Chest Computed Tomography versus Serum Galactomannan Enzyme Immunoassay for the Diagnosis of Probable Invasive Aspergillosis: To Be Decided

Dionissios Neofytos
Division of Infectious Diseases, Johns Hopkins University, Baltimore, Maryland

(See the article by Nucci et al, on pages 1273–1280.)

Clinical outcomes in patients with invasive aspergillosis have significantly improved [1, 2]. This may, in part, be related to earlier diagnosis, leading to earlier institution of treatment and better tolerated, effective, and safe treatment options [2, 3]. The study of diagnostic and therapeutic modalities for invasive aspergillosis has been greatly facilitated by the introduction of definitions for invasive fungal infections established by the European Organization for Research and Treatment of Cancer and the Mycosis Study Group (EORTC-MSG) in 2002, which have recently been updated and published in this journal [4, 5].

On the basis of the EORTC-MSG definitions, an invasive fungal infection is considered to be proven (usually requiring tissue biopsy), probable, or possible. The presence of a microbiologic diagnosis in addition to host, clinical, and radiographic factors differentiates a probable from a possible invasive fungal infection [4, 5]. These definitions, established to facilitate enrollment in clinical trials, have helped investigators maintain a relative homogeneity among the subjects enrolled and, therefore, ascertain that the observed results can be reproducible.

The serum galactomannan enzyme immunoassay (GM-EIA; Platelia Aspergillus EIA; Bio-Rad) was cleared by the Food and Drug Administration at an optical density index cut-off of 0.5 and included in the guidelines for a probable diagnosis of invasive aspergillosis [5]. Until the advent of the serum GM-EIA, a significant number of patients with invasive aspergillosis enrolled in clinical trials were patients who only had suggestive findings on chest computed tomography (CT), without microbiologic findings. On the basis of the revised EORTC-MSG definitions, the following 3 chest CT findings are considered to be suggestive of invasive aspergillosis: a well-defined dense lesion (with or without a halo sign), a crescent sign, or a cavity [4, 5].

Nucci et al [8] hypothesized that using a positive serum GM-EIA result without concomitant chest CT findings consistent with invasive aspergillosis on the basis of the EORTC-MSG definitions may increase enrollment in randomized clinical trials [8]. The authors performed a retrospective review of 121 patients with cancer with 125 consecutive episodes of invasive aspergillosis at a single institution from 2003 through 2009. Using a GM-EIA optical density index of >0.5 as a positive result, the authors identified 42 (33%) of 125 cases of invasive aspergillosis without the classic chest CT findings. Cases were more likely to have a higher baseline platelet count \( (P = .03) \), shorter duration of neutropenia \( (P = .007) \), and lack of fever \( (P = .003) \). Notably, 11 (42.3%) of 26 cases in patients who underwent additional imaging were reclassified as controls on the basis of the EORTC-MSG definitions. No significant differences were found between cases and controls in terms of risk factors, microbiology data, and GM-EIA–specific characteristics (eg, peak value, time to peak, etc). On the basis of
these results, the authors concluded that a significant number of patients who would normally not qualify to participate in a randomized clinical trial on the basis of chest CT findings would eventually be enrolled.

Historically, nodular lesions with the halo or air crescent signs have been associated with invasive aspergillosis [9–11]. Although infections due to bacteria (eg, *Pseudomonas* species) and molds other than *Aspergillus* (eg, the *Zygomycetes*) can have similar presentations, these imaging findings are commonly used to make a presumptive diagnosis and initiate empirical treatment for invasive aspergillosis in high-risk patient groups (eg, neutropenic fever in patients with hematologic malignant neoplasms) [9, 12, 13]. As clinical practices evolve and patient populations at risk for invasive aspergillosis change, patients with pulmonary invasive aspergillosis may present with lesions other than nodular, predominately in nonneutropenic hosts [14, 15]. For instance, Kojima et al [14] reported that a number of hematopoietic stem cell transplant recipients with late (postengraftment) invasive aspergillosis had variable chest CT findings, including ill-defined consolidations, ground-glass opacities, or pleural effusions [14]. Similarly, solid organ transplant recipients with invasive aspergillosis may present with a wide array of chest CT findings, including peribronchial consolidation or ground-glass opacities, and may be less likely to have macronodules and halo or air crescent signs, compared with neutropenic patients [15]. The appreciation that more variable, less traditional chest CT findings may be associated with pulmonary invasive aspergillosis necessitates further study to validate and standardize new imaging findings for their use in clinical practice and enrollment in randomized clinical trials.

In this context, Nucci et al raise a valid question, “Is the serum GM-EIA a better tool for the diagnosis of invasive aspergillosis in the setting of a wide array of atypical chest CT findings?” But perhaps the question should be rephrased to “How good of a surrogate diagnostic test is the GM-EIA for the diagnosis of invasive aspergillosis?” The study and validation of new diagnostic tests for invasive aspergillosis have been hindered by the lack of a good gold standard [16]. The study of serum GM-EIA has been quite controversial with regard to the optimal optical density index (0.5 vs 1 vs 1.5), frequency of testing, and patient population studied [17–22]. In fact, the sensitivity and specificity of the test have been variable, seemingly affected by a multitude of factors [21, 22]. The test does not perform similarly in all patient groups; it appears to be more sensitive in patients with hematologic malignant neoplasms and neutropenia and in hematopoietic stem cell transplant recipients rather than solid organ transplant recipients [22]. False-positive results have been associated with the administration of piperacillin-tazobactam or amoxicillin-clavulanate [23, 24] and the presence of organisms that share cross-reacting antigens with *Aspergillus* species (eg, *Penicillium* species).

Considering results of a test such as the serum GM-EIA with a dichotomous “yes or no” viewpoint toward infection may be rather simplistic. After all, *Aspergillus* antigens can be found in the airway and likely other places of the body (gut) in the absence of invasive disease. As with other diagnostic tests to detect opportunistic organisms, such as cytomegalovirus, results need to be interpreted in the context of the hosts’ immunosuppression and clinical presentation. Relying solely on the serum GM-EIA may lead to enrollment of “different” subjects in future randomized clinical trials, compared with historical controls. For instance, a positive serum GM-EIA result has been associated with earlier diagnosis of invasive aspergillosis, as suggested in the study by Nucci et al, and thus earlier treatment initiation [18, 25]. These factors may introduce potential biases when comparing outcomes to previous randomized clinical trials. The lack of specificity of the test may also lead to more patients without invasive aspergillosis enrolled in clinical trials and, most importantly, a high number of patients receiving inappropriate treatment, increasing the risk for potential drug-related toxic effects.

Before concluding, it should be pointed out that the results of this study should be interpreted with caution. This was a rather small, single-institution retrospective review of patients who mostly had multiple myeloma and were tested 3 times weekly with a serum GM-EIA. The implications of this study in other patient populations and at institutions where the test is used less frequently may be different. The serum GM-EIA is not always performed on site; therefore, relying on a “send-out” test with variable reporting time may have significant implications. Finally, the cost of the test may be another potential limitation to routinely screen patients, depending on the setting.

The benefits of applying the approach suggested by Nucci et al [8] are limited to a higher enrollment, perhaps by 30%. However, the ultimate goal when performing a randomized clinical trial is to ensure high enrollment while maintaining accurate inclusion criteria supported by reliable and reproducible diagnostic tests. The serum GM-EIA appears to have the potential to be a helpful surrogate diagnostic tool. However, I am afraid that we are far from using the test as a panacea to accurately predict the presence of invasive aspergillosis. This study by Nucci et al raises new questions and opens new possibilities in the performance of randomized clinical trials for the study of invasive aspergillosis in the future. However, adjusting the EORTC-MSG guidelines for the diagnosis of invasive aspergillosis to optimize enrollment in randomized clinical trials should be performed with careful and well-documented steps to ensure high-quality data and result reproducibility. This study may represent the start of a new era in the study of invasive aspergillosis.
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References