

Aspergillosis Complicating Severe Influenza in ICU Patients: A Retrospective Cohort Study

Caitlin Visek, MD¹, Hannah Nam, MD, MSCI², Michael G. Ison, MD, MS³

¹Division of General Internal Medicine, Northwestern University Feinberg School of Medicine ²Division of Infectious Diseases, University of California, Irvine ³Divisions of Infectious Diseases and Organ Transplantation, Northwestern University Feinberg School of Medicine

Background and Objectives

- Invasive pulmonary aspergillosis (IPA) has been identified as a common complication of severe influenza infection even in immunocompetent hosts in recent studies
- We aimed to ascertain the incidence of IPA among critically ill influenza patients over multiple seasons, identify predisposing risk factors, and assess outcomes

Methods

- Retrospective cohort study
- Single-center in Chicago, IL
- Data collected across 9 flu seasons (March 2009 – March 2018)
- Included patients \geq age 18 with a positive influenza PCR test who were admitted to ICU with respiratory distress
- IPA defined by both EORTC/MSG and *AspICU* criteria

Results

- 224 ICU patients with influenza during the study period
- IPA incidence was 3.1% (7/224)
- History of stem cell transplant was a statistically significant risk factor ($p=0.015$)
- Only 1/7 patients with IPA was not immunosuppressed
- Trend toward significance in those with: hematological malignancy ($p=0.09$), lung disease ($p=0.098$), and obesity ($p=0.051$)
- Significantly increased length of stay in IPA-positive patients ($p=0.046$)
- No significant difference in need for mechanical ventilation, renal replacement therapy, or death

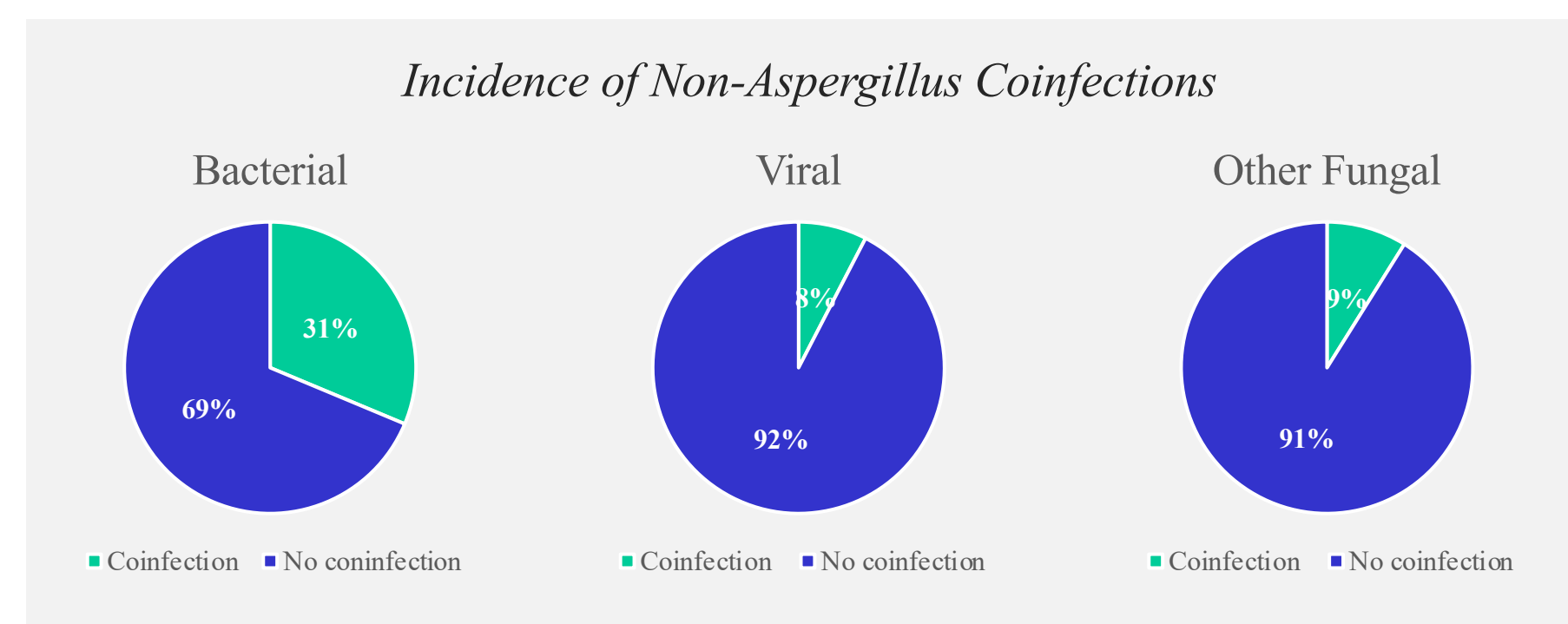


Table 1. Baseline Characteristics and Morbidity/Mortality

Baseline characteristics	All patients with Influenza (N=224)	With invasive pulmonary aspergillosis (N=7)	Without invasive pulmonary aspergillosis (N=217)	p-value
Median age, years (IQR)	60 (49, 72)	58 (57, 66)	60 (49, 72)	0.844
Male sex	114 (50.89)	1 (14.3)	113 (52.1)	0.062
Median LOS (IQR)	10.5 (5.5, 21.2)	24.1 (10.6, 31.8)	10.4 (5.4, 20.6)	0.046
Median ICU LOS (IQR)	4.4 (1.9, 13.0)	7.1 (1.9, 19.0)	4.3 (1.9, 12.3)	1.000
BMI over 30	81 (36.2)	0 (0.0)	81 (37.3)	0.051
Lung disease	101 (45.1)	1 (14.3)	100 (46.1)	0.098
Heart disease	99 (44.2)	1 (14.3)	98 (45.2)	0.107
Diabetes	49 (21.9)	1 (14.3)	48 (22.1)	0.524
Liver cirrhosis	6 (2.7)	1 (14.3)	5 (2.3)	0.175
Chronic kidney disease	48 (21.43)	0 (0.00)	48 (22.1)	0.180
Rheumatologic Disease	27 (12.1)	1 (14.3)	26 (11.9)	0.598
Known risk factors				
Hematological malignancy	37 (16.5)	3 (42.9)	34 (15.7)	0.090
Stem Cell Transplant	19 (8.5)	3 (42.9)	16 (7.3)	0.015
GVHD	4 (1.79)	0 (0.0)	4 (1.84)	0.880
Solid Organ Transplant	17 (7.6)	1 (14.3)	16 (7.4)	0.429
Immune Suppression not due to transplant	35 (15.7)	3 (42.9)	32 (14.8)	0.103
Solid organ malignancy	14 (6.3)	0 (0.0)	14 (6.5)	0.632
Neutropenia	52 (23.3)	1 (14.3)	51 (23.6)	0.485
Lymphopenia	146 (54.5)	4 (57.1)	142 (65.7)	0.457
ICU Data				
Mechanical ventilation	111 (49.6)	5 (71.4)	106 (48.9)	0.216
Renal replacement therapy	34 (15.2)	1 (14.3)	33 (15.2)	0.712
ECMO	8 (4.8)	1 (20.0)	7 (4.3)	0.220
Death within 1 year	25 (11.2)	0 (0.0)	25 (11.5)	0.432
Influenza Subtype and Treatment				
Influenza A	172 (83.9)	5 (71.4)	167 (84.3)	0.314
Influenza B	51 (27.3)	2 (28.6)	49 (27.2)	0.614
Treatment with oseltamivir	206 (91.9)	7 (100.0)	199 (91.7)	0.552
Treatment with zanamivir	3 (1.3)	1 (14.3)	2 (0.92)	0.091
Treatment with peramivir	3 (1.3)	0 (0.00)	3 (1.4)	0.909
Treatment with IVIG	22 (9.8)	2 (28.6)	20 (9.2)	0.143
Treatment with Steroids	136 (60.7)	3 (42.9)	133 (61.3)	0.437

Table 2. Patient Characteristics in IPA

	Number of patients in the influenza cohort with IPA (n=7)
BAL culture positive	3 (42.8%)
BAL galactomannan test positive	2 (28.5%)
Serum galactomannan test positive	2 (28.5%)
EORTC/MSG criteria	
Proven	0 (0%)
Probable	2 (28.5%)
Possible	5 (71.4%)
AspICU Criteria	
Proven	0 (0%)
Putative	4 (57.0%)
Colonization	3 (42.8%)
Not classifiable	0 (0%)
Initial Treatment	
Voriconazole	7 (100%)
Echinocandins	1 (14.3)
Isavuconazole	0 (0%)
Posaconazole	0 (0%)
Liposomal amphotericin B	2 (28.5%)
Combination	3 (42.8%)
No treatment	0 (0%)

Conclusions

- Overall incidence of IPA was significantly lower than previously reported despite having no proven cases (3.1% here compared to as high as 16-28% in the literature)
- Only one IPA positive patient in our study was not immunosuppressed over 9 years
- History of stem cell transplant was a strong risk factor for the development of IPA
- IPA did not clearly predict morbidity and mortality among these critically ill patients

1. Kallil AC, Thomas PG. Influenza virus-related critical illness: pathophysiology and epidemiology. Crit Care. 2019;23(1):258.
 2. Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, et al. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. The Lancet. 2018;391(10127):1285-300.
 3. 4. Crum-Cianflone NF. Invasive Aspergillosis Associated With Severe Influenza Infections. Open Forum Infect Dis. 2016;3(3):ofw171.
 4. Huang L, Zhang N, Huang X, Xiong S, Feng Y, Zhang Y, et al. Invasive pulmonary aspergillosis in patients with influenza infection: A retrospective study and review of the literature. Clin Respir J. 2019;13(4):202-11.
 5. Schauwvlieghe AFAD, 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;6(10):782-92.
 6. van de Groep K, Verboom DM, van de Veerdonk FL, Haas PA, van der Poll T, Schultz MJ, et al. Detection of invasive aspergillosis in critically ill patients with influenza: the role of plasma galactomannan. American Journal of Respiratory and Critical Care Medicine. 2019;200(5):636-8.
 7. van de Veerdonk FL, Kolwijck E, Lestrade PP, Houdamont 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.
 8. Wauters J, Baer 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;38(11):1761-8.