, lateral flow device (LFD) tests became available for detection of *Aspergillus* antigens in serum and BAL. The main advantage of the LFD assay is that results are available within 30 min, although the concentration of the antigen is not quantified [62].

In geographical regions in which azole resistance has been described, the detection of resistance should be pursued in clinically relevant isolates [63]. As mixed infections (e.g. azole-susceptible and azole-resistant co-infection) have been reported in patients with IAA, multiple colonies should be investigated in culture-positive patients. Screening through agar-based systems such as the VIPcheck test enables detection of resistance within 24–48 h. If the screening test indicates resistance, minimum inhibitory concentration (MIC) testing can be performed [64]. Culture and phenotypic resistance screening and MIC testing can take up to a week or longer, and therefore may be too late to guide antifungal therapy. Indeed, a recent study in culture-positive patients with invasive aspergillosis indicated that initial voriconazole therapy corresponded with a 27% higher mortality in patients with voriconazole-resistant *A. fumigatus* compared with patients with voriconazole-susceptible infection. Despite resistance screening and MIC testing, the median time to change to appropriate antifungal therapy was 10 days, indicating that resistance information should be available earlier to prevent mortality [65]. In culture-negative patients, resistance PCR can be performed directly on clinical specimens. Two commercial PCR tests are available (Mycogenie and AsperGenius), which detect one or two common resistance markers. Generally, the assays show acceptable sensitivity when done on BAL fluid, and results are available within a working day [66,67]. In culture-positive patients, these PCR tests can also be performed directly on a suspension of multiple colonies with excellent sensitivity and with additional advantage that, compared with phenotypic resistance testing, the PCR result will be available the same day. The limitation is that resistance mechanisms other than the mutations included in the PCR will go unnoticed.

Given the rapid disease progression in IAA, a diagnostic pathway could include early BAL, followed by LFD, and, if positive, *Aspergillus* and resistance PCR. Although such a strategy still needs to be validated, IAA diagnosis could be made within 48 h including information regarding the presence of resistance markers.

TREATMENT

In this section, an overview of current knowledge on the pharmacological treatment, comprising antivirals, antifungals and corticosteroid therapy, is given. Respiratory organ support techniques, such as prone positioning and ECMO contribute to improved survival, but fall outside the scope of this review [68].

Antiviral therapy

Neuraminidase inhibitors (NAIs) (oseltamivir, zanamivir and very recently peramivir) form the only drug class that are licensed and recommended for the treatment of influenza infection in Europe [69,70]. Current evidence supports the use of oseltamivir in severe influenza, if administered early. Timely administration has indeed shown reduced ICU length of stay, reduced mechanical ventilation days and improved survival in several cohorts of ICU patients [71–73]. During the pandemic 2009 H1N1 infection, the WHO listed oseltamivir as a ‘core drug’, and advised to treat with oseltamivir at a higher dose (150 mg twice daily instead of 75 mg twice daily) and for longer duration (standard treatment duration being 5 days) in severely ill patients [1]. These recommendations are based on animal models, with only limited evidence for benefit in human cohorts [74]. No prospective studies on optimal duration of treatment in critically ill influenza patients exist; yet extended treatment duration with oseltamivir was associated with a trend towards improved mortality in a retrospective analysis of 19 892 adult ICU patients [75]. Regarding the optimal dosing of oseltamivir in severe influenza patients, the evidence is inconclusive as well. The only three prospective studies comparing standard and high-dose oseltamivir in hospitalized patients show conflicting evidence on improved virological clearance without obvious clinical benefit of high-dose therapy [76–78]. Additional retrospective studies corroborate the absence of effect on clinical outcome such as ICU length of stay or mortality [79–80]. In light of this conflicting data, the WHO downgraded oseltamivir on its drug list [81]. Furthermore, pharmacokinetic analysis in critically ill pandemic H1N1 influenza virus patients showed that enteric absorption of oseltamivir at standard dose was adequate, resulting in trough levels and area under the curve of the active carboxylate metabolite well above the 50% maximal inhibitory concentration of the influenza virus [82].

Dosing of oseltamivir in critically ill patients should be adapted to the provided organ support. Despite the fact that ECMO can alter pharmacokinetics, by increasing the volume of distribution and sequestration of drugs in the circuit among others, no dose adjustment for oseltamivir seems warranted based on current reports [83–85]. Dose reduction to 75 mg once daily is, however, recommended in patients on renal replacement therapy (RRT), depending on type of RRT and patient characteristics [83,84,86–88]. Recommendations are based on limited available evidence in small patient

populations; thus better evidence is clearly required. Present research is focusing on new NAIs (such as peramivir), new antiviral drug classes (e.g. endonuclease inhibitors) and the role of combination therapy [89,90].

Antifungal therapy

Voriconazole, the current gold standard therapy for IPA according to ECIL/ESCMID-ECMM-ERS/IDSA guidelines, led to a higher overall survival compared to conventional amphotericin B [60,63,91]. The intravenous formulation is used in ICU setting, to avoid erratic absorption and to warrant therapeutic plasma levels. Although voriconazole has earned its merit, its use is hindered by nonlinear pharmacokinetics, risk for neuro- and hepatotoxicity, and frequent involvement in drug–drug interactions. These factors underscore the need for therapeutic drug monitoring (TDM), aiming at trough levels of 2–5.5 mg/l [60,63]. Especially during ECMO, TDM is warranted because voriconazole sequestration and subsequent saturation of binding sites of the ECMO circuit can significantly alter drug levels [92,93]. Moreover, multiple drugs are known to interact with voriconazole based at the level of cytochrome P450 metabolizing enzymes [94,95]. Next to these classic CYP450-mediated interactions, also other interactions have been described in literature. A new and clinically relevant interaction was described between flucloxacillin and voriconazole showing sub-therapeutic levels of voriconazole in 11 of 20 patients treated simultaneously with both drugs [96].

Isavuconazole is a new extended-spectrum triazole that can be administered as a pro-drug via oral or intravenous formulation. Its longer half-life compared to voriconazole allows once daily dosing after an initial 2-day period of three times daily loading. Compared to voriconazole, isavuconazole has a more favourable profile, regarding safety and spectrum (including some of the Mucorales) while being non-inferior for primary treatment of suspected invasive mould disease [97–99]. This is reflected in current treatment guidelines; isavuconazole has the same level of evidence as voriconazole [60,63]. More clinical data are needed to provide insight in the efficacy and safety of isavuconazole at the ICU, the need for therapeutic drug monitoring and optimal dosing in patients on ECMO [100,101].

For many years, the polyene conventional amphotericin B was the mainstay therapy for invasive mould infection, and its liposomal formulations have been associated with a better safety profile. However, its use is, at present, limited to patients in whom voriconazole is contra-indicated, for example, in case of hepatic insufficiency or in

cases of suspected or proven azole resistance. Importantly, with the widespread use of azoles in the environment, resistance has been observed worldwide, with resistance rates of up to 26% in certain Dutch ICUs [102,103]. Recent guidelines recommend to start voriconazole-echinocandin combination or liposomal amphotericin B as initial therapy in regions with environmental resistance rates of above 10% [63]. If susceptibility testing demonstrates azole-susceptible *Aspergillus* (voriconazole MIC \leq 1 mg/l), voriconazole monotherapy is recommended, whereas in azole-resistant *Aspergillus* (voriconazole MIC $>$ 2 mg/l), ongoing therapy should consist of an antifungal drug to which the recovered species is susceptible [104,105]. Furthermore, combination therapy is recommended in IDSA guidelines for salvage therapy [60]. Regardless of the initial treatment regimen, timely administration of appropriate antifungal therapy is the single most crucial intervention to improve outcome; therefore initiation of treatment at suspicion of aspergillosis is advocated [60,106]. Primary prophylaxis with posaconazole is, at present, only recommended in high-risk patient groups (i.e. acute myelogenous leukaemia or myelodysplastic syndrome receiving induction chemotherapy) [63]. The effect of prophylactic antifungal administration in critically ill influenza patients requires further investigation.

Corticosteroids

Corticosteroid treatment is frequently used in the ICU, both as adjunctive treatment in septic shock and in the late phase of ARDS, although its value in septic shock remains a matter of debate [107–109]. Moreover, guidelines on treatment of severe pneumonia are being reviewed, considering corticosteroid treatment early in the disease course to improve morbidity and mortality [110,111]. Influenza pneumonia is, however, deemed an exception, based on low-quality evidence showing an association between corticosteroids and prolonged viral shedding with increased risk of mortality [1,112–114]. The available evidence on the value of corticosteroids in patients with influenza argues against its use as long as data from a prospective randomized clinical trial are lacking. Additionally, corticosteroids were an independent risk factor for the development of IPA in ICU patients in general, but very recently also in patients admitted with influenza [4,35,115,116,117].

PATHOGENESIS

The underlying mechanisms that render influenza patients prone to develop IAA remain to be

elucidated and are mainly derived from studies regarding influenza–bacterial super-infection. Influenza induces damage to the respiratory tract epithelial lining, interferes with normal mucociliary clearing and, in this way, can provide a gateway for *Aspergillus* infection. Moreover, immunological host responses are altered in the setting of severe influenza, with dysregulation of Th-cell differentiation and impaired cell-mediated immunity [3,118]. Additionally, treatment strategies in the ICU may enhance susceptibility to secondary aspergillosis. Corticosteroids are well known to down-regulate innate and more importantly adaptive immunity, contributing to IPA development. *In vitro*, NAIs are able to diminish viral–bacterial synergism that may contribute to severe influenza lethality [119]. The opposite might be true for the influenza–aspergillosis association as initial *in-vivo* experiments in immunodeficient mice show more severe IPA development in cortisone-treated animals exposed to oseltamivir compared to controls, a difference that was not observed in neutropenic mice [120¹¹]. Further research is needed to clarify the multiple contributing factors in the pathophysiology of this disease.

CONCLUSION AND PERSPECTIVES

Influenza-associated aspergillosis is a frequent and severe complication of influenza in ICU, occurring early after admission. High diagnostic awareness, incorporating a multiple biomarker-diagnostic strategy and prompt initiation of antifungal treatment are crucial to improve outcome. We recommend considering *Aspergillus* infection in all ICU patients with severe influenza, irrespective of previous medical history. Although the optimal diagnostic work-up remains to be validated, early bronchoscopy and BAL with the use of biomarkers seem to be important to diagnose IAA as early as possible. If initial assessments are negative for aspergillosis, this strategy should be repeated in case of respiratory deterioration. Further studies are needed to provide better epidemiological insights; at present, a multicentre observation trial is ongoing (NCT03391492); to investigate the potential of antifungal prophylaxis (NCT03378479) and to elucidate the pathophysiology of this super-infection.

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Conflicts of interest

None.

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