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Correspondence

Bronchoalveolar Lavage Fluid Galactomannan for Diagnosis of Invasive Pulmonary Aspergillosis

TO THE EDITOR—We read the article by Maertens et al [1] with great interest. In a series of 58 patients who received a diagnosis of proven or probable invasive aspergillosis (IA), the authors confirmed previous work that the diagnostic performance of galactomannan antigen levels in bronchoalveolar lavage (BAL) fluid samples is good and that the procedure is safe in critically ill hematology patients.

However, the article leaves both the readers of *Clinical Infectious Diseases* and the treating physicians of patients who have a high risk of IA with the burning question whether performance of BAL has additional diagnostic yield in comparison with serum galactomannan testing. The most convincing argument to persuade hematologists and pulmonologists to perform BAL would be that determination of galactomannan levels in BAL fluid samples has a higher sensitivity without a loss of specificity. In addition, for patients with a positive serum galactomannan level, attempts to make a culture-positive diagnosis can be done by performing BAL, which is increasingly important in the context of recent data on emerging azole resistance in *Aspergillus fumigatus* [2]. Furthermore, patients might be diagnosed with a mixed (bacterial and/or fungal) infection.

To our surprise, the authors did not provide any data on the sensitivity of galactomannan in BAL in comparison with in serum samples. As an explanation, they state that such a comparison is not possible, because a positive serum galactomannan test result was part of the gold standard for the diagnosis of IA. Although

this argument is true for probable cases of IA, incorporation of a positive serum galactomannan test result as a criterion for case classification is unnecessary for proven cases.

Therefore, we hope that Maertens et al [1] can provide us the data on the sensitivity of BAL galactomannan measurements for the substantial subset of patients with proven pulmonary IA (31 of 58 patients). We are particularly interested in the data for patients with proven pulmonary IA and not other molds, because other molds will not be detected by means of galactomannan testing. Therefore, even if galactomannan levels in BAL samples would yield 100% sensitivity, a negative BAL sample test result should always be followed by tissue diagnostics to exclude other invasive fungal infections. In addition, data on mixed infections, which were diagnosed after BAL performance but were unrecognized before, would also be valuable, to serve as another argument in favor of BAL performance.

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Potential conflicts of interest. B.J.A.R. and L.S.: no conflicts.

Bart J. A. Rijnders and Lennert Slobbe

Departments of Medical Microbiology and Internal Medicine, Section of Infectious Diseases, Erasmus Medical Centre, Rotterdam, the Netherlands

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Reprints or correspondence: Dr Bart J. A. Rijnders, Dept of Medical Microbiology and Infectious Diseases, Erasmus Medical Centre, Rotterdam, the Netherlands (b.rijnders@erasmusmc.nl).

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Galactomannan Detection and Diagnosis of Invasive Aspergillosis

TO THE EDITOR—The article on bronchoalveolar lavage (BAL) galactomannan enzyme immunoassay (EIA) for diagnosis of invasive aspergillosis of patients with hematologic diseases raises some important points [1]. The authors, like others before them, seem not to have fully appreciated the fact that, with such a high prior probability of disease—35% in their series—the galactomannan EIA is being used to confirm the diagnosis. Thus, the posterior probability for a positive test result (ie, the positive predictive value [PPV]) should be the highest possible. Their data show that the highest PPV was 80.4% and was associated with a threshold optical density (OD) index of 1.5–2. One cannot confirm and exclude a diagnosis using the same threshold without paying a price in terms of false-positive and false-negative results, respectively. This is shown clearly in this article and also in a recent meta-analysis of serum and plasma galactomannan [2]. These effects are displayed in Table 1 for 2 hypothetical populations of 100 patients: one with a prior probability (prevalence) of IA of 8% for whom serum and plasma specimens are tested once or twice weekly for galactomannan, and the other with a prevalence of 35% in which a BAL fluid specimen was tested for the same antigen. It is clear that one needs to choose a low threshold in both

Table 1. Hypothetical Populations of 100 Patients

OD index threshold	Plasma/serum prevalence of IA, 8%		BAL prevalence of IA, 35%	
	Cases of IA, 8	Cases of no IA, 92	Cases of IA, 35	Cases of no IA, 65
	False-negative results	False-positive results	False-negative results	False-positive results
0.5	2	17	0	12
1	2	8	2	7
1.5	3	5	3	6

NOTE. BAL, bronchoalveolar lavage; IA, invasive aspergillosis; OD, optical density.

scenarios to obtain the lowest rate of false-negative results and that the converse is true to obtain a low number of false-positive results. The numbers differ but the principle remains the same. The question is: what do we want from a test? Staring at the bare facts does not help us here to address the issue. BAL fluid samples are not suitable in a screening test for obvious reasons and should only be used to determine an etiology. Then, we need confidence in knowing that the test has a high PPV. On the other hand, the galactomannan test is most often used for screening, and here we want the lowest number of false-negative results, because we want to exclude the diagnosis of IA. Consequently, an optical density index of 0.5 is the most appropriate. It may be that using the higher threshold to confirm a case of IA on the basis of plasma or serum test result is appropriate, but that requires further study.

In any event, we clearly have at least 2 ways in which to employ galactomannan: first, screening when the prevalence is low (eg, <10%) to exclude IA when the test result is negative (optical density index, ≤ 0.5); second, testing BAL fluid, in which case a positive test result (optical density index, ≥ 1.0) supports the diagnosis of IA. One could reason that blood or serum samples that yield an optical density index >1.5 could also support a diagnosis of IA, especially if the prevalence is relatively high (eg, $>10\%$). This will mean several thresholds for different purposes, different samples, and perhaps different patient populations, which will help us use the test optimally, allowing it to come of age.

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J. Peter Donnelly¹ and Mariske M. Leeflang²

¹Department of Haematology, Radboud University Nijmegen Medical Centre, Nijmegen, and ²Department of Epidemiology, Academic Medical Center, Amsterdam, the Netherlands

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Reprints or correspondence: Dr J Peter Donnelly, Dept of Haematology, Radboud University Nijmegen Medical Centre, Geert Grooteplein Zuid 8, 6525 GA Nijmegen, the Netherlands (p.donnelly@usa.net).

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Reply to Rijnders and Slobbe and to Donnelly and Leeflang

TO THE EDITOR—We appreciate the comments by Rijnders and Slobbe [1]. Regular testing for the detection of serum or plasma galactomannan (GM) has become increasingly popular for the early diagnosis of invasive aspergillosis (IA), especially in patients with prolonged profound neutropenia and in allogeneic stem cell

transplant recipients. However, the excellent performance characteristics of serum GM testing that are usually seen in these particular patient groups cannot be demonstrated in nonneutropenic hematology patients [2] and in nonhematology patients, including intensive care unit patients [3]. This limitation calls for other microbiological tests, including analysis of bronchoalveolar lavage (BAL) fluid, to establish the diagnosis of IA. As stated by Rijnders and Slobbe, the question remains whether GM testing on BAL fluid results in any additional diagnostic yield in comparison with serum GM testing. In our study [4], paired BAL fluid and serum GM test results (taken on the same day and before antifungal treatment was given) were available from 10 neutropenic and 19 nonneutropenic patients with proven IA (Table 1). Using a cutoff index of 1.0, the sensitivity of GM detection in BAL fluid was 100% in neutropenic patients and 94.7% in nonneutropenic patients ($P > .99$); however, using a cutoff index of 0.5, the sensitivity of serum GM testing was significantly better in neutropenic versus nonneutropenic patients (90% vs 36.8%; $P = .008$). Overall, determination of GM levels in BAL fluid seems to have a higher sensitivity than serum testing.

Although we tend to disagree with the general statement that azole resistance in *Aspergillus fumigatus* is emerging [5] and that a negative BAL sample result should always be followed by tissue diagnostics, we certainly appreciate the added value of BAL fluid examination. BAL fluid was culture positive for *Aspergillus* species in 18 of 29 cases, allowing species identification