Summary

Although the association of influenza with an increased risk for bacterial superinfections is well known, the risk of developing a fungal disease such as invasive pulmonary aspergillosis (IPA) is less well characterised. In recent years, cases of influenza-associated IPA have been reported from several countries with increasing frequency. The evidence base for an association between influenza infection and IPA among severely ill patients admitted to hospital intensive care units (ICUs) is convincing, despite the fact that the studies conducted so far have limitations with regard to sample size, study design, and criteria used for diagnosis.

The diagnosis of IPA requires clinicians’ awareness in order to conduct timely and appropriate testing. As IPA has traditionally been considered a disease occurring only in severely immunocompromised patients, ICU physicians might not suspect IPA in severely ill influenza patients without additional immunosuppression or classic risk factors. Influenza-associated IPA might therefore be underdiagnosed or diagnosed with a delay, possibly leading to worse patient outcomes. Furthermore, the published literature only discusses ICU-admitted cases; however, the short interval between ICU admission and diagnosis of IPA in the most recent studies suggests that efforts should be enhanced to understand the magnitude of the problem, also among other hospitalised severe influenza cases.

During the 2017–18 influenza season, a total of 9 317 laboratory-confirmed cases of influenza were reported to ECDC from ICUs in 10 EU Member States participating in the surveillance of severe influenza. In most of these 10 Member States, only a selected number of ICUs participate in this surveillance scheme. Therefore, the actual number of ICU admissions of influenza patients in the 28 EU Member States during a severe influenza season such as 2017–18 will be in the order of tens of thousands of confirmed cases. Current data are insufficient to accurately estimate the frequency of influenza-associated IPA; incidence might vary widely between hospitals and countries. However, a recent multicentre study in Belgium and the Netherlands showed that a considerable proportion of severe influenza cases may develop IPA as a superinfection, increasing the likelihood of poor outcomes. Therefore, the timely and appropriate diagnosis and management of IPA could result in improved outcomes among severely ill influenza patients in ICUs.

Due to the association of severe influenza infections with IPA among ICU-admitted patients, its early occurrence after ICU admission, and the associated poor outcomes, public health authorities should raise awareness about this issue among ICU physicians and clinical microbiologists. For options for response, please see the respective section in this document.


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Risk assessment question

What is the risk of invasive pulmonary aspergillosis (IPA) among patients with severe influenza in hospital ICUs in the European Union (EU)/European Economic Area (EEA)?

Event background

IPA is typically a disease of severely immunocompromised patients, but recent reports describe the diagnosis of IPA in patients with severe influenza. In the early period, cases of IPA were described, for example in influenza patients in Belgium and the Netherlands [1-3]. In the last two decades, several studies specifically investigating IPA in influenza patients were performed in Belgium and the Netherlands [1-3]. IPA in patients with severe influenza has been reported from several non-European countries, for example Japan [7], Korea [8], Taiwan [9,10], Australia [11], South Africa [11] and the US [12-16]. The US Centers for Disease Control and Prevention highlights the association of IPA with influenza on its webpage: ‘Recent studies suggest that healthcare providers may also consider Aspergillus infection as a possible cause of worsening respiratory function and sepsis in critically ill immunocompetent patients with severe influenza’ [17].

Influenza-associated IPA cases have been described as early as 1952 [18]. The first case series, which included six cases of influenza-associated IPA in previously healthy patients, was published in 1985 [19]. The number of publications related to influenza-associated IPA increased after the influenza pandemic in 2009 [11], when increased availability of diagnostic tests became available. IPA is the most common manifestation of Aspergillus infection in influenza patients, but systemic involvement (brain, myocardium) has also been described [13]. The majority of IPA cases have been associated with influenza A, but cases associated with influenza B virus have also been reported [1,13,20]. A surprising finding was the short interval between ICU admission and onset of IPA [11].

A recent review summarised 128 influenza-associated IPA cases from case reports and series published up to June 2018 [11]. Most of these cases had at least one underlying medical condition; however, 28% of the included patients were described as previously healthy. In addition, several cohort studies described influenza-associated IPA cases, for example in a cohort of 2 901 influenza patients in 148 ICUs in Spain during the period 2009 to 2015 [21]. In this cohort, 482 critically ill influenza patients developed co-infection, and Aspergillus spp. was the fourth most common pathogen after Streptococcus pneumoniae, Pseudomonas aeruginosa and Staphylococcus aureus. Twenty-seven co-infections were confirmed (histopathological confirmation) or probable (compatible computed tomography findings) Aspergillus infections [21].

A cohort study of 19 697 patients on extracorporeal membrane oxygenation (ECMO) in the Extracorporeal Life Support Organisation Registry identified 2 129 patients with a diagnosis of fungal infection or colonisation; 272 of these patients had a diagnosis of aspergillosis or a microbiological culture positive for Aspergillus. In this study, influenza was an independent risk factor for Aspergillus infection or colonisation [22]. In a much smaller but more specific study of patients with IPA on ECMO in one tertiary medical centre in the UK, immunosuppression and influenza A were associated with an increased risk of IPA [23].

In July 2018, a retrospective multicentre study, which included patients from seven ICUs in Belgium and the Netherlands for the period 2009 to 2016, reported a high incidence of IPA (19%, 83 of 423 patients) in a cohort of influenza patients [1]. In the subgroup of patients without other known risk factors for IPA (i.e. non-immunocompromised patients), the incidence was 14% (45 of 315 patients), while for patients who were immunocompromised and had influenza, the incidence increased to 32% (38 of 117 patients) [1]. The study reported a 90-day mortality of 28% in the patients with influenza but not IPA compared with 51% in patients with influenza and associated IPA. In this study, only patients older than 18 years of age were included. The other publications mentioned above focus on adults or do not report the age ranges. Therefore, the presented data cannot be generalised to young people and children.

Disease background

Disease characteristics

Humans inhale large numbers of conidia (Aspergillus spores) every day, and most people do not develop disease manifestations [24]. Invasive aspergillosis mainly occurs when patients have risk factors that result in a compromised immune system [24]. Among human-pathogenic Aspergillus species, A. fumigatus is the most frequent cause of infections, followed by A. flavus, A. terreus, A. niger and A. nidulans [25]. Aspergillus can cause multiple forms of human disease, ranging from allergic manifestations to invasive aspergillosis, depending on the immunocompetence of the human host [25]. IPA is a rapidly progressive disease with mortality rates up to 90% in specific patient groups [25]. Mortality can be reduced with prompt initiation of effective antifungal treatment [26].
However, the development of resistance to azole antifungals in *A. fumigatus* limits treatment options in some patients and has been associated with increased mortality [27,28].

Classically, IPA has been a disease of severely immunocompromised patients such as neutropenic patients and organ transplant recipients. However, additional risk factors, such as corticosteroid treatment and chronic obstructive pulmonary disease (COPD), have received increasing attention [29]. According to a recent review, only 10–15% of patients with IPA in ICUs present with neutropenia as the underlying risk factor, while about 50% of patients have underlying COPD [30], suggesting an important role for ciliary clearance and other lung defence mechanisms. Moreover, several additional potential risk factors for invasive aspergillosis in ICU patients have been identified, such as extended ICU stay, haemodialysis, advanced liver disease, antibiotic treatment, congestive heart failure, mechanical ventilation, diabetes, and major infections [31,32]. Due to the heterogeneity of the ICU population in terms of underlying diseases and being immunocompromised, the specific role of risk factors for IPA is difficult to determine [32]. Infection with respiratory viruses such as influenza may increase the risk of invasive aspergillosis by breaking down the bronchial mucosa facilitating *Aspergillus* invasion, disrupting mucusiliary clearance mechanisms, inducing lympho- and/or neutropenia or other immunomodulatory effects such as the secretion of interleukin (IL)-10 [11,24,33,34].

As a positive respiratory culture for *Aspergillus* spp. can be a sign of infection as well as colonisation, the diagnosis of IPA is based on a combination of clinical, microbiological and radiological criteria. Several sets of criteria and algorithms have been developed to standardise diagnosis; they can, however, only be applied to subgroups of IPA patients [35]. For example, the European Organization for Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) criteria were primarily developed for haemato-oncologic patients and require the presence of at least one classic host risk factor related to immunosuppression and of radiological signs that typically occur in neutropenic patients, but not as often in less immunocompromised patients [36]. For studies on non-immunocompromised patients, such as the recent influenza-associated IPA cohort study described above [1], these criteria were therefore modified by broadening the radiological criteria and removing the classic host risk factors.

Other criteria that were developed more specifically for the diagnosis of IPA in ICU patients (BLOT or AspICU criteria) [37,38] are limited in their use because they do not include the use of the galactomannan test and depend on a positive *Aspergillus* culture from the lower respiratory tract, which can be negative in patients with IPA. Fungal cultures have low sensitivity for the diagnosis of invasive aspergillosis [39] and, depending on the patient population, are positive only in about 25%–65% of patients with invasive aspergillosis [39,40]. However, in patients with influenza-associated IPA, a higher culture sensitivity of 63%–88% was reported [1-3]. Clinical microbiology laboratories also need to be aware of the suspicion of IPA not to discard moulds from respiratory specimens as ‘contaminant’ without reporting to clinicians. Moreover, moulds usually grow more slowly than bacteria, and plates or slants should be incubated longer. The sensitivity of testing broncho-alveolar lavage fluid for galactomannan – an exo-antigen released by *Aspergillus* spp. hyphae – is higher than microbiological culture for the diagnosis of IPA [39]. However, the galactomannan test is also dependent on the patient population and has a lower sensitivity in non-neutropenic patients [35]. The galactomannan test result can be affected by antibiotic or antifungal treatment and the broncho-alveolar lavage (BAL) procedure [39]. The multitude of diagnostic approaches and criteria used to diagnose IPA complicates the assessment of the evidence for the association between influenza and IPA.

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The diagnosis of IPA requires clinicians’ awareness in order to conduct timely and appropriate testing. As IPA has traditionally been considered a disease occurring only in severely immunocompromised patients, ICU physicians might not suspect IPA in severely ill influenza patients without additional immunosuppression or classic risk factors. Influenza-associated IPA might therefore be underdiagnosed or diagnosed with a delay, possibly leading to worse patient outcomes. Furthermore, the published literature only discusses ICU-admitted cases; however, the short interval between ICU admission and diagnosis of IPA in the most recent studies suggests that efforts should be enhanced to understand the magnitude of the problem, also among other hospitalised severe influenza cases.

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proportion of severe influenza cases may develop IPA as a superinfection, increasing the likelihood of poor outcomes. Therefore, the timely and appropriate diagnosis and management of IPA could result in improved outcomes among severely ill influenza patients in ICUs.

Options for response

Due to the association of severe influenza infections with IPA among ICU-admitted patients, its early occurrence after ICU admission, and the associated poor outcomes, public health authorities should raise awareness about this issue among ICU physicians and clinical microbiologists. IPA should be considered as a possible complication of severe influenza, and appropriate diagnostic procedures (including BAL) should be considered to be performed in time. Antifungal treatment should be initiated along the relevant national and international guidelines, when indicated, based on careful clinical judgement and also taking into account the side effects of antifungal drugs. Considering the recent publications about the emergence of azole resistance in Aspergillus fumigatus, antifungal susceptibility testing should be considered.

Further studies are needed to assess the biological mechanisms (including the role of corticosteroids and antibiotic treatment of influenza patients) and the public health impact of the association between influenza and IPA, for example through case-based data collection. A closer look at data from national registries would be instructive, as would be an analysis of surveillance/clinical data in order to explore the association between influenza and IPA. ECDC will review the data collection from ICU-admitted influenza patients for the possibility of adding information on IPA as a co-infection.

Source and date of request

ECDC internal decision, 9 November 2018.

Consulted experts

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All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

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References


