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Influenza-associated invasive aspergillosis in patients admitted to the intensive care unit in Sweden: a prospective multicentre cohort study

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ABSTRACT

Background: The purpose of this study was to prospectively investigate the incidence of influenza-associated pulmonary aspergillosis (IAPA) in influenza patients admitted to intensive care units in Sweden.

Methods: The study included consecutive adult patients with PCR-verified influenza A or B in 12 Swedish intensive care units (ICUs) over four influenza seasons (2019–2023). Patients were screened using serum galactomannan and β -d-glucan tests and fungal culture of a respiratory sample at inclusion and weekly during the ICU stay. Bronchoalveolar lavage was performed if clinically feasible. IAPA was classified according to recently proposed case definitions.

Results: The cohort included 55 patients; 42% were female, and the median age was 59 (IQR 48–71) years. All patients had at least one galactomannan test, β -d-glucan test and respiratory culture performed. Bronchoalveolar lavage was performed in 24 (44%) of the patients. Five (9%, 95% CI 3.8% – 20.4%) patients were classified as probable IAPA, of which four lacked classical risk factors. The overall ICU mortality was significantly higher among IAPA patients than non-IAPA patients (60% vs 8%, $p = 0.01$).

Conclusions: The study represents the first prospective investigation of IAPA incidence. The 9% incidence of IAPA confirms the increased risk of invasive pulmonary aspergillosis among influenza patients admitted to the ICU. Therefore, it appears reasonable to implement a screening protocol for the early diagnosis and treatment of IAPA in influenza patients receiving intensive care.

Trial registration: ClinicalTrials.gov NCT04172610, registered November 21, 2019

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Introduction

Influenza-associated pulmonary aspergillosis (IAPA) is increasingly observed among critically ill patients in intensive care units (ICU). The reported incidence of IAPA ranges from 5 to 29% [1–6], with most patients lacking classical risk factors, such as immunosuppression or neutropenia. The underlying mechanism of IAPA remains unclear, but viral-induced epithelial damage, ciliary dysfunction, and suppressed production of reactive oxygen species may all play a role [7,8]. In addition, the neuraminidase inhibitor oseltamivir has been linked to a decreased killing capacity of monocytes against *Aspergillus* species in mice [9].

Aspergillus colonisation occasionally occurs in the airways of ICU patients, and the interpretation of the clinical significance of a positive sputum/tracheal aspirate culture can be challenging [10,11]. However, the reported mortality rate of influenza patients diagnosed with IAPA is twice as high as those without pulmonary aspergillosis [1].

Previous studies have all been retrospective and, in most cases, have utilised case definitions that were not explicitly developed for the targeted patient population. Notably, the criteria do not incorporate bronchoalveolar lavage (BAL) galactomannan (GM) and often require clinical signs lacking in ICU patients [12]. Recently, Verweij et al. published a proposed case definition for IAPA in ICU patients, which includes influenza as a host factor and incorporates both serum and BAL GM into the diagnostic criteria [13]. In this present study, we sought to prospectively determine the cumulative incidence of IAPA in Swedish ICUs using the proposed case definition. A predefined diagnostic protocol was employed. Secondary outcomes included IAPA risk factors, length of ICU stay, invasive mechanical ventilation use, continuous renal replacement therapy (CRRT), vasopressor therapy, and mortality at ICU discharge and 30 days.

Methods

We conducted a prospective, multicentre cohort study in 12 tertiary care ICUs in Sweden from December 2019 to April 2023, spanning four influenza seasons. The

centres are located in four out of the six larger regions in Sweden, catering to approximately 2.5 million people, corresponding to a quarter of the Swedish population. The study included consecutive patients aged ≥ 18 years with a polymerase chain reaction (PCR)-verified influenza A or B diagnosis within seven days prior to ICU admission or during ICU care. At inclusion, patients were screened by using analysis of serum GM (Platelia *Aspergillus*; Bio-Rad Laboratories, France) and β -d-glucan (BDG) tests (Fungitell assay, Cape Cod, USA) and fungal microscopy and culture of respiratory samples. If feasible, BAL was performed to obtain samples for fungal culture, microscopy, and GM testing. Serum BDG and GM tests were repeated twice weekly, and respiratory samples were sent for fungal culture and microscopy weekly for the remainder of the ICU stay. A new BAL was performed if any of the tests returned positive. A positive GM test result was defined using a cut-off optical density index (ODI) value of ≥ 0.5 in a serum sample and >1.0 in a BAL sample, and the positivity threshold for BDG was >80 pg/ml. Patients were assessed with simplified acute physiology score (SAPS 3) and the sequential organ failure assessment (SOFA) score upon ICU admission and daily registration of invasive mechanical ventilation use, continuous renal replacement therapy (CRRT) use, vasopressor therapy use, corticosteroid treatment and the use of antibiotic and fungal treatment. IAPA was diagnosed using the diagnostic criteria recently proposed by Verweij et al. [13] (Table 1).

The primary analysis was the cumulative incidence of IAPA at ICU discharge. Secondary analyses included comparisons of ICU length of stay, invasive mechanical ventilation treatment, vasopressor treatment, CRRT,

Table 1. Influenza-associated pulmonary aspergillosis case definition (according to Verweij et al. [13]).

Proven	Lung biopsy showing invasive fungal elements and <i>Aspergillus</i> growth on culture or a tissue sample showing positive <i>Aspergillus</i> PCR results
Probable	Pulmonary infiltrate and at least one of the following: Serum GM index >0.5 BAL GM index ≥ 1.0 Positive BAL culture Cavitating infiltrate and a positive sputum/tracheal aspirate culture

BAL, Bronchoalveolar lavage, GM, Galactomannan.

corticosteroid treatment and ICU and 30-day mortality in IAPA and non-IAPA patients.

Statistical analyses were performed using STATA version 16.1 (Stata Corp, TX, USA). Categorical variables are expressed as counts and percentages, and continuous variables are expressed as medians and interquartile ranges. The Wilcoxon rank-sum test was used to analyse continuous variables, and Fisher's exact test was used for categorical variables. A binomial confidence interval at the 95% level was calculated for the patients diagnosed with IAPA. A p-value less than 0.05 was considered statistically significant. Statistical analyses for secondary endpoints were not adjusted for multiplicity, suggesting the findings should be viewed as exploratory. The study was approved by the Swedish Ethical Review Board (DNR 2019-00557), and the need for informed consent was waived. The study followed the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study was financially supported by the Regional research council Uppsala-Örebro and the Centre for Clinical Research Västmanland.

Results

The study included 55 patients, of which 23 (42%) were female, with a median age of 59 (IQR 48-71) years, Table 2. According to the Swedish Intensive Care Registry, during the study period, the included centres admitted 87 patients who had influenza, which corresponds to an inclusion rate of 63%. However, patients

with only brief admissions to the ICU are also included in the registry. All included patients had at least one respiratory fungal culture obtained (median 1, range 1-4), and serum GM and BDG were analysed at least once (median 1.8, range 1-6). BAL was performed in 24 (44%) patients, all receiving invasive mechanical ventilation at inclusion. No patients received antifungal therapy at the time of inclusion. All patients had respiratory illness and pulmonary infiltrates visible on chest X-ray or CT scan, and none exhibited cavitory infiltrates.

Five (9%, 95% CI 3.8% – 20.4%) of the 55 patients met the definition of probable IAPA, and no patient had proven IAPA, Table 3. IAPA was diagnosed at inclusion in three of the five patients. One of the five patients fulfilled the EORTC/MSG criteria for a susceptible host [14] (haematologic malignancy and high-dose corticosteroid treatment).

All five patients diagnosed with IAPA underwent a BAL, and BAL GM was positive in all these patients. Out of them, *Aspergillus* growth was identified in the BAL of three patients (all *A. fumigatus*) and two patients had microscopic evidence of *Aspergillus*. One patient (2%) had a positive serum GM test, with BAL confirming GM positivity as well as *Aspergillus* growth and positive microscopy, which correlates to a serum GM sensitivity of 20% (1/5) and specificity of 100% (1/1). Seven patients (13%) had at least one positive BDG test, of them two (4%) had consecutive positive tests. Two of these seven patients underwent BAL, which confirmed IAPA through positive *Aspergillus* culture and BAL GM. These findings correspond to a BDG sensitivity of 40%

Table 2. Baseline characteristics.

	Total cohort (n = 55)	IAPA (n = 5)	Non-IAPA (n = 50)	p value
Age, median (IQR), years	59 (48-71)	65 (60-70.5)	59 (47-72)	0.34
Sex, female, n (%)	23 (42)	0 (0)	23 (46)	0.07
Influenza A, n (%)	49 (89)	5 (100)	44 (88)	1.0
Body Mass Index >30 kg/m ² (%)	17 (31)	1 (20)	16 (32)	1.0
Chronic Kidney Disease*, n (%)	7 (13)	1 (20)	6 (12)	0.51
Haemodialysis, n (%)	0 (0)	0 (0)	0 (0)	–
Liver cirrhosis, n (%)	2 (4)	0 (0)	2 (4)	1.0
Diabetes mellitus, n (%)	10 (18)	1 (20)	9 (18)	1.0
COPD, n (%)	12 (22)	1 (20)	9 (18)	1.0
Smoking in the past year, n (%)	12 (22)	3 (6)	9 (18)	0.06
Heart failure †, n (%)	4 (7)	0 (0)	4 (8)	1.0
Solid organ malignancy, n (%)	0 (0)	0 (0)	0 (0)	–
Haematologic malignancy, n (%)	5 (9)	1 (20)	4 (8)	0.39
Solid-organ transplant, n (%)	0 (0)	0 (0)	0 (0)	–
HSCT, n (%)	3 (5)	0 (0)	3 (6)	1.0
Neutropenia <0.5 10 ⁹ /L, n (%)	1 (2)	0 (0)	1 (2)	1.0
Corticosteroid treatment, n (%)	8 (15)	1 (20)	7 (14)	0.56
>15 mg/day prednisone equivalent, n (%)	7 (13)	1 (20)	6 (12)	–
Antibiotic therapy at inclusion, n (%)	55 (100)	5 (100)	50 (100)	–
Oseltamivir treatment, n (%)	51 (93)	5 (100)	46 (92)	1.0
SAPS 3, median (IQR)	60 (49-68)	72 (55-73)	61 (50-69)	0.14
SOFA score, median (IQR)	8 (5-11)	10 (7-11)	7 (5-11)	0.27

*Creatinine Clearance <30 mL/min according to the Cockcroft-Gault formula, † Ejection Fraction <40%, IAPA, Influenza-associated Pulmonary Aspergillosis, COPD, Chronic Obstructive pulmonary disease, HSCT, Haematopoietic stem cell transplantation, IQR, Interquartile range, SAPS, Simplified Acute Physiology Score, SOFA, Sequential Organ Failure Assessment.

and specificity of 90%. Without BAL, only one patient would have been diagnosed with IAPA (positive serum GM test). One patient with IAPA was diagnosed with *Aspergillus* tracheobronchitis via bronchoscopy. Screening using serum GM, BDG and sputum/tracheal aspirate cultures did not yield additional IAPA cases or prompt further investigation with BAL.

There was a statistically significant difference ($p=0.02$) regarding whether BAL was performed between IAPA and non-IAPA cases, accounting for 5 (100%) and 19 (38%) patients, respectively. Among the 13 patients (24%) who did not receive invasive mechanical ventilation, none underwent a BAL. However, all were successfully discharged from the ICU alive. The incidence of probable IAPA, when including only mechanically ventilated patients, was 5 out of 42 (12%).

For the secondary outcomes, we found no statistically significant risk factors for IAPA, Table 2. Patients diagnosed with a probable case of IAPA exhibited a longer length of stay in the ICU, compared to patients without IAPA, Table 4. All patients diagnosed with probable IAPA were mechanically ventilated and received vasopressor

treatment during their ICU stay but were not statistically different to non-IAPA patients. The overall ICU mortality in the cohort was 13%. Among patients diagnosed with IAPA, the ICU mortality was 60%, compared to 8% in patients not diagnosed with IAPA, a statistically significant difference ($p=0.01$). The mortality rate at 30 days continued to be higher among patients diagnosed with IAPA, Table 4.

Discussion

In this first prospective study investigating the incidence of IAPA using a targeted screening protocol, we found an incidence of 9%, confirming an increased risk of invasive pulmonary aspergillosis among influenza patients admitted to the ICU. The study included 12 Swedish intensive care units and spanned four influenza seasons. Until now, all published studies have been retrospective, presenting a significant risk of bias as the diagnosis of IAPA depends on specific diagnostic tests. Since the initial report by Wauters et al. in 2012 raised awareness about a potential association between influenza and invasive pulmonary aspergillosis [15], several retrospective studies have replicated this association. The first major study was published in 2019 by Schauwvlieghe et al. [1] and found the IAPA incidence to be as high as 19% in a retrospective cohort of 432 influenza patients admitted to ICUs in Belgium and the Netherlands. The finding prompted studies from many other regions, studies which generally have reported significantly lower incidences [16]. The most recent major study, published in 2021, found an IAPA incidence of 5.3% in a retrospective cohort of 524 ICU patients in France [6].

There are several possible explanations for the significant regional variations, such as differences in the patients' underlying health conditions, concurrent use of corticosteroids, and exposure to *Aspergillus* due to environmental factors. Other important explanations are the limitations inherent to a retrospective study design, and until recently, lack of accepted criteria for diagnosing

Table 3. Characteristics of IAPA cases.

IAPA cases	Case 1	Case 2	Case 3	Case 4	Case 5
Age, sex	64, m	65, m	71, m	56, m	70, m
Haematologic malignancy	No	No	No	No	Yes
Corticosteroid treatment	No	No	No	No	Yes
Smoking in the past year	Yes	No	Yes	Yes	No
COPD	No	Yes	No	No	No
Baseline SOFA score	11	10	11	6	8
SAPS 3	72	65	72	45	74
Cavitating infiltrates on CT	No	No	No	No	No
BAL culture	<i>A. fumigatus</i>	<i>A. fumigatus</i>	Neg	<i>A. fumigatus</i>	Neg
BAL GM, ODI	3.8	1.6	2.8	3.8	2.6
Serum GM, ODI	Neg	0.6	Neg	Neg	Neg
Serum BDG, pg/mL	Neg	800	Neg	130	Neg
BAL microscopy	Neg	Pos	Neg	Pos	Neg
ICU days to IAPA diagnosis	13	1	1	8	1
ICU mortality	No	Yes	No	Yes	Yes

BAL, Bronchoalveolar lavage; BDG, β -d-glucan; GM, Galactomannan; COPD, Chronic Obstructive pulmonary disease; CT, Computer Tomography; ICU, Intensive Care Unit; IAPA, Influenza-associated Pulmonary Aspergillosis; ODI, Optical Density Index; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

Table 4. Outcome measures.

	Total cohort (n = 55)	Mechanically ventilated (n = 42)	IAPA patients (n = 5)	Non-IAPA patients (n = 50)	p value*
Invasive mechanical ventilation, n (%)	42 (76)	42 (100)	5 (100)	37 (74)	0.32
Ventilator days, median (IQR)	7 (3–12)	7 (3–12)	4 (3–13)	7 (3–12)	–
Vasopressor, n (%)	35 (64)	31 (74)	5 (100)	30 (60)	0.15
Vasopressor duration, median (IQR)	4 (3–6)	4 (1–8)	5 (4–7)	4 (3–6)	–
CRRT, n (%)	7 (13)	7 (17)	1 (20)	6 (12)	0.51
Length of ICU stay, median (IQR)	5 (3–13)	9 (3–16)	11 (6–17)	4 (3–13)	–
Corticosteroid treatment	32 (58)	26 (62)	4 (80)	28 (56)	0.39
ICU mortality, n (%)	7 (13)	7 (17)	3 (60)	4 (8)	0.01
30 day mortality, n (%)	10 (18)	9 (21)	3 (60)	7 (14)	0.04

IAPA, Influenza-associated Pulmonary Aspergillosis; IQR, Interquartile range; CRRT, Continuous renal replacement therapy; ICU, Intensive Care Unit.

* IAPA and non-IAPA comparison.

IAPA. The problem with using criteria not explicitly tailored to the target population was recently addressed in a study by Schroeder et al. [17], revealing that the concordance among four earlier classification systems for invasive pulmonary aspergillosis was as low as 4%.

In the present study, these limitations were addressed by a prospective design and application of the IAPA classification proposed by Verweij et al. The IAPA incidence of 9% found in the study aligns with the results from a recent meta-analysis [16], which included a large set of retrospective cohorts. In the metanalysis, the IAPA incidence varied considerably from 2% to 31%, but with an overall estimated IAPA incidence of 10%.

An important finding from the study was that screening with non-invasive test, i.e. serum BDG and GM and upper respiratory cultures, had limited sensitivity and specificity both for identifying and establishing IAPA cases. Serum GM had a very limited sensitivity of 20%, but with a 100% specificity it could prove valuable in situations where a BAL is not feasible. The utility of BDG appeared limited, with a 40% sensitivity for IAPA, and a specificity of 90%, it will generate an excessive number of false positives in a population with low IAPA prevalence. This outcome was predictable given that the test is not *Aspergillus*-specific. The very limited sensitivity of non-invasive tests for identifying IAPA cases strongly indicates that BAL is necessary in most cases for identifying IAPA, and thus should be performed in all severely ill patients if possible.

Our study has several limitations, the major one being the small cohort size, which hampered our ability to determine the incidence of IAPA in Sweden with high accuracy. (9%, 95% CI 3.82% – 20.4%). The limited number of IAPA cases also hinders any multivariate analyses of risk factors and outcomes. The lower-than-expected enrolment rate was primarily due to the COVID-19 pandemic, which significantly reduced the incidence of influenza. Nevertheless, we managed to include the majority of influenza patients admitted to the study centres during this period, thus maintaining the validity of our results. Despite promoting BAL in the screening protocol, it was only performed for 45% of the patients, probably due to concerns of respiratory failure. This could have led to underestimating the true prevalence, as only one IAPA patient would have been diagnosed without a BAL. However, BAL was predominantly not performed in less ill patients. In fact, none of the patients who did not receive mechanical ventilation underwent BAL. Despite this, all patients not

mechanically ventilated were successfully discharged alive from the ICU, which could suggest that IAPA was not missed.

The ICU mortality rate of 13% in our cohort was low compared to previous cohorts, ranging from 19% to 29% [1,2,6]. The severity of the disease, measured by the SAPS 3 and SOFA, was also lower. These factors may influence the incidence of IAPA, as illness severity has been reported to be associated with an increased risk of IAPA [1].

In conclusion, this is the first-ever prospective study to investigate the incidence of IAPA. Additionally, it is the only report on the incidence of IAPA in the Nordic region, providing regional data that were previously lacking. We observed a high mortality among IAPA patients, underlining the urgency to raise awareness about this often-fatal superinfection. Most patients diagnosed with IAPA lacked traditional risk factors, underscoring the importance of routine testing for aspergillosis in influenza patients in the ICU. Non-invasive testing has a low sensitivity, and BAL with fungal culture and GM testing should be considered in all mechanically ventilated influenza patients.

Author contributions

All authors made substantial contributions to the present study. Anders Krifors, Ola Blennow, Johan Petersson, and Markus Castegren developed the original concept and research design. The preparation of materials, as well as data collection and analysis, were conducted collaboratively by all authors. The initial manuscript draft was written by Anders Krifors, with each author providing critical comments and suggestions for revisions. All authors reviewed and approved the final version of the manuscript to be published.

Disclosure statement

The authors declare that they have no conflicts of interest.

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