Correspondence

Serum Galactomannan Diagnosis of Breakthrough Invasive Fungal Disease

To the Editor—We read with interest the article by Duarte and colleagues describing their experience with serum galactomannan–based antigen detection of invasive fungal disease (IFD) among high-risk hematology patients receiving posaconazole prophylaxis [1]. The authors concluded that serum galactomannan screening was unreliable during mold-active prophylaxis, given their low pretest probability of breakthrough disease (1.9%) and a relatively high rate (13.8%) of false-positive results, which often triggered unnecessary diagnostic studies in asymptomatic patients. The authors concluded that serum galactomannan still aids the diagnosis of breakthrough aspergillosis in symptomatic patients during prophylaxis. However, their conclusion appears to be based on sensitivity and specificity calculations derived in part from patients with probable disease (Table 4). In these cases, the diagnostic performance is skewed by the fact that a positive galactomannan result is also serving as a “de facto” gold standard for classification of positive cases.

We believe the clinical utility of serum galactomannan testing is still questionable even if one accepts the literature-reported sensitivity and specificity of 70% and 90%, respectively, for diagnosis of breakthrough fungal disease. The authors reported in Table 5 that among patients with suspected breakthrough IFD, the pretest probability of disease was 55.5%. Converting their diagnostic performance to likelihood ratios (positive likelihood ratio of 7.00 and negative likelihood ratio of 0.33), we estimate that the probability of invasive aspergillosis increases in their cohort from 55.5% to 90% with a positive serum galactomannan result. Most clinicians would treat for aspergillosis at both of these probability thresholds. Unfortunately, gains in diagnostic certainty with a positive test do not necessarily support discontinuation of other therapies, as up to 49% of patients with galactomannan–diagnosed mold disease have non-Aspergillus co-pathogens [2].

On the other hand, a negative galactomannan result would only reduce the probability of suspected breakthrough IFD in their cohort from 55.5% to 30%, which is not enough in our opinion to avoid changing or discontinuing empiric antifungal therapy. Interestingly, 17 of 25 patients excluded in their analysis because of switch to other antifungals had persistently negative galactomannan results and no findings on chest computed tomography (CT), suggesting a lack of “real life” confidence in the test for ruling out IFD.

Ultimately, an intensive galactomannan sampling approach with bronchial alveolar lavage, as discussed in the accompanying editorial [3], may improve the diagnostic sensitivity of the test, although this point is still debated [4, 5]. We would argue that ruling out IFD in the small numbers of patients with suspected breakthrough infection is probably more practical, as it will help direct earlier non-fungal-related diagnosis, and reduce unnecessary empirical antifungal use. Improvements in the sensitivity and specificity of radiographic diagnosis of breakthrough mold disease, using tools such as CT pulmonary angiography [6] or novel biomarkers, may ultimately be a more viable strategy than serum galactomannan for identifying which patients do not have breakthrough IFD.

Note

Potential conflicts of interest. R. E. L. has received personal fees from Gilead Inc and Merck and Co, Inc. P. V. has received personal fees from Astellas, Novartis, Pfizer, Sanofi-Aventis, Bayer, and GlaxoSmithKline, and grants from Merck and Gilead. M. G. reports no potential conflicts.

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Russell E. Lewis,1,2 Maddalena Giannella,2 and Pierluigi Viale1,2
1Infectious Diseases Unit, S. Orsola-Malpighi Hospital, and 2Department of Medical Sciences and Surgery, University of Bologna, Italy

References


Correspondence: Russell E. Lewis, PharmD, Department of Medical Sciences and Surgery, Alma Mater Studiorum University of Bologna, Infectious Disease Unit, Building 6, S. Orsola Malpighi Hospital, Via Massarenti 11, 40138 Bologna, Italy (russel.edward.lewis@unibo.it).

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