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Aspergillosis in the ICU: Hidden Enemy or Bogeyman?

To the Editor:

Loughlin and colleagues (1) report on the important possibility of pulmonary aspergillosis in patients with suspected ventilator-associated pneumonia. Aspergillosis is increasingly reported as a potential pathogen in nonimmunocompromised ICU patients, as the authors and editorialist point out (1–4). However, many of these reports have unavoidable but significant methodological limitations that make their conclusions provisory, and the current report is no exception. The authors purport to establish the estimated prevalence of *Aspergillus* infection in nonimmunocompromised ICU patients with ventilator-associated pneumonia, using a combination of tests with imperfect specificity for pathologic disease (microscopy, culture, galactomannan assays, etc.). The test most commonly leading to "probable diagnosis" was the BAL fluid galactomannan assay (BALF GM). The authors claim that the specificity of the BALF GM assay is on the order of 95–100% citing two studies showing some of the highest specificities reported (5, 6); other studies report more modest specificities within a range of confidence limits (7, 8). All studies of BALF GM have a tendency to overstate specificity because they do not require a gold standard for true disease classification, instead lumping proven, probable, and possible invasive aspergillosis together in different combinations. Furthermore, most studies are in immunocompromised patients, and the assumption that sensitivity and specificity are independent of prevalence is not always fulfilled; if they are not, tests may have worse performance in low-prevalence populations, such as nonimmunocompromised patients. These major caveats notwithstanding, even if the specificity is as high as 95% (with a corresponding sensitivity of 65%) (6), but the true base rate of aspergillosis is 1%, the posterior probability of aspergillosis with a positive BALF GM test would be just 12% according to Bayes' Theorem. However, the authors would dichotomize this as a "probable" case, falsely inflating the prevalence in the cohort. This is a form of base rate neglect: in low prevalence populations, the majority of positive tests represent false positives. The problem will be worse if the specificity is a more modest 85% (the lower end of the confidence limit in the most widely referenced meta-analysis [7, 9]), with the posterior probability falling to a mere 4%. The crux of the problem is that with tests of imperfect specificity it is impossible to determine the prevalence of disease in the population because it requires knowing the prevalence of disease in the population! An ancillary problem arises from the policy of allowing any of multiple positive components of the mycological criteria to count for diagnosis (3). This increases the overall sensitivity of the diagnostic strategy at the expense of specificity, amplifying the aforementioned problems. Histology was among the criteria for diagnosis, but it appears that no cases were diagnosed using histopathology of tissue samples. The only way to reliably diagnose aspergillosis in a low-prevalence cohort is to use a gold standard, in this case a biopsy (or necropsy) specimen showing fungal invasion (9). We worry that if the immanent methodological limitations of this and similar studies are not adequately acknowledged—they are not listed among the possible explanations for the results enumerated by the editorialist (2)—an avalanche of testing for aspergillosis in ICUs may ensue, resulting in an epidemic of overdiagnosis and overtreatment. We caution readers of this report that it cannot establish the true prevalence of *Aspergillus* infection in patients with ventilator-associated pneumonia in the ICU, but it does underscore the fact that when tests with imperfect specificity are applied in low-prevalence cohorts, most positive results are false positives (10). Prospective cohort studies using tissue sampling and histopathology, perhaps guided by tests such as BALF GM, are necessary to establish the true prevalence of this disease in nonimmunocompromised patients in the ICU. ■

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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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