Improving diagnostic accuracy for invasive pulmonary aspergillosis in the intensive care unit

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Aspergillus spp is a widespread saprofytic fungus, frequently affecting the respiratory system and leading to variable clinical syndromes. Invasive pulmonary aspergillosis (IPA) is a well known life-threatening infection in patients with prolonged neutropenia, hematological malignancy, bone marrow or solid organ transplantation (1). Because of the difficult diagnosis of *Aspergillus* spp infections the European Organization for the Research and Treatment of Cancer/ Mycoses Study Group (EORTC/MSG) has introduced a diagnostic algorithm that incorporates clinical, laboratory findings and risk factors for the stratification of patients into proven, probable or possible IPA (2). From the other side the incidence of IPA in critically ill patients is growing and has serious effects on survival (3). Although classic immunosuppression related to severe neutropenia or hematological malignancies is rather infrequent in the intensive care unit (ICU), other host risk factors have been recognized. Prolonged steroid treatment and comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes, liver cirrhosis or end-stage chronic renal disease may occur in up to 50% of cases (4,5). In this group of patients the isolation of *Aspergillus* spp from the respiratory tract is difficult to be interpreted as IPA because of the lack of a diagnostic tool able to discriminate colonization from infection (except biopsy) and because IPA is usually associated with non-specific clinical signs and symptoms and atypical radiological findings (6). The above mentioned EORTC/MSG diagnostic criteria are validated only in immunosuppressed patients and probably lead to underdiagnosis and undertreatment in the ICU setting (7,8).

In critically ill patients, an adapted form of the EORTC

diagnostic algorithm has been proposed using a modified interpretation of radiological findings and microbiological evidence while the clinical relevance of this algorithm has been evaluated in a multicenter prospective observational study in ICU patients with *Aspergillus* spp positive cultures and microscopy as microbiologic evidence of *Aspergillus* presence (the AspICU study) (9,10). Recently, Schroeder *et al.* in a prospective observational study, used the AspICU clinical algorithm in 85 critically ill patients, 43 patients with positive *Aspergillus* culture (PAC group) and 42 patients with negative culture but with positive galactomannan (GM) antigen (OPG group) in respiratory samples. After a complete diagnostic workup that included bronchoscopy and computed tomography, the authors evaluated the physicians' decision to treat IPA. According to their results culture positive patients were significantly more likely to receive antifungal treatment than patients in the OPG group. The two groups of patients didn't differ in CT findings or baseline characteristics apart from neutropenia and preceding chemotherapy that were more frequently observed in the OPG group. The main conclusion of this study was that in the absence of histopathologic evidence, positive culture consisted of a more powerful trigger than increased GM levels for the initiation of antifungal treatment regardless of patients' risk factors and clinical findings (11).

Histopathological identification of *Aspergillus* spp in tissue specimens was and remains the gold standard for the diagnosis of IPA (12). However, lung biopsies are difficult to be performed in critically ill patients because of the frequently met severe comorbidities and coagulation

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disorders. From the other side traditional microbiological methods for *Aspergillus* diagnosis include direct microscopy of stained specimens and culture in Sabouraud agar with gentamycin and chloramphenicol. Culture is considered as a low cost and easy to perform method that offers also the advantage of susceptibility testing. However, its sensitivity doesn't exceed 50% at best and can't discriminate colonization from invasive infection. Indirect methods of detecting fungal components such as DNA or cell wall components are also available. GM, a polysaccharide component of *Aspergillus*' cell wall, detected by immunoenzymatic assays, is the most commonly used (13). The diagnostic value of GM in serum has been repeatedly shown in patients with hematologic malignancies and bone marrow transplants but its specificity seems to decrease by the concomitant use of b-lactam-b-lactamase inhibitors combinations or the presence of cross reactive antigens (14,15). The sensitivity of GM in serum is inferior in non-neutropenic patients because of the increased clearance of GM by circulating neutrophils (16). Determination of GM in specimens of other biological fluids such as urine, cerebrospinal fluid and bronchoalveolar lavage (BAL) has also been studied (17). GM is released in biological fluids during tissue invasion by fungal hyphae and it better correlates with invasive aspergillosis than with colonization compared to culture, especially in respiratory *Aspergillus* infections (13). Numerous clinical studies have addressed the value of BAL-GM in diagnosing IPA in critically ill patients with reported sensitivity and specificity up to 88% and 87% respectively (18). Moreover, it has been shown to be more sensitive than serum GM and culture in diagnosing IPA in critically ill patients with COPD (19). However, despite this promising data, a debate about the value of BAL-GM as a diagnostic tool still exists based on conflicting studies' results (20). This may be attributed to different study populations (especially regarding the immunological status and previous anti fungal exposure) and cut-off variability. A systemic review and meta-analysis of thirty studies that evaluated BAL-GM for IPA diagnosis indicated a higher sensitivity compared to the serum testing and PCR, when using the cut-off value of 1.0 (21). The results of Schroeder *et al.* impressively point out how strongly the decision to treat a life threatening infection can be influenced by the results of a method that is shown to be neither sensitive nor specific. At the same time ICU physicians had the tendency to ignore a positive BAL-GM in patients with similar clinical and radiological findings in the PAC group. Surprisingly, the two cases of histologically

proven IPA were culture negative and BAL-GM positive leading the authors to conclude that excluding GM testing from the diagnostic set-up of critically ill patients with possible IPA makes the underdiagnosis of the infection more possible (11).

Overdiagnosing and treating patients based on microbiological results that could depict colonization probably increases the incidence of pharmaceutical toxicity and further pushes antifungal resistance. On the other hand, the late administration of treatment leads to higher mortality and other collateral consequences as higher length of stay in the ICU, higher costs etc. The AspICU algorithm seems to be a useful adaptation of EORTC/MSG criteria to non-immunosuppressed ICU patients, but needs further validation. The determination of GM in BAL specimens, although not perfect, has been proved a reliable marker in discriminating colonization from invasive respiratory infection in critically ill patients. Combinations with other techniques [immunochromatographic lateral flow device (LFC) that uses a monoclonal antibody for the detection of *Aspergillus* glycoprotein released during multiplication] may improve its diagnostic yield (13,22). Randomized trials applying clinical algorithms in homogeneous ICU study populations in conjunction with combinations of microbiological tools will help determine the panel of biomarkers with the best diagnostic accuracy for IPA.

Acknowledgements

Footnote

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