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ORIGINAL ARTICLE

Higher mortality of severe influenza patients with probable aspergillosis than those with and without other coinfections

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Background/Purpose: *Aspergillus*-associated infection might comprise up to 23–29% of severe influenza patients from the community throughout stay in an intensive care unit (ICU). In Taiwan, cases of severe influenza with aspergillosis are increasingly reported. Therefore, we describe the relative risk of mortality among severe influenza patients with aspergillosis and other coinfections compared to severe influenza patients without *Aspergillus* coinfections.
Methods: We retrospectively reviewed 124 adult patients with severe influenza in a tertiary medical center in southern Taiwan from January 2015 through March 2016. The definition of probable aspergillosis required abnormal radiological findings and positive *Aspergillus* galactomannan (GM) antigen and/or *Aspergillus* isolation.
Results: Probable aspergillosis (detected throughout the whole course) and other coinfections (only community-acquired) were diagnosed in 21 (17%) and 38 (31%) of all patients respectively. *Klebsiella pneumoniae* (36.8%), *Pseudomonas aeruginosa* (31.6%) and *Staphylococcus aureus* (31.6%) were the most frequent isolates of other coinfections. In-ICU mortality of *Aspergillus* group (66.7%) was significantly higher than other coinfections (23.7%, $p = 0.001$) or control group without coinfections (15.4%, $p < 0.001$), with significant odds ratios after adjusting for important variables. The factor of GM index $\geq$0.6 had a 19.82 (95% CI, 4.91 to 80.07, $p < 0.0001$) odds of expiring in an ICU among the *Aspergillus* group.

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: Dual *Aspergillus* and influenza infection is emerging in southern Taiwan. Meanwhile, community-acquired *P. aeruginosa* should be listed in the common copathogens with severe influenza. The 67% mortality linked to aspergillosis highlights the need for physicians to focus attention on patients with GM $\geq$ 0.6.

Introduction

Severe influenza infections are usually defined as cases requiring medical intensive care unit (ICU) admission. Invasive pulmonary aspergillosis (IPA) may occur in the setting of severe influenza even among immunocompetent hosts.[1,2] Such cases of a dual influenza and IPA coinfection have increasingly been reported since 2010. Among them, 65% of cases lacked classic immunosuppressive conditions at diagnosis,[1] which is essentially required as host factors (neutropenia, hematologic cancer and stem cell or bone marrow transplantation) 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.[3] Therefore, there is a need for newly revised diagnostic criteria of IPA, especially for severe influenza patients without host criteria of immunosuppression, or directly regarding severe influenza as a status of immunosuppression to fulfill the revised host criteria of EORTC/MSG for diagnosing "probable" IPA in the absence of histological confirmation.

According to EORTC/MSG criteria, the diagnosis of probable IPA requires a host factor, a typical radiological feature, and a mycological criterion like either *Aspergillus* culture or galactomannan (GM) antigen detected in serum or bronchoalveolar (BAL) fluid. Possible IPA indicates presence of host factors and clinical features but in the absence of or negative mycological criteria.[3] The second issue frequently raised for difficulty in diagnosis of IPA for the critically ill patients in ICU would be non-specific consolidation in mechanically ventilated patients and lack of radiological features of EORTC/MSG criteria in chest-computed tomographic (CT) findings. Therefore, for critically ill patients in ICU, a diagnostic algorithm was proposed for "IPA", which was less strict than EORTC/MSG criteria in a Belgium study.[4] For example, abnormal but non-specific chest X-ray imaging could be a radiological criteria and steroid treatment with a prednisone equivalent of >20 mg/d could be a host factor; whereas EORTC/MSG criteria require typical CT imaging and prolonged use of steroids with a prednisone equivalent of >0.3 mg/kg/d for >3 week respectively.[3,4] According to the ICU algorithm, the typical findings of cavity, halo sign or an air-crescent sign occurred in only 5% of critically ill patients with "IPA" (17 definite, 68 probable).[4]

In a prospective, multicenter cohort research of 220 patients hospitalized with severe presentation of pandemic (H1N1)v influenza A infection in the ICUs from the European Society of Intensive Care Medicine (ESICM) H1N1 registry before 11 February 2010,[5] hospital-acquired pneumonia (HAP) was clinically suspected in 79 patients (35.9%). Among them, *Aspergillus* spp. was the 5th top common pathogen and accounted for 4 (8.7%) of the 46 microbiologically documented patients. However, the study did not define IPA by the EORTC/MSG criteria. In the study, patients who received early corticosteroid therapy had HAP more frequently than patients who did not (26.2% versus 13.8%, $p < 0.05$). Adjusted Cox regression analysis identified that early use of corticosteroids was not significantly associated with mortality, but was still associated with an increased rate of HAP.[4]

Later, a large prospective, observational study was conducted from 2009 to 2015 in a large cohort of ICUs patients with influenza in Spain.[6] Community-acquired respiratory coinfection was defined as diagnosis within first 2 days of hospital admission. A total of 2901 ICU patients with influenza were enrolled. Overall, coinfection was diagnosed in 482 (16.6%) of patients. *Aspergillus* spp. was the 4th top common pathogen, accounting for 35 (7.3%) of patients with the community-acquired coinfection, comprising 2 definitive IPA, 25 probable IPA and 8 possible IPA, by applying "modified" EORTC/MSG criteria. In addition, *Aspergillus* spp. was an independent risk factor for ICU mortality ($p = 0.001$).[6] The study might highlight an important role of diagnosing IPA coinfection earlier in the course within 2 days among critically ill influenza patients.

With regard to the prevalence of IPA among the influenza patients in the ICUs, community-acquired and nosocomial IPA accounted for 1.2% (35/2901) and 1.8% (4/220) respectively.[5,6] In Belgium, Wauters and colleagues reported 9 (23%) IPA in 40 critically ill H1N1 patients, including 5 patients with proven disease and 4 ''probable'' infections, based on ''modified" EORTC criteria with broader definitions of risk factors.[7] For example, they enrolled Child C cirrhosis, human immunodeficiency virus (HIV) infection, cancer on therapy within recent 3 months and relatively shorter courses of steroid use as host factors.[8] In France, Guervilly and colleagues reported 5 (29.4%) patients with proven or probable IPA in a prospective cohort study of 17 H1N1 patients, based on the EORTC/MSG criteria. The mycological evidence included fungal culture and a novel diagnostic strategy of serum galactomannan and PCR for *Aspergillus* sp.[9] Therefore, the prevalence of IPA in critically ill influenza patients appears to be 15 times higher by applying broader definitions of host factors and/or mycological criteria.

In Taiwan, cases of IPA in association with severe influenza have been increasingly reported.[10–15] Yet, the relative risk of mortality associated with IPA in the influenza patients has