

The role of galactomannan testing to diagnose invasive pulmonary aspergillosis in critically ill patients

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Invasive aspergillosis (IA) is an opportunistic infection caused by *Aspergillus* spp., a saprophytic filamentous fungus that is frequently isolated in the environment. The infection occurs most frequently in the lower respiratory tract (LRT) of immunocompromised patients with prolonged neutropenia or hematopoietic organ transplants (1,2). Significant progress has been made over the last 20 years in the development of diagnostic tools and decision algorithms as well as of effective antifungal drugs for IA (3), allowing for improved outcomes in non-critically ill immunocompromised patients due to the rapid initiation of appropriate therapy (4).

Symptoms or signs suggestive of invasive pulmonary aspergillosis (IPA) are fever refractory to at least 3 days of appropriate antibiotic therapy, recrudescence fever after a period of defervescence of at least 48 hours while still on antibiotics, pleuritic chest pain or rub, dyspnea, hemoptysis, or worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support (5). Nevertheless, these symptoms are not specific for IPA and may result in under-diagnosing of this infectious disease, in particular in those patients without evidence of *Aspergillus* from tracheal aspirate or sputum. Thus, the European Organization for the Research and Treatment of Cancer/Mycosis Study Group (EORTC/MSG) has developed a combination of diagnostic criteria that can differentiate patients with “proven”, “probable”, and “possible” IPA from those with *Aspergillus* colonization (5). These criteria include chest imaging based on computed tomography (CT-scan), the presence of “host factors”, direct and indirect positive mycological tests and positive histopathology results. In particular, the “typical” signs of IPA on chest CT-scan are dense, well-circumscribed lesions with or without a “halo”

sign (e.g., a region of ground-glass attenuation surrounding a pulmonary nodule), an air-crescent sign or pulmonary cavity. Host factors are a history of severe neutropenia (less than 500 neutrophils/mm³) for at least 10 days, allogeneic stem-cell transplant recipient, prolonged corticosteroids use (≥ 20 mg/day of prednisolone or equivalent for at least 3 weeks), T-cell immunosuppressant treatment during the previous 3 months and inherited severe immunodeficiency. Positive mycology results refer to positive direct (e.g., identification of *Aspergillus* spp. by direct microscopy, culture, or cytology on LRT or sterile pulmonary samples) and indirect tests (e.g., high levels of detect antigen or cell-wall constituents either in blood or LRT sampling). Histopathological evidence of IPA must show tissue invasion branching filamentous fungi with septae on lung or tracheal biopsy. As such, proven IPA refers to a patient with histopathological evidence of IPA; probable IPA requires the simultaneous presence of at least one host factor, one clinical feature and the mycological evidence of *Aspergillus* in the LRT; possible IPA requires that a host factor and clinical features are present, without mycological positive tests (5).

Recently, IA has also been recognized as an emerging infectious disease associated with high morbidity, mortality and healthcare costs in critically ill patients without traditional risk factors for the disease (6-9). This issue was well depicted by the increase in the prevalence of invasive fungal infections from 2.2% to 5.1% over a 12-year period, mostly due to an increase in the rate of *Aspergillus* infection, reported in a non-selected patient population at an academic hospital (10). Currently, incidence and mortality rates due to IA in critically ill patients vary widely from 0.02% to

19%, and from 46% to 95%, respectively (7,11). This large variability is probably due to the great heterogeneity of the different patient populations included in these studies as well as the poor performance of diagnostic criteria that were applied in these patients. Indeed, post-mortem samplings are sometimes the only proof of IPA in critically ill non-survivors and several studies have shown that invasive fungal infections are the most commonly missed diagnoses in ICU patients (12-14). These data clearly underline a knowledge gap in the accuracy of diagnostic algorithms used in this setting. As such, clinical and radiological presentation of IPA is often non-specific and lung biopsy is frequently contraindicated in critically ill patients (7,15). Also, risk factors for IPA in these patients include chronic obstructive pulmonary disease (COPD), short-term corticosteroid use, acute respiratory distress syndrome (ARDS), severe sepsis, H1N1 virus infection, decompensated chronic liver disease and acute renal failure (7-9). However, as these conditions are not recognized among the EORTC/MSG diagnostic criteria, most of IPA in critically ill patients is considered as “non-classifiable” (15).

A significant improvement in IPA has been recently made by the development of an “easy-to-use” decisional algorithm (the “AspICU” decision tree), which showed a high predictive negative value for IPA and could help clinicians to distinguish colonization from IPA (15). Moreover, the definition of “putative” IPA was created to classify those patients who had *Aspergillus* positive LRT samples, compatible clinical symptoms, an abnormal chest X-ray or CT-scan and either typical host factors or positive *Aspergillus* culture in the broncho-alveolar lavage (BAL) sampling. Despite this diagnostic approach performed much better than the EORTC/MSG diagnostic criteria to diagnose IPA, it was limited by the necessity to have a positive LRT sample for *Aspergillus* spp.; however, IPA may evolve without a positive respiratory culture, which is present in only 40–50% of patients with the disease (16), and the need for further improvement of diagnostic criteria of IPA in critically ill patients is warranted.

The measurement of the cell-wall constituent galactomannans (GM), a [1-3]- β -D-glucan (BD) that is released during fungal growth, has been widely used as a biomarker for early diagnosis of IPA in neutropenic patients, together with polymerase chain reaction (PCR) assay. GM and BD are polysaccharide of the *Aspergillus* wall that can be detected during the invasive disease in different body fluids (e.g., serum, BAL and cerebrospinal fluid). In a recent Cochrane Review, the sensitivity and the specificity of the

GM assay measured in the serum with a cut-off of 0.5 optical density index was 82% and 81%, respectively, to detect IPA in neutropenic patients where the prevalence of the disease is estimated around 10% (17). Nevertheless, in non-neutropenic patients, serum GM assays result in significantly poorer results because these molecules are cleared by neutrophils, thus limiting the diagnostic value of this test to detect IPA in such population. Thus, in a retrospective study evaluating critically ill patients, serum GM was increased in only 53% of patients with IPA (18). The accuracy of GM to diagnose IPA in this setting could be increased by performing consecutive serum GM determinations. In one study including critically ill COPD patients (n=90), two consecutive positive serum GM tests were performed on the first and fourth day after ICU admission had positive and negative predictive values of 89% and 85% to diagnose IPA (19). In another study (n=110) a GM cut-off of 0.5 into the BAL showed a sensitivity and specificity of 88% and 87% to diagnose IPA in critically ill patients, while the sensitivity of serum GM was only 42% (20).

In a recent issue of Critical Care, Schroeder *et al.* evaluated for the first time the AspICU algorithm to diagnose IPA in critically ill patients in patients with both positive (n=43) and negative (n=42) LRT cultures for *Aspergillus* spp. (21). The authors observed that the two groups of patients had similar demographic and clinical characteristics. The median GM titre in BAL fluid was significantly higher in patients with positive *Aspergillus* cultures than others [5.9 (3.2–5.7) *vs.* 1.7 (0.9–4.5); $P < 0.001$]. Interestingly, when a modified AspICU algorithm including positive (>0.5) GM assessment on BAL fluid was applied in those patients with negative LRT cultures, the proportion of patients with proven/putative IPA was similar in the groups (36/43 if positive cultures *vs.* 33/42 if negative cultures). According to the authors, without the use of GM assessment as an additional entry point to the decision tree, these patients would have considered as “non-classifiable” and therefore not treated thereafter.

Although interesting, the results of the study must however be interpreted with caution. First, there were more neutropenic patients in the group of patients with *Aspergillus*-negative respiratory samples than in the group of patients with positive cultures (6/42 *vs.* 0/43; $P = 0.012$), which increased the risk for IPA independently from the results of LRT samples. Thus, the question about the effectiveness of biomarkers to increase the detection of IPA in a completely non-neutropenic critically ill population remains unsolved. Second, clinical diagnosis of IPA was

based on the decision of the attending physician to start antifungal treatment, but treatment was very short in the majority of cases (the majority of patients received treatment for 3 weeks or less). As length of treatment of IA is usually around 6 weeks (5), it is possible that some of the diagnoses of IPA would have revised or infirmed thereafter. Finally, only 4/25 and 8/25 patients who died in the group of patients with a positive and negative *Aspergillus* cultures, respectively, had a post-mortem examination that could confirm IPA. Thus, in the absence of direct tissue invasion demonstrated on specific assays, it remains unclear the accuracy of this modified AspICU algorithm to diagnose IPA in critically ill patients.

How the results of these studies can be compared with other investigations on GM measurement in ICU patients? The optimal cut-off of GM assessment in the BAL fluid has been widely debated. In the present study, the receiver operating characteristics curve (ROC) analyses for GM to predict positive *Aspergillus* cultures was 0.71 for an index of 0.5 and was not significantly improved for higher values (21). In previous studies, a GM cut-off of 0.8 for BAL fluid was associated with a high sensitivity and specificity (89% and 100%, respectively) and an AUC of 0.91 to diagnose IPA in COPD patients (22). Other studies showed that a cut-off of 0.5 was accurate to diagnose IPA in critically ill non-neutropenic patients (20,23). Moreover, GM assay in the BAL fluid could become positive earlier than the *Aspergillus* LRT culture by 2 to 10 days, which could have a significant impact on the timing of initiation of therapy (24). However, the time from positive test to initiation of therapy was not evaluated in the Schroeder's study. Finally, the combination of several biomarkers could provide an even more accurate diagnostic approach to identify IPA in such patients. [1-3]- β -D-glucan offered similar diagnostic accuracy as serum GM in two different studies, but lower accuracy than the GM BAL detection (25,26) and cannot be considered as a valuable alternative in this setting. Although promising, PCR techniques showed only moderate diagnostic accuracy when used as screening tests for IPA in high-risk patients and could be integrated in a diagnostic algorithm to exclude the diagnosis of IPA only when repeated at least twice, as a single PCR test may have around 20% of missed diagnosis (27). As only few patients had concomitant PCR assessment in the Schroeder's study, this issue remains to be further evaluated.

In conclusion, Schroeder *et al.* have provided promising results concerning the utilization of GM determination to identify critically ill patients at risk of IPA. The results

suggest that by using the modified AspICU clinical algorithm with positive GM in the BAL fluid as an additional entry point may increase the diagnostic detection of IPA in ICU patients. More studies including proven IPA from post-mortem or biopsy tests should be performed to confirm these preliminary results. Furthermore, the use of other biomarkers (either in combination with GM or to replace GM detection) should be considered as well.

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Footnote

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