Reply to Aberegg and Wolfe

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Reply to Aberegg and Wolfe

From the Authors:

In their letter, Aberegg and Wolfe highlight the effect of disease prevalence on the performance of diagnostic tests with reference to our publication in which we provided estimates of the prevalence of aspergillosis in critically ill adults with suspected ventilator-associated pneumonia (VAP) (1). We thank them for their interest in this understudied topic and for articulating the uncertainty that is implicit in prevalence estimates when no perfect method for disease classification is available. They express understandable concern that overestimating the burden of aspergillosis in this population could lead to an epidemic of overdiagnosis and treatment.

In our publication, we emphasized the uncertainty in our prevalence estimate that arises from the definition of aspergillosis that we used; this definition balances the risks of underdiagnosis and overdiagnosis, as we set out (1). To express this uncertainty, we considered the 95% confidence limits in our main analysis, the effect of using higher thresholds for classifying BAL fluid (BALF) galactomannan (GM) as positive, and corroboration of BALF GM with serum GM as well as other *Aspergillus* biomarkers in both BALF and serum. Aberegg and Wolfe contend that the prevalence of this disease may be substantially lower, based on the posterior probability of aspergillosis with a positive BALF GM, in a low-prevalence population. This is certainly possible, though is not readily incorporated in our estimate because neither the diagnostic accuracy of BALF GM nor true disease prevalence in nonneutropenic patients with suspected VAP is established. They illustrate the point using an assumed disease prevalence of 1%, but this is not a robust prevalence assumption. It is correct that the majority of positive BALF GM results would be falsely positive if the disease prevalence is only 1%; by comparison, the majority would be true positives if the prevalence is greater than 8%, based on a test specificity of 95% (2).

There is no doubt that the prevalence of aspergillosis in the population we describe remains uncertain and we do not purport to have definitively established this. The dependency of prevalence estimates on the accuracy of diagnostic tests used, and vice versa, creates a circular argument that cannot be readily resolved. We acknowledge the superior specificity offered by a tissue diagnosis, which could reduce the uncertainty; however, our experience is that obtaining such material is challenging in both research and clinical practice. This, in itself, increases the risk of sampling bias, leading to error if histology is used as the basis for prevalence measurement.

We certainly do not wish for our publication to drive an epidemic of overdiagnosis. In support of this, our manuscript concluded that use of GM testing on BALF in patients with suspected VAP could highlight those for whom more extensive clinical investigation is warranted. Although overtreatment is not desirable, we are also concerned that the common assumption that aspergillosis is so infrequent as not to justify investigation in this patient group risks underdiagnosis and underdiagnosis. There is a difficult balance to be struck in the face of uncertainty relating to both the prevalence of aspergillosis and diagnostic test accuracy in the nonneutropenic critically ill population. Well-designed prospective studies to address this would certainly be of high value; however, other efforts to reduce uncertainty—even if imperfect—may help to guide clinical practice. ■

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Retraction: Isoniazid and Rifapentine Treatment Eradicates Persistent *Mycobacterium tuberculosis* in Macaques

The authors of the article (1), published in the February 15, 2020, issue of the *Journal*, have discovered that infection and 3HP treatment of a cohort of the animals did not conform to the stated experimental protocol. Since analysis of the other cohort of animals that did not experience protocol deviation generated similar results, the conclusions of the article may be correct. However, the authors believe that retraction is appropriate because of the differences in performance of the study, and because the published article does not accurately reflect how all of the animals were infected and treated with 3HP. ■

Reference

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Erratum: Home Oxygen Therapy for Adults with Chronic Lung Disease. An Official American Thoracic Society Clinical Practice Guideline

There are typographical errors in the quality of evidence for Question 3 (Should ambulatory oxygen be prescribed for adults with COPD who have severe exertional room air hypoxemia?) in the ATS clinical practice guideline published in the November 15, 2020, issue of the *Journal* (1). The guideline panel's recommendation for Question 3 is, however, unchanged: "*In adults with COPD who have severe exertional room air hypoxemia, we suggest prescribing ambulatory oxygen.*" For the Question 3 recommendation, the panel made the suggestion that ambulatory oxygen be prescribed for adults with COPD who have severe exertional room air hypoxemia as a conditional recommendation based on low-quality evidence. The panel had downgraded the evidence to "low" on the basis of both imprecision and indirectness. However, the quality of evidence for this recommendation was inadvertently misstated as "moderate" instead of "low" in certain places in both the main document and the Executive Summary.

In the main document, the third recommendation in the abstract on page e121 should be corrected to read "conditional recommendations for ambulatory oxygen use in patients with COPD (**low**-quality evidence)." The third bullet point of the Summary of Recommendations on page e122, as well as the third column in Question 3 in Table 4, page e126, should be corrected to "**low**-quality evidence." In addition, on page e130, Panel judgments, the wording should be corrected to "**low** GRADE evidence."

In the Executive Summary, the third recommendation in the abstract on page 1345, the third bullet point of the Summary of Recommendations on page 1346, and the third column in Question 3 in Table 4, page 1350, should be corrected as indicated above. In the Question 3 Conclusions, page 1351, the wording should be corrected to read "(**low** Grading of Recommendations Assessment, Development and Evaluation evidence)."

These changes are reflected in detail in the various GRADE domains in the online supplement that have now been updated to reflect serious concerns regarding imprecision and indirectness (almost all studies are crossover trials, and most report effects of oxygen during laboratory tests, not daily life). As such, on page E59, the Certainty of Evidence should be downgraded from "moderate" to "low" for the St. George's Respiratory Questionnaire (SGRQ) and the Short-Form

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