Journal de Mycologie Médicale 29 (2019) 97–98

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Letter to the editor

Is Aspergillus lateral device ready to implement to the daily practice? The question rising from the new European Invasive Aspergillosis management guideline

Keywords:
Invasive aspergillosis
Aspergillus lateral flow device

Dear Editor,

Prompt and accurate diagnosis of invasive aspergillosis (IA) is mandatory for the effective treatment of IA in immunocomprimised patients. Although microscopy and culture are the gold standards for the diagnosis of IA, serological tests are commonly used due to the difficulties for obtaining deep tissue samples. However, well-known serological tools such as galactomannan antigen (GM) and beta-d-glucan (BDG) require high quality laboratory staff and special equipments [1].

Aspergillus lateral flow device (Aspergillus LFD) is a new point-of-care test, which detects an extracellular mannoprotein antigen secreted during growth of *Aspergillus* species by using a monoclonal antibody (mAb JF5). The result is available in minutes and the test is reported as weak, moderate or strong positive according to the band intensities observed by the technician [2]. In addition to GM and BDG, the recent European Society for Clinical Microbiology and Infectious Diseases, the European Confederation of Medical Mycology and the European Respiratory Society (ESCMID-ECMM-ERS) Joint Clinical Guideline recommended to use Aspergillus LFD to diagnose IA in broncohoalveolar lavage (BAL) fluid and serum. The grade of the recommendation was B II.

This new test has a comparable performance with GM particularly in BAL fluid [3,4]. The major advantage is applying neat BAL fluid to LFD. There is no need for sophisticated pre-treatment protocols and devices. The test results in 15–20 minutes [2]. In animal models, the Aspergillus LFD successfully detected aspergillus monoclonal antibodies in experimentally infected animal serum without any pre-treatment protocol. The reports were highly reproductable even the test was performed either by processing with the pretreatment protocol or not [5]. The inventors of this promising tool recommended to test human serum without any pre-treatment based on these findings [6]. There is only one real-life study, which followed this protocol and failed to show the benefit of the test when compared with GM and BDG. Aspergillus LFD was positive in serum of only 1 out of 11 patients with positive GM antigen, unfortunately [7].

Two studies that used pre-treatment protocols were published before the release of new ESCMID-ECMM-ERS Aspergillosis guideline. The results and testing protocols were quite different in each study [8,9]. The recommendation in the recent guideline was derived from the study performed by Held et al. [8]. The sensitivity and specificity of Aspergillus LFD was reported as 40% and 86.8%. Aspergillus-LFD was positive in serum of 4 out of 10 patients with proven/probable invasive fungal diseases. Aspergillus LFD band intensity was moderate positive in one patient and weak positive in three patients. The authors did not detect any strong positive Aspergillus-LFD even from cases with positive serum GM antigen or culture proven aspergillosis. The test of several serum samples resulted with non-specific band intensities [8]. In the other study that was not referred in the ESCMID-ECMM-ERS Aspergillosis guideline; the authors investigated the performance of Aspergillus LFD in 103 adult haematology patients at high risk of developing IA. Sensitivity and specificity of Aspergillus LFD in serum was as; 81.8% and 84.7% when compared with GM antigen as 72.2% and 81.3% [9].

The pre-treatment protocols were quite different in two studies. Held et al. [8], mixed 50 μL of serum with 100 μL of EDTA, while 200 μL of serum was mixed with 75 μL of EDTA acid solution in the second study [9]. Both of the research groups heated the solution three minutes, but they used different centrifugation protocols. Apart from the pre-treatment protocols, White et al. [9], determined Aspergillus specific test line in a period 10–20 minutes while this period was 15 minutes in the study by Held et al. [8].

In a multicenter study from Brazil, the authors followed the manufacturers' instructions (OLM Diagnostics, England) to perform Aspergillus LFD and reported a very low sensitivity, but, they have retracted the research letter including these findings from the journal since the tests were performed by using a non-CE marked prototype device [10]. However, ESCMID-ECMM-ERS guideline recommendations for Aspergillus LFD were based on a study that used this prototype device [8].

A better performance of newly formatted Aspergillus LFD test in BAL fluid was reported recently [11]. This new LFD was used to test serum from patients with IA in another study. After mixing with the accompanying buffer, serum samples were vortexed, heated and centrifuged at 14,000G and then 70 μL supernatant was applied to the new LFD assay. When the tests were read after 15 minutes, Aspergillus LFD was negative in all of the serum samples from 11 patients with probable IA. The test revealed a positive result in serum of 1 (9%) out of 11 patients with IA when it was read after 45 minutes. Major limitation of this study was; 10 out of 11 patients with IA received mold active antifungal therapy $\geq$ 2 days. On the other hand, Aspergillus LFD was positive in BAL fluid of 8 (73%) out 11 of these patients [12].

Sōna Aspergillus Galactomannan Lateral flow assay (LFA) (IMMY, Norman, Oklahoma, USA) is the second CE-marked

https://doi.org/10.1016/j.mycmed.2018.11.003

point-of-care test for diagnosis of IA. The manufacturer recommended a pre-treatment procedure for both BAL fluid and serum which is similar with the detection of galactomannan antigen by ELISA. The results are available in 30 minutes [13]. A recent study compared the performance of Aspergillus LFD with Sōna Aspergillus Galactomannan LFA in BAL fluid. When Aspergillus LFD was read after 25 minutes both of the tests had a sensitivity and specificity of 89 and 88%. The sensitivity of Aspergillus LFD decreased to 78% but specificity was increased to 100% when the test was read 15 minutes later [14]. Currently, there is no study comparing the performance of these two tests in serum.

Briefly, there are four clinical studies that examined the performance of Aspergillus LFD in serum with variable testing methodologies [7–9,12]. In the light of the current literature, testing methodology in serum still needs standardization and validation. These technical details have to be well addressed before implementing Aspergillus LFD in daily clinical practice to avoid unexpected confusing results.

Disclosure of interest

The author declares that he has no competing interest.

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Received 26 September 2018
Received in revised form 12 November 2018
Accepted 22 November 2018
Available online 4 December 2018