

CORRESPONDENCE



Critical influenza and prophylactic antifungal therapy for aspergillosis: a nuanced approach to a pertinent infectious disease

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We thank Coste et al. for their interest [1] in our open-label randomised pilot trial on antifungal prophylaxis in critically ill influenza patients, recently published in Intensive Care Medicine [2].

Coste and colleagues question the modified AspICU case definition used in our study. The original AspICU algorithm published by Blot et al. [3] was aimed to distinguish between *Aspergillus* colonization and invasive pulmonary aspergillosis (IPA) in patients admitted to the intensive care unit (ICU). A drawback of the algorithm was the dependency on *Aspergillus* culture, which lacks sensitivity. As there is good autopsy-controlled evidence to support bronchoalveolar lavage galactomannan (BAL GM) as a diagnostic criterion [4], BAL GM is generally accepted for IPA classification in the ICU. Moreover, influenza-associated pulmonary aspergillosis (IAPA) diagnosis based on modified AspICU criteria was independently associated with 90-day mortality in a cohort of 432 critically ill influenza patients, confirming the clinical validity of these diagnostic criteria [5]. The ICM2020 expert panel (including Blot) diagnostic criteria also rely on BAL GM as important criterion to classify IAPA patients [6].

Coste and colleagues state that the number of IAPA cases may have been overestimated due to classifying colonized patients as invasive cases. Of the 21 patients classified as IAPA, 13 had more than one mycological test (culture, GM, PCR) positive [2]. Of the remaining eight patients with a single positive test, one case

was proven and two had evidence for invasive *Aspergillus* tracheobronchitis. Thus in >75% of patients multiple markers supported IAPA diagnosis. In contrast, 10 of 21 (48%) IAPA cases were culture positive, which would have underestimated the number of IAPA cases. We only identified one case of *Aspergillus* colonization in our cohort, based on a single positive upper respiratory tract culture. The clear discrepancy in mortality rates between our IAPA and non-IAPA critically ill patients (57% vs 18%, $p = 0.0013$) stands in sheer contrast with the comparable baseline characteristics and APACHE II score upon ICU admission [2] and supports the validity of GM-based IPA diagnosis.

Finally, Coste and colleagues suggest that we state that prompt empirical antifungal therapy should be started at ICU admission whereas they conclude that in regions with low IAPA prevalence prophylaxis should not be used. This indiscriminate statement was not made by the authors. We do propose a differentiated approach which includes prompt mycological work-up (including BAL GM) in influenza patients admitted to the ICU, and antifungal prophylaxis to prevent late IAPA as the prevalence of late IAPA was still 11% [2]. As indicated in our study, the extent of the initial diagnostic work-up depends on a safety evaluation performed by the treating physician, and any benefit of the proposed differentiated strategy requires further study. Of course, any strategic approach will depend on the local incidence of IAPA and, in case of very low IAPA incidence (<5%), high awareness with watchful waiting might be the preferred strategy.

Our study underscores that IAPA is a pertinent and dire infectious disease in the ICU that requires differentiated strategic responses depending on prompt mycological diagnostic evaluation at ICU admission.

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Declarations

Conflicts of interest

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