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Influenza Coinfection: Be(a)ware of Invasive Aspergillosis

To the Editor—Uyeki et al [1] recently published the 2018 update of the clinical practice guideline regarding the diagnosis, chemoprophylaxis, and institutional outbreak management of seasonal influenza. The document discusses several aspects related to influenza, including the occurrence and management of coinfections. Although the guideline is primarily aimed to guide US clinicians, the recommendations are implemented in many countries worldwide. We therefore draw attention to recent observations regarding invasive aspergillosis as coinfection in patients with severe influenza in some regions [2]. Although the guideline states that invasive fungal coinfection is rare in adults with influenza, 3 cohort studies performed in Belgium and the Netherlands showed that influenza-associated aspergillosis (IAA) had occurred in 16%–23% of influenza patients in the intensive care unit (ICU) [3–5]. The largest cohort study investigated 7 ICUs over a period of 7 flu seasons and showed that influenza and the use of corticosteroids before ICU admission were independent risk factors for IAA [5]. IAA was observed in every flu season and both in patients with influenza A and influenza B pneumonia [5]. The mortality of severe influenza patients with IAA was 51% compared with 28% in those without IAA [5]. Furthermore, IAA coinfection occurred in patients with a broad variety of underlying conditions, and up to 30% of patients had been previously healthy [4, 5].

Influenza virus has been shown to cause ulceration of the tracheobronchial epithelium, thus providing an opportunity for *Aspergillus* to cause invasive infection [6]. Indeed, up to 25% of patients with IAA present with *Aspergillus* tracheobronchitis, a manifestation of invasive aspergillosis where the infection is primarily confined to the tracheobronchial tree. Invasive *Aspergillus* tracheobronchitis is difficult to diagnose as the main radiologic feature is tracheal and bronchial thickening, and therefore visualization of epithelial plaques through bronchoscopy is the recommended diagnostic procedure [7].

The frequency of IAA may vary between geographic regions, but IAA cases have been reported in at least 16 countries, including the United States [8, 9]. Furthermore, the epidemiology of IAA may be underestimated due to cases remaining undiagnosed since respiratory deterioration is considered to be caused by bacterial coinfection rather than fungal infection and appropriate diagnostics are not performed. International surveys are needed to investigate diagnostic procedures commonly used in influenza patients with suspected coinfection and to determine the frequency of IAA. However, at this point, guidelines, such as the one published by Uyeki et al, should include the aforementioned observations to overcome lack of awareness of coinfection with *Aspergillus* in ICU patients with influenza.

Given the high mortality of IAA it is recommended to consider IAA as a possible cause of coinfection in adult patients with severe influenza irrespective of their underlying condition and to perform a diagnostic workup for invasive aspergillosis, including bronchoscopy and bronchoalveolar lavage (BAL) [10]. Microbiological analysis should include microscopy, fungal culture, and galactomannan testing of BAL and serum if BAL is not available. If any of these tests indicate the presence of *Aspergillus*, immediate antifungal therapy is indicated. This approach will help to diagnose and treat patients with IAA early and to determine the true epidemiology of this coinfection.

Notes

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Reply to Verweij et al

To the Editor—We agree with Verweij et al [1] that invasive pulmonary aspergillosis (IPA) is a complication reported in severely ill influenza patients and that clinicians caring for influenza patients, particularly immunocompromised persons, should be aware of the potential for IPA. The Infectious Diseases Society of America's influenza guidelines listed fungal coinfection as a complication in Table 3 [2]. The guidelines included studies published through January 2018 [2], so we were unable to include recent reports of IPA in intensive care unit (ICU) patients in the Netherlands and Belgium [3].

To date, IPA does not appear to be a common influenza complication in North America, the target audience for the guidelines. IPA might be underdetected in regions where it has not been studied as intensively as in the Netherlands and Belgium [3]. We are unaware of prospective population-based surveillance data for influenza-associated IPA in North America. Nevertheless, the population at highest risk for IPA and most likely to undergo appropriate fungal studies are hematopoietic stem cell transplant (HSCT) and solid organ transplant recipients, particularly lung transplant recipients. However, in a prospective 5-year cohort of 616 HSCT recipients with influenza in the United States, Canada, and Spain, only 2 patients (0.3%) had cultured-confirmed IPA, and neither were hospitalized [4]. Data on serum or bronchoalveolar lavage (BAL) galactomannan testing were not collected, but it is unlikely that many IPA cases were missed as patients were monitored for 28 days for evidence of complications [4]. Furthermore, a prospective 5-year surveillance study of 437 HSCT recipients in Seattle, Washington, reported that respiratory syncytial virus and adenovirus upper respiratory tract infections, but not influenza A virus, and detection of any respiratory virus in BAL fluid, were significantly associated with IPA [5].

Although data are incomplete, there appears to be substantial geographic variation in the frequency of IPA identified in critically ill influenza patients. Many of the Dutch and Belgian patients were diagnosed with IPA soon after ICU admission, suggesting that they may have become colonized with *Aspergillus* in the community [3]. One possibility is that the high frequency of IPA reported in the Netherlands and Belgium [3] reflects greater environmental exposure to *Aspergillus*. Corticosteroids also appear to be a potential risk factor for possible or probable IPA (corticosteroid use in 56% with IPA vs 29% without [$P < .001$]) [3]; this association was also reported in another study [6]. Because evidence shows that corticosteroid use likely increases mortality in influenza patients, these data further support recommendations to avoid corticosteroids for treatment of influenza [2].

Clinicians should be cognizant of the risk of IPA in critically ill patients, particularly immunocompromised patients or those receiving corticosteroids. Except where IPA prevalence is reported to be high, we disagree with Verweij et al that diagnostic evaluation for IPA, including bronchoscopy and BAL, should be routinely performed regardless of underlying condition in adult patients with severe influenza [1]. The sensitivity and specificity of galactomannan testing outside of HSCT recipients is unknown and results should be interpreted with caution [7]. Rather, studies to understand the incidence, risk factors, and clinical features of IPA in influenza patients are needed worldwide.

Notes

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Timothy M. Uyeki,[1] Michael G. Ison,[2] Cameron R. Wolfe,[3] and Andrew T. Pavia[4]; on behalf of the Infectious Diseases Society of America Panel on Clinical Practice Guidelines: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza

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