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Overtreating or underdiagnosing invasive pulmonary aspergillosis (IPA) in critically ill H1N1 patients: who is right?

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Bacterial co-infection has been found in $\approx 25\%$ of all influenza-related deaths [1, 2]. However, information regarding the impact of bacterial co-infection in critically ill H1N1 patients shows conflicting results. Based on previous reports [3, 4], the presence of bacterial co-infection was not associated with increased mortality rates, but was an independent risk factor for severe presentation [5] and showed higher morbidity defined by longer ICU stay. In the pre-antibiotic era, during the 1918–1919 pandemic, the bacteria most often recovered from the sputum, lungs, and blood of pneumonia patients, alive or dead, were common colonizers of the upper respiratory tracts of healthy persons, i.e., *H. influenzae*, *S. pneumoniae*, *S. pyogenes*, and *S. aureus* [6]. In this issue of *Intensive Care Medicine*, Wauters and colleagues [7] present a retrospective analysis of a cohort of 40 adult patients with confirmed H1N1 infection admitted to the ICUs of two tertiary care hospitals. The major finding was that almost 25 % of the patients developed invasive pulmonary aspergillosis (IPA); all of them received corticosteroids (CS) either before or during ICU admission.

Invasive pulmonary aspergillosis represents a dreaded complication in critically ill patients with high mortality rates. Whereas IPA is typically manifested in the immunocompromised host, the epidemiology of IPA in the ICU may be shifting away from those classically considered at risk. The diagnosis of definitive IPA requires histopathologic confirmation; the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group (EORTC) and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (MSG) published standard definitions for invasive fungal infections for clinical and epidemiological research [8]. Nevertheless, the EORTC/MSG criteria represent a challenge as the clinical manifestations are not specific, and a histological diagnosis is often unfeasible. Some points should be taken into account. Diagnostic criteria such as a “probable IPA” diagnosis based on bronchoalveolar lavage with *Aspergillus*-positive cultures or galactomannan antigen criteria may not be appropriate in immunocompetent patients because of low sensitivity and may contribute to some patients perhaps being over-treated. Interestingly, in the Wauters study [7], where the IPA diagnosis was based on the EORTC/MSG criteria, all the patients (probable or proven) received CS, and half of them (probable) had traditional risk factors for IPA, but the ICU mortality for IPA versus non-IPA patients was similar (33 vs. 29 %, p 0.8). Based on the previous controversial points, Blot and colleagues developed an alternative clinical algorithm for the EORTC/MSG criteria [9] that attempted to discriminate *Aspergillus* colonization from IPA in critically ill patients. From a multicenter cohort of 524 patients with *Aspergillus*-positive endotracheal aspirate cultures, the authors studied 22 % of the patients with histopathologic data. The proposed algorithm had a fairly good sensitivity and negative predictive value that may better identify IPA. Based on this algorithm, some patients with *Aspergillus*-positive respiratory findings from the study published by Wauters and

colleagues might represent colonization, and preemptive or prophylactic therapy would not be appropriate. Whereas the cited algorithm seems to be feasible, it needs to be prospectively evaluated in immunocompetent and/or H1N1 critically ill patients.

Risk factors for IPA include prolonged and severe neutropenia, hematopoietic stem cell and solid organ transplantation, human immunodeficiency virus (HIV), and chronic granulomatous disease, among others [10]. Natural immunity plays a major role in the defense against IPA by recognition and clearance of the organism in immunocompetent hosts. In addition, studies of cell-mediated T cell immunity in humans are lacking, and only conducted in HIV-infected patients in whom dysfunctional CD4 T-cell lymphocytes are well known [11]. The immune response associated with severe viral infections is still unclear. Critically ill H1N1 patients may

have an impaired immune response, characterized by a slower control of viral load and the presence of immunodysregulation in those with severe presentation, leading to an unremitting cycle of viral replication and innate cytokine-chemokine release [12]. With the additive effect of a potent anti-inflammatory drug such as CS to critically ill H1N1 patients, several groups have reported the presence of IPA in low rates (<2 %) [3, 13].

In summary, the use of CS in H1N1 critically ill patients may increase the risk of super infections, such as IPA. The high mortality/morbidity of IPA, combined with suboptimal diagnostic tools, has driven the overuse of antifungal drugs. It is imperative to define effective antifungal stewardship tactics based on validated diagnostic and clinical treatment algorithms. Therefore, the true burden of IPA in critically ill H1N1 patients is still unknown. Overtreating or underdiagnosing: who is right?

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