RAPID RISK ASSESSMENT

Influenza-associated invasive pulmonary aspergillosis, Europe

30 November 2018

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 notable proportions of patients with severe influenza without immunosuppression or underlying diseases [1,2]. While most of the multicentre studies specifically investigating IPA in influenza patients were performed in Belgium and the Netherlands [1-3], IPA in patients with severe influenza with or without immunosuppression has also been reported from several other EU Member States, such as France [4], Germany [5] and Spain [6]. In addition, cases have 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], probably due to increased availability of diagnostic tests. 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 case 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 a 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 mucociliary 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.

ECDC risk assessment for the EU/EEA

Although the association of influenza with an increased risk for bacterial superinfections is well known, the risk of developing a fungal disease such as 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 ICU-admitted, severely ill patients is convincing [1,11,22,23], 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.

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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.

Disclaimer

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This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

References

1. Schauwvlieghe A, Rijnders BJA, Philips N, Verwijs R, Vanderbeke L, Van Tienen C, et al. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. The Lancet Respiratory medicine. 2018 Oct;6(10):782-92.
2. van de Veerdonk FL, Kolwijck E, Lestrade PP, Hodiamont CJ, Rijnders BJ, van Paassen J, et al. Influenza-Associated Aspergillosis in Critically Ill Patients. Am J Respir Crit Care Med. 2017;196 (4):524-7.
3. Wauters J, Baar I, Meersseman P, Meersseman W, Dams K, De Paep R, et al. Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. Intensive Care Med. 2012 Nov;38(11):1761-8.
4. Guervilly C, Roch A, Ranque S, Forel JM, Hraiech S, Xeridat F, et al. A strategy based on galactomannan antigen detection and PCR for invasive pulmonary aspergillosis following influenza A (H1N1) pneumonia. J Infect. 2012 Nov;65(5):470-3.
5. Vehreschild JJ, Brockelmann PJ, Bangard C, Verheyen J, Vehreschild MJ, Michels G, et al. Pandemic 2009 influenza A(H1N1) virus infection coinciding with invasive pulmonary aspergillosis in neutropenic patients. Epidemiol Infect. 2012 Oct;140(10):1848-52.
6. Garcia-Vidal C, Barba P, Arnan M, Moreno A, Ruiz-Camps I, Gudiol C, et al. Invasive aspergillosis complicating pandemic influenza A (H1N1) infection in severely immunocompromised patients. Clin Infect Dis. 2011 Sep;53(6):e16-9.
7. Ohnishi T, Andou K, Kusumoto S, Sugiyama H, Hosaka T, Ishida H, et al. [Two cases of successfully treated invasive pulmonary aspergillosis following influenza virus infection]. Nihon Kokyuki Gakkai Zasshi. 2007 Apr;45(4):349-55.
8. Park DW, Yhi JY, Koo G, Jung SJ, Kwak HJ, Moon JY, et al. Fatal clinical course of probable invasive pulmonary aspergillosis with influenza B infection in an immunocompetent patient. Tuberculosis and respiratory diseases. 2014 Sep;77(3):141-4.
9. Su PA, Yu WL. Failure of extracorporeal membrane oxygenation to rescue acute respiratory distress syndrome caused by dual infection of influenza A (H1N1) and invasive pulmonary aspergillosis. J Formos Med Assoc. 2017 Jul;116(7):563-4.
10. Ku YH, Chan KS, Yang CC, Tan CK, Chuang YC, Yu WL. Higher mortality of severe influenza patients with probable aspergillosis than those with and without other coinfections. J Formos Med Assoc. 2017 Sep;116(9):660-70.
11. Vanderbeke L, Spriet I, Breynaert C, Rijnders BJA, Verweij PE, Wauters J. Invasive pulmonary aspergillosis complicating severe influenza: epidemiology, diagnosis and treatment. Curr Opin Infect Dis. 2018 Dec;31(6):471-80.
12. Lat A, Bhadelia N, Miko B, Furuya EY, Thompson GR, 3rd. Invasive aspergillosis after pandemic (H1N1) 2009. Emerg Infect Dis. 2010 Jun;16(6):971-3.
13. Crum-Cianflone NF. Invasive aspergillosis associated with severe influenza infections. Open forum infectious diseases. 2016 Sep;3(3):ofw171.
14. Shah MM, Hsiao EI, Kirsch CM, Gohil A, Narasimhan S, Stevens DA. Invasive pulmonary aspergillosis and influenza co-infection in immunocompetent hosts: case reports and review of the literature. Diagn Microbiol Infect Dis. 2018 Jun;91(2):147-52.
15. Alshabani K, Haq A, Miyakawa R, Palla M, Soubani AO. Invasive pulmonary aspergillosis in patients with influenza infection: report of two cases and systematic review of the literature. Expert Rev Respir Med. 2015 Feb;9(1):89-96.
16. Ajmal S, Mahmood M, Abu Saleh O, Larson J, Sohail MR. Invasive fungal infections associated with prior respiratory viral infections in immunocompromised hosts. Infection. 2018 Aug;46(4):555-8.
17. Centers for Disease Control and Prevention. Information for healthcare professionals about aspergillosis Atlanta, USA: CDC; 2018. Available from: https://www.cdc.gov/fungal/diseases/aspergillosis/health-professionals.html.
18. Abbott JD, Fernando HV, Gurling K, Meade BW. Pulmonary aspergillosis following post-influenzal bronchopneumonia treated with antibiotics. Br Med J. 1952 Mar 8;1(4757):523-5.
19. Lewis M, Kallenbach J, Ruff P, Zaltzman M, Abramowitz J, Zwi S. Invasive pulmonary aspergillosis complicating influenza A pneumonia in a previously healthy patient. Chest. 1985 May;87(5):691-3.
20. Nulens EF, Bourgeois MJ, Reynders MB. Post-influenza aspergillosis, do not underestimate influenza B. Infection and drug resistance. 2017;10:61-7.
21. Martin-Loeches I, M JS, Vincent JL, Alvarez-Lerma F, Bos LD, Sole-Violan J, et al. Increased incidence of co-infection in critically ill patients with influenza. Intensive Care Med. 2017 Jan;43(1):48-58.

22. Cavayas YA, Yusuff H, Porter R. Fungal infections in adult patients on extracorporeal life support. Crit Care. 2018 Apr 17;22(1):98.
23. Rodriguez-Goncer I, Thomas S, Foden P, Richardson MD, Ashworth A, Barker J, et al. 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. 2018 Jul;37(7):1251-7.
24. Garcia-Vidal C, Viasus D, Carratala J. Pathogenesis of invasive fungal infections. Curr Opin Infect Dis. 2013 Jun;26(3):270-6.
25. Dagenais TR, Keller NP. Pathogenesis of *Aspergillus fumigatus* in invasive aspergillosis. Clin Microbiol Rev. 2009 Jul;22(3):447-65.
26. Cadena J, Thompson GR, 3rd, Patterson TF. Invasive aspergillosis: current strategies for diagnosis and management. Infect Dis Clin North Am. 2016 Mar;30(1):125-42.
27. Verweij PE, Chowdhary A, Melchers WJ, Meis JF. Azole resistance in *Aspergillus fumigatus*: Can we retain the clinical use of mold-active antifungal azoles? Clin Infect Dis. 2016 Feb 1;62(3):362-8.
28. European Centre for Disease Prevention and Control. Risk assessment on the impact of environmental usage of triazoles on the development and spread of resistance to medical triazoles in *Aspergillus* species. Stockholm: ECDC; 2013. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/risk-assessment-impact-environmental-usage-of-triazoles-on-Aspergillus-spp-resistance-to-medical-triazoles.pdf.
29. Lionakis MS, Kontoyiannis DP. Glucocorticoids and invasive fungal infections. Lancet. 2003 Nov 29;362(9398):1828-38.
30. Garnacho-Montero J, Olaechea P, Alvarez-Lerma F, Alvarez-Rocha L, Blanquer J, Galvan B, et al. Epidemiology, diagnosis and treatment of fungal respiratory infections in the critically ill patient. Rev Esp Quimioter. 2013 Jun;26(2):173-88.
31. Stevens DA, Melikian GL. Aspergillosis in the 'nonimmunocompromised' host. Immunol Invest. 2011;40(7-8):751-66.
32. Patterson TF, Thompson GR, 3rd, Denning DW, Fishman JA, Hadley S, Herbrecht R, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016 Aug 15;63(4):e1-e60.
33. Yu X, Zhang X, Zhao B, Wang J, Zhu Z, Teng Z, et al. Intensive cytokine induction in pandemic H1N1 influenza virus infection accompanied by robust production of IL-10 and IL-6. PLoS One. 2011;6(12):e28680.
34. Bermejo-Martin JF, Martin-Loeches I, Rello J, Anton A, Almansa R, Xu L, et al. Host adaptive immunity deficiency in severe pandemic influenza. Crit Care. 2010;14(5):R167.
35. Salzer HJF, Lange C, Honigl M. [*Aspergillus* in airway material : Ignore or treat?]. Internist (Berl). 2017 Nov;58(11):1150-62.
36. De Pauw B, Walsh TJ, Donnelly JP, Stevens DA, Edwards JE, Calandra T, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. Clin Infect Dis. 2008 Jun 15;46(12):1813-21.
37. Blot SI, Taccone FS, Van den Abeele AM, Bulpa P, Meersseman W, Brusselaers N, et al. A clinical algorithm to diagnose invasive pulmonary aspergillosis in critically ill patients. Am J Respir Crit Care Med. 2012 Jul 1;186(1):56-64.
38. Dabas Y, Mohan A, Xess I. Serum galactomannan antigen as a prognostic and diagnostic marker for invasive aspergillosis in heterogeneous medicine ICU patient population. PLoS One. 2018;13(4):e0196196.
39. Arvanitis M, Anagnostou T, Fuchs BB, Caliendo AM, Mylonakis E. Molecular and nonmolecular diagnostic methods for invasive fungal infections. Clin Microbiol Rev. 2014 Jul;27(3):490-526.
40. Meersseman W, Lagrou K, Maertens J, Wilmer A, Hermans G, Vanderschueren S, et al. Galactomannan in bronchoalveolar lavage fluid: a tool for diagnosing aspergillosis in intensive care unit patients. Am J Respir Crit Care Med. 2008 Jan 1;177(1):27-34.
41. European Centre for Disease Prevention and Control. Seasonal influenza. In: ECDC. Annual epidemiological report for 2017. Stockholm: ECDC; 2018. Available from: https://ecdc.europa.eu/sites/portal/files/documents/seasonal-influenza-annual-epidemiological-report-2017.pdf.