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.

**References**

1. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. Clin Infect Dis 2019; 68:895–902.

2. Lamoth F, Calandra T. Let’s add invasive aspergillosis to the list of influenza complications. Lancet Respir Med 2018; 6:733–5.

3. Wauters J, Baar I, Meersman P, et al. Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study. Intensive Care Med 2012; 38:1761–8.

4. van de Veerdonk FL, Kolwijck E, Lestrade PP, et al. Influenza-associated aspergillosis in critically ill patients. Am J Respir Crit Care Med 2017; 196:524–7.

5. Schauwheleghe AFAD, Rijnders BIA, Philips N, et al. Dutch-Belgian Mycosis Study Group. Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study. Lancet Respir Med 2018; 6:742–92.

6. Gill JR, Sheng ZM, Ely SF, et al. Pulmonary pathologic findings of fatal 2009 pandemic influenza A/H1N1 viral infections. Arch Pathol Lab Med 2010; 134:235–43.

7. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 2016; 63:e1–60.
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 culture-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

Disclaimer. The views expressed are those of the authors and do not necessarily reflect the official position of the Centers for Disease Control and Prevention.

Potential conflicts of interest. M. G. I. reports grants from AiCuris, Chimerix, and Gilead and personal fees from Celltrion, Shionogi, and VirBio during the conduct of the study. M. G. I. also reports grants from AlCuris, Chimerix, and Gilead and personal fees from Viracor Eurofins outside the submitted work. A. T. P. reports grants from BioFire Diagnostics, royalties from Antimicrobial Therapy Inc as associate editor of Sanford Guide, personal fees from WebMD for the preparation of educational materials, and personal fees as a consultant for Genentech, outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Timothy M. Uyeki,1 Michael G. Isom,2 Cameron R. Wolfe,3,4 and Andrew T. Pavl1, 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

1Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; 2Divisions of Infectious Diseases and Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, Illinois; 3Division of Infectious Diseases, Duke University Medical Center, Durham, North Carolina; and 4Division of Pediatric Infections Diseases, University of Utah, Salt Lake City

References

1. Verweij PE, Bruggemann JM, Wauters J, Ruijnders BJA, Chiller T, van de Veerdonk F,