Acute hypoxaemic respiratory failure in immunocompromised patients: abandon bronchoscopy or make it better?

To the Editor:

Acute hypoxemic respiratory failure (AHRF) in immunocompromised patients is a challenging clinical problem associated with mortality rates of 40–60% in children and adults [1, 2]. Thus, we read with great interest the results of a pre-planned secondary analysis of a large multicentre observational cohort of 1611 immunocompromised adults with AHRF, as reported by Bauer *et al.* [3]. The authors described the diagnostic yield and outcomes of fibreoptic bronchoscopy (FOB) in this group of vulnerable patients with the *a priori* hypothesis that "bronchoscopy, with limited complications, would reduce the number of unidentified causes of respiratory failure and be associated with reduced hospital mortality." After a rigorous analysis of a highly annotated dataset, the authors conclude that "bronchoscopy was associated with improved diagnosis and changes in management but also increased hospital mortality."

We commend the authors for undertaking such a study, which attempts to answer an age-old question regarding the benefits and harms of bronchoscopy in patients with acute respiratory failure. While the results did not confirm the *a priori* hypothesis, we caution clinicians inclined to take the results as evidence to not perform bronchoscopy in clinically appropriate situations, given the inherent limitations of the study design. Since FOB was not randomised, a selection bias exists for the intervention group. To account for this bias, the authors identified 14 confounding factors measured at the time of intensive care unit (ICU) admission that were both associated with mortality and varied significantly in incidence between the noninvasive testing and FOB groups. Not surprisingly, patients who underwent FOB were at higher risk for both acquiring severe infections and for suffering poor outcomes from undiagnosed infection, factors that likely played into physicians' decision to perform FOB. After propensity score matching using these 14 confounders, patients who received FOB still showed significantly greater hospital mortality than their matched counterparts who underwent noninvasive testing alone.

Several scenarios could explain the finding of the propensity-adjusted analysis. The possibility exists that FOB precipitated events leading to death in an already tenuous clinical situation. While respiratory worsening was associated with 11% of FOB, it remains unclear whether FOB can actually be implicated as the cause for respiratory worsening, given that many patients were likely progressing in their disease course concurrently. On the other hand, the apparent discrepancy in mortality despite accounting for day 1 confounders could be driven by the subset of patients who underwent bronchoscopy later in the ICU course at a point when empiric therapies had failed and illness severity had increased from the baseline Sequential Organ Failure Assessment score and arterial oxygen tension/inspiratory oxygen fraction ratio. The clinical decision to perform bronchoscopy is complex and guided by many factors, including the trajectory of the patient's condition. The authors acknowledge they were unable to account for the time-varying nature of the intervention (FOB) as well as time-varying covariates, namely the severity of illness at the time of the non-randomised intervention, which are likely the most significant confounders not accounted for by propensity score matching (figure 1). The timing of FOB with respect to both the onset of AHRF and the initiation of empirical therapies plays a significant role in microbiological yield [4]; whether patients who underwent early FOB had better outcomes than those who underwent later FOB could not be assessed in this study. As such, future studies that detail both the timing of FOB with respect to illness onset, as well as the illness severity at the time of FOB, are needed before concluding that FOB is harmful to immunocompromised patients with AHRF.

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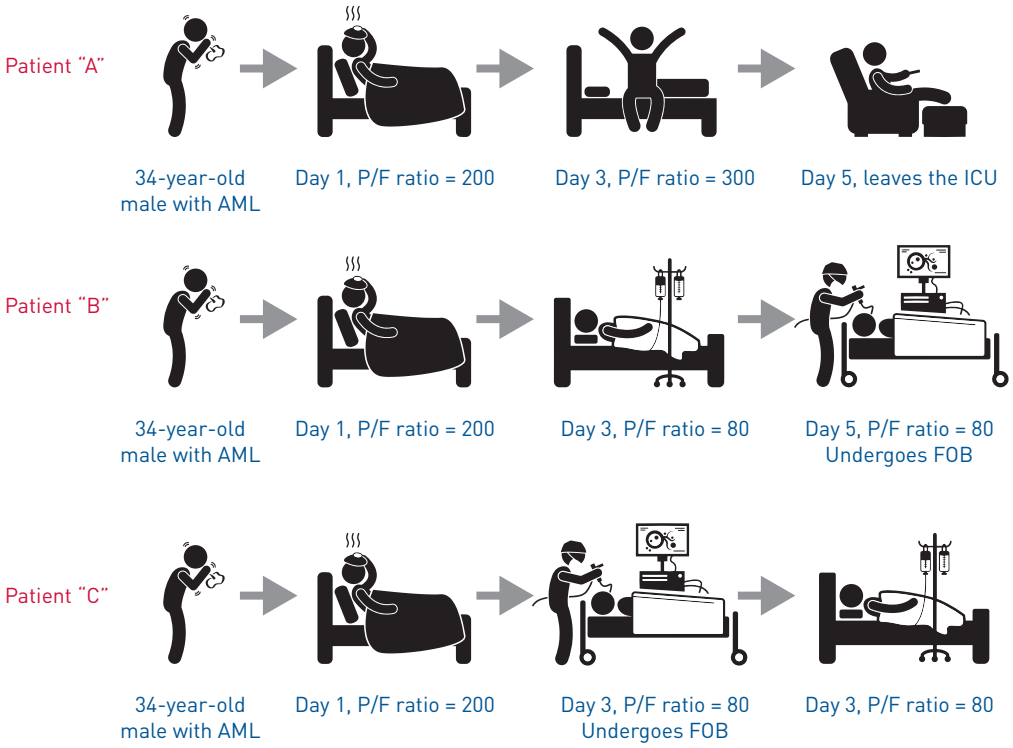

FIGURE 1 Time-variant interventions and covariates in acute hypoxemic respiratory failure. This hypothetical vignette compares three patients with identical disease characteristics, identical illness severity on intensive care unit day 1, and hence identical propensity scores for mortality risk. Patient A *versus* patient B: illness severity is a time-varying covariate. Over time, patient "A" improves and does not undergo fibreoptic bronchoscopy (FOB), whereas patient "B" worsens clinically and undergoes FOB. While the patients are matched based on day 1 illness severity, they are not matched based on illness severity at the time that patient "A" undergoes FOB. The impact of illness severity at the time of FOB could not be assessed in this study and remains an area of future investigation. Patient B *versus* patient C: bronchoscopy is a time-varying intervention. Patient "B" undergoes FOB later in the illness course whereas patient "C" undergoes FOB earlier. The impact of the timing of FOB on the outcome of mortality could not be assessed in this study and remains an area of future investigation. P/F ratio: arterial oxygen tension/inspiratory oxygen fraction ratio. AML: acute myeloid leukaemia. Images used with license.

The mortality endpoint, with the above caveats, should not overshadow the important finding regarding the utility of bronchoscopy. When noninvasive testing does not yield an AHRF aetiology, FOB is the best next option for pursuing a specific diagnosis, as surgical lung biopsy is even more invasive and empiric therapy is potentially harmful. In this study, the overall diagnostic yield of FOB was 49%; FOB resulted in addition of a new treatment in 12% and antimicrobial cessation in 26%, for an overall therapeutic yield of 38%. Hence, rather than be dissuaded by these results to perform bronchoscopy in immunocompromised patients with AHRF, we advocate for utilising FOB specifically in cases where identifying or refuting a specific diagnosis will aid in the patient's clinical management.

Taking the long view, additional work is needed to improve the clinical utility of FOB. We and others have demonstrated that novel genomic sequencing techniques can identify infectious culprits in half of previously negative respiratory samples and elucidate microbiome composition in immunocompromised patients [5, 6]. In addition, a significant opportunity exists to interrogate and integrate components of human biology into FOB-based tests. Ongoing work incorporating human gene expression and protein biomarkers may significantly increase the utility of FOB [7]. Further, the ability for FOB to impact management decisions depends on the development of novel targeted treatments for AHRF in immunocompromised patients [8], and the development of such pathobiology-targeted treatments depends on tissue-level biologic data accessible only by FOB [9].

In sum, we propose that the future studies assessing clinical outcomes of patients who undergo FOB should consider the timing of FOB with respect to ICU admission and should consider potential changes in illness severity between ICU admission and the time of FOB. We hope that this study by Bauer *et al.* [3] will stimulate the respiratory and intensive care community to work towards improving both our approach

to the utilisation of FOB as well as the development of novel FOB-based diagnostic tests in order to better diagnose, understand, and treat AHRF in this high-risk population.

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From the authors:

In their letter to the Editor, M.S. Zinter and G-S. Cheng raise concerns about the conclusion of our study that immunocompromised patients with acute hypoxaemic respiratory failure who undergo fibreoptic bronchoscopy have inferior survival relative to those who do not undergo fibreoptic bronchoscopy. They offer an alternative explanation to our findings by emphasising the role of the time-varying nature of the bronchoscopy as well as the time-varying nature of other covariates, including illness severity leading up to bronchoscopy, when performing the propensity score matching.

We showed that bronchoscopy, as an invasive testing for establishing the initial diagnosis of acute hypoxaemic respiratory failure in immunosuppressed patients, was associated with improved diagnosis and changes in management but also increased hospital mortality [1]. We concluded that the indication of bronchoscopy should be considered in terms of pre- and post-test probability while balancing risk and benefit in individualised cases. In other terms, a diagnostic bronchoscopy should have a specific indication,

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an assessment for potential risks and likelihood of impacting treatment. It should not be performed simply after empirical therapy has failed.

In the intensive care unit (ICU), the decision-making process depends on multiple factors, such as patient's characteristics, severity and trajectory of the disease, values and preferences, as well as clinician assessment, expertise and experience [2]. Severity may actually influence the decision both ways, to do or not to do bronchoscopy, that is, the patient is not sick enough or is too sick to proceed. Therefore, the timing of bronchoscopy is more a reflection of the complexity of the decision-making process, especially in an observational study [3]. In that setting, the propensity score allowed us to incorporate those potentially time-varying confounders measured at the time of bronchoscopy, as if a randomised trial has been conducted where patient's allocation would have been stratified by severity. The decision to perform a bronchoscopy may actually reflect the inability to achieve a diagnosis otherwise. In a randomised controlled trial comparing early *versus* delayed bronchoscopy (*i.e.* after 3 days), bronchoscopy itself did not influence the outcome whereas the lack of diagnosis did [4]. In our study, there were more bronchoscopy procedures performed prior to ICU admission among those who also underwent bronchoscopy in ICU, but this factor itself did not influence outcome, meaning that repeat bronchoscopy is usually not helpful. This justifies the development of new diagnostic tools for use with or without bronchoscopy. Moreover, those in the bronchoscopy group had delayed ICU admission, were more severely ill, and underwent more testing that was more often negative. Delayed ICU admission for cancer patients with acute respiratory failure is associated with worse outcome [5]. The more uncertain a diagnosis is the more testing is usually performed, which may be detrimental. Clinicians tend to overestimate the benefit and underestimate the risk of testing [6]. We did not intend to study, and therefore did not match for, bronchoscopy delay effects [7]. Actually, if bronchoscopy had such efficacy with limited side-effects, one could think that early bronchoscopy would be associated with a better outcome than delayed bronchoscopy or no bronchoscopy which we did not find. All that the bronchoscopy achieved was to reduce the gap between those with no diagnosis, suggesting that the sooner the diagnosis is made, by whatever means, the better the outcome. Therefore, the timing of bronchoscopy may only be relevant when performed early and when the diagnosis is not already achieved by noninvasive testing.

In the figure provided by M.S. Zinter and G-S. Cheng, one can assume that patient A had a rapidly confirmed diagnosis and did not need a bronchoscopy. It would be very exceptional in our practice to perform an initial diagnostic bronchoscopy on day 3, like in patient B, at a time where hospital acquired complications begin to occur, or even more unusual on day 5, like in patient C, when the patient is now critically ill with a arterial oxygen tension/inspiratory oxygen fraction (P/F) ratio of 80. We would not wait until such a degree of severe hypoxaemia was reached before performing a bronchoscopy to apprehend the initial cause of acute hypoxaemic respiratory failure, such as in the case of suspected *Pneumocystis jirovecii* pneumonia, with still minimum oxygen requirement, in a patient unable to provide reliable induced sputum, where time from onset of symptoms to diagnosis is associated with worse outcome [8]. Moreover, P/F ratio can be falsely decreased (*e.g.* in case of hyperleukocytosis with leukostasis) and does not always reflect severity. If anything, this cartoon illustrates what we would not want to recommend: wait until a patient is too sick to perform appropriate testing. This is exactly what we intended to demonstrate in our paper. If one believes that bronchoscopy maybe useful, one should do it right away, otherwise it may not be useful and may even be harmful, and it certainly should not be repeated if the first one was negative, unless new clues are revealed.

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