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Introduction:
Invasive pulmonary aspergillosis (IPA) typically occurs in immunosuppressed hosts but is occasionally described in ICU patients with severe influenza. Whether influenza is independently associated with IPA is unknown. We aimed to measure the incidence of IPA in influenza-infected ICU patients and to evaluate whether influenza is independently associated with IPA.

Methods:
Multicenter observational case-control study. Data were collected from patients admitted with influenza to 7 ICUs during 7 consecutive influenza seasons (2009-2016). A case-control study was performed in the subgroup of patients without EORTC/MSG risk factors for IPA. Cases were ICU patients with influenza and controls were ICU patients with severe community-acquired pneumonia (CAP) without influenza. A multivariate binary logistic regression analysis was performed to determine the adjusted odds ratio (aOR, 95% CI) of influenza for the development of IPA.

Results:
432 patients were admitted to ICU with influenza, 315 of them had no EORTC/MSG host factor. 315 CAP patients served as controls. 19% (83/432) of influenza patients developed IPA, median 2 days after influenza diagnosis. The incidence of IPA in 117 patients with influenza and an EORTC/MSG host factor was 32% (38/117) while it was 14% (45/315) in patients with influenza and without EORTC/MSG developed IPA. 45% (37/83) influenza-patients with IPA died on ICU while 20% (70/349) of those without IPA died (p<0.001). Only 5% (16/315) of influenza-negative CAP patients were diagnosed with IPA (p<0.001). In the case-control study, influenza was independently associated with IPA (aOR 5.19, 2.63-10.26). Higher APACHE II-score, male sex and the use of corticosteroids were independently associated with the development of IPA in influenza patients.

Conclusion:
IPA is independently associated with influenza in ICU patients and has substantial mortality. Future studies should evaluate if faster IPA diagnosis or prophylaxis can improve outcome