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EDITORIAL COMMENTARY

Influenza-Associated Pulmonary Aspergillosis: A Local or Global Lethal Combination?

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(See the Brief report by Schwartz et al on pages 1760–3.)

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Superinfections with *Streptococcus pneumoniae* and *Staphylococcus aureus* have been a well-known complication of seasonal influenza. More recently, invasive pulmonary aspergillosis (IPA) was described as another important complication. Influenza-associated IPA (IAPA) has so far been predominantly described in critically ill patients admitted to the intensive care unit (ICU) with influenza pneumonia [1–3]. Following a number of single-center case series, the Dutch-Belgian Mycoses Study Group (DB-MSG) evaluated the incidence of IAPA in the largest cohort study of patients admitted to the ICU with influenza so far. In this study, 19% of the 432 patients admitted to the ICU during 7 consecutive influenza seasons were diagnosed with IAPA. The study also demonstrated that, in patients admitted to the ICU with community-acquired pneumonia, the detection of influenza was strongly associated with a subsequent diagnosis of IPA and half of the patients diagnosed with IAPA died in the ICU [1].

In this issue of *Clinical Infectious Diseases*, a single-center retrospective cohort study performed over 5 consecutive influenza seasons at a large tertiary care center in Alberta, Canada, reports on the incidence of IPA in 111 patients admitted to the ICU for respiratory failure caused by an influenza infection [4]. These data are a welcome addition to the data currently available in the literature. In contrast with the incidence of IAPA of 12% to 28% described in Europe and Asia so far, Schwartz et al found a substantially lower incidence of 7.2% (8 of 111 patients). Before we start wondering about why the incidence of IAPA in Canada may be lower than in Europe or Asia, it is important to put this incidence of 7% into perspective. Indeed, apart from patients undergoing remission induction chemotherapy for acute myeloid leukemia, patients with severe graft-versus-host disease, and perhaps also lung transplant patients, no other patient population has an incidence of IPA as high as 7%.

Histopathological evidence of the presence of *Aspergillus* species from a sterile body site remains the gold standard of an invasive aspergillosis diagnosis. However, sampling lung tissue in an ICU patient is clearly not without risk and actually rarely performed. Sputum or tracheal aspirate cultures are a low-cost and easy-to-perform diagnostic test, but the sensitivity when used to diagnose IPA in ICU patients does not exceed 50% [5]. Several non–culture-based assays are now available to demonstrate the presence of *Aspergillus* in blood or airway samples and testing for the presence of galactomannan (GM), a cell-wall component of *Aspergillus*, is the most validated of these non–culture-based tests. Because most studies that evaluated the value of GM testing for the diagnosis of invasive aspergillosis in ICU patients included few patients with a proven infection, doubts remain regarding its value in ICU patients. However, in a unique prospective study that was conducted in the setting of a very high autopsy rate, a substantial number of proven infections were included. In this unique study, testing for the presence of GM on bronchoalveolar lavage (BAL) fluid had a sensitivity of 88% and specificity of 87%. One of the most striking observations in this study was that GM testing on BAL identified 11 of a total of 26 (autopsy) proven IPA cases. Without GM testing these cases would have been missed if only fungal cultures would have been used. As expected, GM testing on serum performed substantially poorer [6, 7]. In the study by Schwartz and colleagues, clinicians tested for the presence of GM on BAL in as few as 16 of the 111 patients. It is therefore very likely that the incidence of 7% would have been higher if GM had been tested on BAL in all patients.

However, a true difference in the incidence of IAPA across continents may well be

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the case and several hypotheses can be postulated here. Differences in the incidence of invasive aspergillosis have been linked to single nucleotide polymorphisms (SNPs) in several genes of the innate immune system. Single nucleotide polymorphisms in the Pentraxin 3 (*PTX3*) gene decrease antifungal clearance and phagocytosis by neutrophils and therefore increase the susceptibility to invasive mold infections. These *PTX3* SNPs have been linked to an increased fungal infection risk in each of the 3 patient groups at highest risk for invasive mold infections: solid organ and allogeneic stem cell transplant recipients and patients with acute leukemia [8–10]. Future studies should look at the role of *PTX3* and other genetic risk factors in IAPA.

Apart from genetic factors, environmental factors are likely to play a role as well, as IAPA is often diagnosed in the first days after and even on the day of ICU admission. This suggests that the infection is caused by *Aspergillus* spores inhaled by the patient preceding hospital admission. Therefore, it is likely that differences in *Aspergillus* spore counts in the air (eg, rural rather than urban, dry versus wet climate) will influence the risk of IAPA. Apart from diagnostic and genetic factors, the way healthcare is organized locally may also influence the incidence of IAPA across countries and continents. Indeed, so far, data on IAPA come almost entirely from tertiary-care ICU centers. But even within these tertiary-care ICU populations, the specific patient referral policy in a country is likely to influence the IAPA risk. For instance, if extracorporal membrane oxygenation is only performed at the sites included in a specific study, the patients admitted at these ICUs will often be referred from first-care hospitals after conventional ventilatory support has been shown to be insufficient. These differences in ventilatory failure may not be reflected in conventional APACHE scores. Also, patients admitted to the ICU in tertiary-care centers may more often have specific underlying disease in which tertiary-care hospitals are typically specialized (eg, vasculitis, solid organ transplantation, autoimmune diseases). Finally, we have more speculative explanations for the observed differences in IAPA. Differences in influenza vaccination policies will influence the uptake of influenza vaccination and could change the severity of illness of an influenza infection in the population under study. Even more speculative is that the reported higher incidence of IAPA in recent years might be caused by the widespread use of neuraminidase inhibitors in patients infected with influenza. Fundamental research indicates that neuraminidase plays a role in the host immunity against *Aspergillus* species and blocking neuraminidase could increase the risk for *Aspergillus* superinfection [11]. Finally, the reported incidences of IAPA in ICU patients may only reflect the tip of iceberg. Some patients in the study by Schwartz et al survived without treatment while others died despite the best antifungal therapy. It might be that *Aspergillus* superinfection is quite common during influenza but only clinically relevant in patients admitted to the ICU.

But what is the clinical relevance of IAPA? Is it just an innocent bystander or is it truly one of the steps on the path from influenza infection to the death of these patients in the ICU? Half of the patients with IAPA in the cohort study from Schwartz et al died. This is in line with the reported mortality of IAPA cases in the DB-MSG study. To try to answer the question of whether the significantly higher mortality observed in patients with IAPA can be attributed to the *Aspergillus* superinfection or if it is just a marker of overall disease severity, we performed a mortality analysis on the DB-MSG study cohort. Remember, in this study 432 patients admitted to the ICU with influenza were included, of whom 117 were immunocompromised according to 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) criteria [12]. A total of 83 of the 432 patients (19%) were diagnosed with IAPA, and the 90-day mortality was 51%, which was substantially higher than the mortality in the 349 patients without IAPA (28%; $P < .001$). A Kaplan–Meier survival curve was made for patients with and without IAPA (Figure 1A) and a Cox regression analysis was performed to determine whether IAPA, as a time-dependent covariate, was independently associated with 90-day mortality, using the independent covariates as depicted in Figure 1B [13]. In the immunocompromised subgroup, 38 patients or 32% developed IAPA and 71% of them died. The Cox regression analysis showed that the emergence of IAPA was independently associated with 90-day mortality (adjusted hazard ratio [aHR], 1.944; 95% confidence interval [CI], 1.307–2.891; $P = .001$) (Figure 1B) as were age (aHR, 1.032; 95% CI, 1.018–1·046), APACHE II score (aHR, 1.046; 95% CI, 1.023–1.069), diabetes (aHR, 1.599; 95% CI, 1.092–2.342), being immunocompromised according to EORTC/MSG criteria (excluding corticosteroid use) (aHR, 1.670; 95% CI, 1.146–2.434), and corticosteroid therapy before ICU admission (aHR, 1.118; 95% CI, 1.035–1.207 per 0.1 mg/kg per day prednisone equivalent). These results strongly suggest that IAPA is independently associated with mortality in patients admitted to the ICU with influenza. Although we acknowledge that observational data can never prove a causal relationship with 100% certainty, the association of IAPA and mortality was independent of confounders such as severity of illness and being immunocompromised at ICU admission. This finding, again, confirms the relevance of diagnosing IAPA in the ICU. In accordance with recent literature, corticosteroid exposition preceding the ICU admission in patients with severe influenza significantly impacted mortality as well, and strongly suggests that caution is needed regarding the use of adjuvant corticosteroid therapy for patients with severe pneumonia during the influenza season [14, 15].

Many outstanding questions remain to be resolved. To answer these questions, the quality of future research on IAPA needs to be improved further. For this we will need a consensus definition of IAPA to be used in future studies. Therefore,

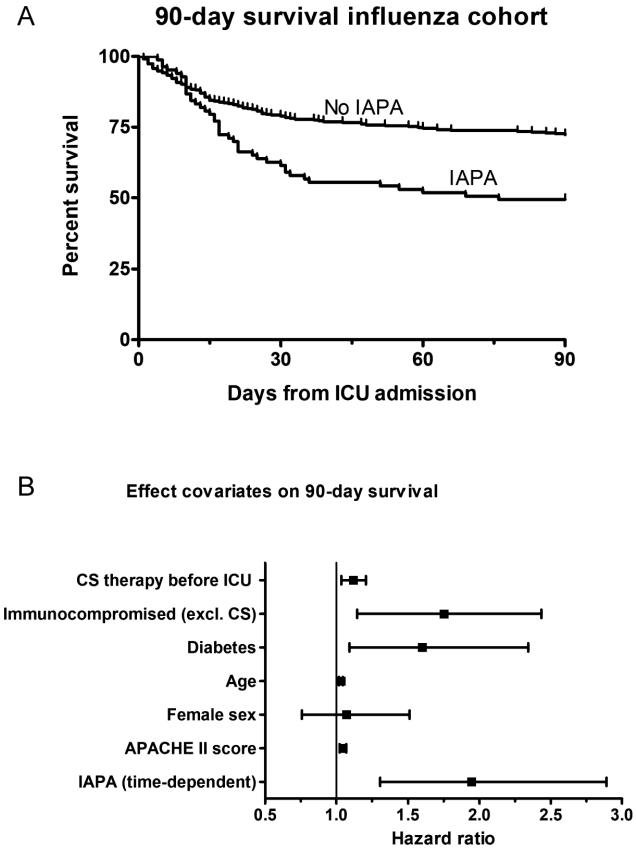

Figure 1. *A,* Kaplan–Meier 90-day survival function of the influenza cohort. *B,* Forest plot showing Cox regression analysis. Corticosteroid therapy before ICU admission means that the patients received CS in the 4 weeks preceding ICU admission. Immunocompromised means that the patient has a host factor as defined by the EORTC/MSG criteria [12]. Abbreviations: CS, corticosteroids; EORTC/MSG, 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; excl., excluding; IAPA, influenza-associated aspergillosis; ICU, intensive care unit.

a group of experts in the field of invasive fungal infections and intensive care medicine met to discuss and eventually formulate a workable set of definitions. We expect these to become publicly available in early 2020. Future studies should try to find risk factors for IAPA other than those already found. This will allow for stratification of patients included in studies on the prevention of IAPA (eg, with systemic or inhaled antifungal prophylaxis). It will also help the clinician when a decision needs to be made upon the invasiveness of diagnostic procedures to be done. Indeed, in a patient at very high risk for IAPA, a more invasive diagnostic strategy is justified. Once the diagnosis is made, the optimal therapy for IAPA needs to be found. Until new data arise, it is logical to treat these patients according to guidelines on the treatment of invasive aspergillosis. However, patients with *Aspergillus* tracheobronchitis may need to be treated differently. Also, it may well be that at least a subset of patients with IAPA can be treated for just a few weeks rather than a typical duration of at least 6 weeks and often many months for patients with a probable invasive aspergillosis according to the EORTC/MSG definition. Finally, we think that a better understanding of the underlying immunological mechanism and pathogenesis of IAPA is clearly needed because this may eventually lead to targeted prevention or therapy.

In conclusion, IAPA is a frequent and potentially lethal complication of influenza in critically ill patients. While its incidence may vary between geographical regions and centers, small primary-care ICUs will also see these patients if a high awareness among physicians is in place. Data like in the study by Schwartz et al demonstrate that, in patients with influenza admitted to the ICU with respiratory insufficiency, a diagnostic bronchoscopy should be done to look for tracheobronchitis and to biopsy visible lesions but also to sample BAL fluid. If the patient is not yet intubated, a very experienced bronchoscopist is often still able to perform a "mini-BAL" in just a few minutes while the patient is receiving high-flow nasal oxygen therapy. Galactomannan testing should be done on serum and preferentially also on BAL fluid. At ICU admission, a fungal culture on sputum or tracheal aspirates should be done. If IAPA is excluded on admission but progressive radiological and/or clinical deterioration is observed during or after ICU admission, a repeated radiological and/or bronchoscopic evaluation is needed to rule out IAPA (again).

Note

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