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BRIEF REPORT

High Rates of Influenza-Associated Invasive Pulmonary Aspergillosis May Not Be Universal: A Retrospective Cohort Study from Alberta, Canada

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From 2014–2019, invasive pulmonary aspergillosis complicated 7.2% (0–23.1% in different influenza seasons) of cases of influenza-associated respiratory failure in Edmonton, Alberta. Disease outcomes ranged from survival without therapy to death despite antifungals. Clinician vigilance, longitudinal local surveillance, and refined criteria to identify patients requiring therapy are needed.

Keywords. *Aspergillus*; aspergillosis; influenza; intensive care; emerging infections.

(See the Editorial Commentary by Rijnders et al on pages 1764–7.)

Invasive pulmonary aspergillosis (IPA) is a serious fungal disease, primarily of immunocompromised individuals. Increasingly, however, IPA has been reported as a complication of severe influenza infection even among immunocompetent patients. Several centers in Europe and Asia have reported that IPA complicated up to 28% of cases of severe influenza [1–4]. However, North American data are limited. We investigated the incidence of influenza-associated IPA (IAIPA) in intensive care unit (ICU) patients at a referral hospital in Edmonton, Alberta, Canada.

METHODS

We performed a retrospective cohort study of adult patients with influenza who were admitted between November 2014 and April 2019 to the ICU at the University of Alberta Hospital. This tertiary-care hospital contains 796 adult, inpatient beds, including 66 ICU beds; provides general medical and surgical care, cardiovascular surgery, advanced mechanical circulatory support, and solid organ transplantation; and has an inpatient hematology ward.

We included patients ≥18 years old with influenza who were admitted to the ICU for ≥24 hours because of respiratory failure. We excluded ICU patients admitted for other reasons and patients previously diagnosed with invasive aspergillosis. Multiple admissions in different influenza seasons were counted separately. We reviewed medical records throughout hospital admission and postdischarge for survival data. Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) scores were calculated within 24 hours of ICU admission [5]. We used the European Organization for Research and Treatment of Cancer/Mycoses Study Group definitions for immunocompromised hosts [6]. We defined corticosteroid therapy as ≥150 mg of a cortisol equivalent within a 24-hour period, given after admission or within the 7 days preceding admission. We defined mold-active antifungal therapy as systemic administration of itraconazole, voriconazole, posaconazole, isavuconazole, amphotericin B, or an echinocandin.

Influenza was diagnosed by multiplex polymerase chain reaction on respiratory samples. Bronchial specimens sent for fungal culture were examined using a calcofluor stain and plated onto thick phytone media for incubation at 30°C for 4 weeks. *Aspergillus* galactomannan testing used the Platelia enzyme immunoassay (Bio-Rad, Hercules, CA).

We defined IAIPA according to the Dutch-Belgian Mycosis Study Group's (DB-MSG's) modifications [1] to the *Asp*ICU criteria [7]. This required ≥1 criterion each from 3 categories: clinical, radiological, and mycological. Clinical criteria included, despite being on appropriate antimicrobials, having a fever ≥72 hours or being recrudescent after ≥48 hours defervescence without alternative etiology; dyspnea; hemoptysis; pleural friction rub or chest pain; and/or worsening respiratory insufficiency despite appropriate antibiotics and ventilator support. The radiological criterion was any pulmonary infiltrate on chest X-ray or computed tomography. Mycological criteria included histopathology or direct microscopic evidence of dichotomous septate hyphae with the growth of *Aspergillus* from tissue; the growth of *Aspergillus* from bronchial fluid; or a galactomannan optical density index of ≥1 on bronchioalveolar lavage or ≥0.5 on serum.

We compared baseline conditions, investigations, management, and 90-day all-cause mortality rates of influenza patients with and without IAIPA. Comparisons of categorical and continuous variables used Fisher's exact, Mann-Whitney U, or *t*-tests, where appropriate (SPSS version 26.0, IBM Corp., Armonk, NY). Any *P* values ≤.05 were considered significant,

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without corrections for multiple testing. The University of Alberta Health Research Ethics Board approved this study (Pro00090272).

RESULTS

Over 5 influenza seasons, 650 unique inpatients were diagnosed with influenza 655 times, and 133 ICU admissions occurred among 132 patients (20.3%). We excluded 22 patients (16.5%), because the ICU admission wasn't for respiratory failure (n = 17), due to a prior IPA (n = 2), because the ICU admission was for ≤ 24 hours (n = 2), and due to insufficient data (n = 1). For 110 unique patients, 111 ICU admissions were included.

The mean age of patients was 56.1 years (standard deviation [SD] 15.8), and 60 (54.1%) were males. There were 19 immunocompromised patients (16.8%) and 43 (38.7%) had chronic lung disease. Intubation was required in 92 patients (82.3%), and 13 (11.7%) required veno-venous extracorporeal membrane oxygenation. The mean APACHE II score (for 96 patients; 86.5%) was 24.2 (SD, 8.4). There were 92 patients (82.3%) infected with influenza A (54 [48.7%] with H1N1; 33 [29.7%] with H3N2; and 5 (4.5%) not typed) and 19 (17.1%) with influenza B.

There were 61 patients (55.0%) who underwent bronchoscopy. There was 1 patient who had visible plaques in the tracheobronchial mucosa (later proven via biopsy as invasive aspergillosis). There were 52 patients (46.8%) who had bronchial fungal cultures: *Aspergillus fumigatus* grew in 8 and 1 additionally had *Aspergillus nidulans*. Direct examinations of bronchial specimens identified hyphae for 1 of these 8 patients. Bronchial fluid galactomannan was measured in 16 (14.4%) patients. Of these, 4 patients were positive, all of whom also had *Aspergillus* grown from bronchial fluid (optical density indices of 3.80, 5.25, 7.05, and 7.72); 2 patients with positive cultures had negative bronchial galactomannan. No patients had serum galactomannan measurements. The median time from detection of influenza to detection of *Aspergillus* was 5 (interquartile range, 0–10) days.

There were 8 patients (7.2%) who had IAIPA (Supplementary Table S1). The incidence of IAIPA varied across influenza seasons (Supplementary Table S2; Supplementary Figure S1): IAIPA occurred just twice among 85 patients from 2014–2018 (range, 0–5.3%, with a cumulative proportion of 2.3%) and among 6/26 patients (23.1%) in 2018–2019 (P = .02). Rates of bronchoscopy and fungal cultures of bronchial specimens were similar between influenza seasons (Supplementary Table S2). More patients in 2018–2019 had bronchial fluid galactomannan measurements, but no patients were diagnosed based on a positive bronchial galactomannan without positive fungal cultures.

Patients with and without IAIPA are compared in Table 1. In both groups, immunocompromising conditions were uncommon (1/8 patients [12.5%] with and 18/103 [18.1%] without IAIPA) and chronic lung diseases were common (4/8 patients [50%] with and 39/103 patients [37.9%] without IAIPA). Corticosteroids were administered in 4/8 patients (50%) with and 63/99 patients (63.6%) without IAIPA. All patients with and 84/102 (82.4%) without IAIPA were intubated, while 5/8 (62.5%) with and 8/103 (7.8%) without IAIPA required extracorporeal membrane oxygenation. Of 8 patients with IAIPA, 7 (87.5%) were infected with influenza A(H1N1). In total, IAIPA complicated 7/54 cases (13.0%) involving influenza A(H1N1).

Death occurred within 90 days of influenza detection in 32 patients (28.3%), including 4/8 patients (50%) with and 28/103 (27.2%) without IAIPA. Among those patients with IAIPA who died, 2 had autopsies. In 1, dichotomous, septate hyphae invaded the tracheobronchial tree, lungs, gastric wall, heart, thyroid, and brain. In the other, the autopsy—which was performed after 21 days of antifungal therapy—found no evidence of IPA. There was 1 patient with IAIPA who survived without antifungal treatment.

DISCUSSION

IAIPA affected 7.2% of patients with severe influenza over 5 seasons, but with significant variation between seasons, ranging from between 0% and 5.3% in 2014–2018 to 23.1% in 2018–2019. Our overall rates are lower than those reported from European and Asian centers [1–4], where IAIPA was reported in 83/432 patients (19.2%) in The Netherlands and Belgium (2016–2019) [1], 10/81 patients (12.3%) in Switzerland (2017–2018) [2], 21/124 patients (16.9%) in Taiwan (2015–2016) [3], and 18/64 patients (28.1%) in China (2017–2018) [4].

The reasons for the observed increase in IAIPA in 2018–2019 are unclear. The predominate influenza strain then was A(H1N1), which has been linked to IAIPA since its reemergence in 2009 [8–10]. Conversely, influenza A(H1N1) also predominated in 2015–2016, comprising at least 28/36 strains (77.8%) among ICU patients in our cohort, and yet IAIPA affected just 1 patient (2.8%) in that influenza season. Moreover, the DB-MSG study did not find an association between the influenza strain and IAIPA; in fact, influenza A and B strains were distributed similarly among patients with IAIPA [1]. The increase we observed is unlikely to be attributable to a diagnostic bias, because rates of bronchoscopy or fungal cultures of bronchial specimens were unchanged. Although bronchial galactomannan measurements increased, no cases were diagnosed solely based on bronchial galactomannan (ie, without *Aspergillus* also being isolated).

The risk of IPA is affected by center-specific environmental factors, such as ventilation systems, nearby construction, hospital building materials, and infection control practices [11]. Host factors are also important, and the DB-MSG study found that male sex, APACHE II score, and corticosteroid use in the 4 weeks preceding ICU admission were independently associated with IAIPA [1]. Compared to the DB-MSG cohort [1], our cohort had similar proportions of males (54% vs 56%, respectively) and initial disease severity (mean APACHE II scores

Table 1. Comparison of Patients with Severe Influenza With and Without Influenza-Associated Invasive Pulmonary Aspergillosis

Characteristic	Patients With IAIPA, n = 8	Patients Without IAIPA, n = 103	*P* Value
Influenza strain			
A(H1N1)	7 (85.7)	47/98[a] (48.0)	.06
A(H3N2)	0	33/98[a] (33.7)	.06
B	1 (12.5)	18 (17.5)	1
Patient Characteristics			
Mean age (SD)	50.5 (10.3)	56.5 (16.2)	.30
Male sex	5 (62.5)	55 (53.4)	.72
Immune compromised	1 (12.5)	18 (17.5)	1
Chronic lung disease	4 (50)	39 (37.9)	.71
Mean APACHE II (SD)	24.7 (6.0)[b]	24.2 (8.6)[c]	.87
Management			
Corticosteroids	4 (50)	63/99 (63.6)	.47
Oseltamivir	8 (100)	94/98 (95.9)	1
Intubated	8 (100)	84/102 (82.4)[d]	.35
Extracorporeal membrane oxygenation	5 (62.5)	8 (7.8)	<.001
Mold-active antifungals	6 (75)	7/102 (6.9)	<.001
Outcome			
All-cause mortality at 90 days	4 (50)	28 (27.2)	.22

All data are presented as n (%) unless otherwise specified.

Abbreviations: APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; IAIPA, influenza-associated invasive pulmonary aspergillosis; SD, standard deviation.

[a]There were 5 patients without IAIPA who were infected with influenza A but in whom the strains could not be typed.

[b]Data missing for 1.

[c]Data missing for 15.

[d]Prior to admission, 1 patient was chronically ventilated.

of 24 [SD, 8] vs 22 [SD, 8], respectively). Our measurement of corticosteroid use differed from that of the DB-MSG study, limiting comparisons.

Our study is from a single center, and our experience may not be generalizable to other North American settings. Some patients with IAIPA may have been misclassified, although mitigating against this is the high rate of bronchoscopies in our cohort (55.0%), similar to the rate in the DB-MSG study (53.9%) [1].

Alternatively, some patients may not have had true IPA. Among IAIPA patients, for example, 1 survived despite not receiving antifungals and IPA was not confirmed on autopsy in another patient, albeit after several weeks of therapy. These findings may suggest that current definitions and tests used to diagnose IAIPA lack specificity in the population affected and are inadequate for guiding treatment decisions.

CONCLUSION

Severe influenza has emerged as a risk factor for IPA, even in nonneutropenic patients. Although IAIPA was less common here than reported elsewhere, our data suggest that rates are dynamic, highlighting the importance of local surveillance. Further study is needed to characterize the epidemiology of IAIPA in different settings over time. Moreover, better definitions are required to distinguish which severe influenza patients with *Aspergillus* in lower respiratory samples require treatment.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Note

Potential conflicts of interest. I. S. S. has received an honorarium for consultancy work from AVIR Pharma Inc. N. L. has received honoraria for consultancy work, speakers fees from educational programs, and/or travel support from Shionogi Inc., Janssen Inc., Sanofi Pasteur Ltd, F. Hoffmann-La Roche Ltd, Genentech Inc., and CIDARA Therapeutics Inc. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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