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Editorial

Aspergillosis: Beyond the oncohematological patient

Aspergilosis: más allá del paciente oncohematológico

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Invasive aspergillosis (IA) is a serious opportunistic infection affecting severely immunocompromised patients, frequently observed in patients with hematological malignancies but also related with another conditions. More specifically, it generally takes place in patients with acute myeloid leukemia (AML), allogeneic hematopoietic stem cell transplantation (HSCT) recipients, solid organ transplant (especially lung, heart-lung, and liver) recipients, and patients who experience prolonged neutropenia.[1–3] With the use of adequate antifungal prophylaxis in high-risk hematological patients, the incidence of IA is below 3%.[4] However, recent data indicate that IA should be considered as an emerging and life-threatening infectious disease in patients with a lower degree of immunosuppression such as critically ill patients,[1] those with chronic obstructive pulmonary disease (COPD),[5–7] patients undergoing treatment with steroids, patients with cancer,[8,9] liver cirrhosis or patients with hematological malignancies receiving targeted threapies.[3,10]

Nowadays, approximately 43–80% of the cases of IA present in patients without a hematological malignancy.[1,11] The incidence of IA in the ICU ranges from 0.3% to 19%, with an overall mortality rate of >80%.[1] Risk factors for IA in non-neutropenic patients admitted to the ICU include prolonged treatment with corticosteroids before ICU admission, COPD, liver cirrhosis with prolonged ICU stay (>7 days), solid organ cancer, HIV infection, lung transplantation[1,12] and, as recently reported, influenza infection.[13] Severe COPD treated with corticosteroids represents the most common underlying disease for IA among non-neutropenic hospitalized patients and carries one of the highest mortality rates.[5,6] In a single centre in Spain, it has been estimated an *Aspergillus* isolation rate from lower respiratory samples of 16.3 patients per 1000 COPD admissions (with 22.1% patients of the 163 with *Aspergillus* presenting invasive pulmonary aspergillosis).[6] In a study published in this journal,[7] four independent risk factors for IA in COPD patients were identified: continuous oxygen therapy (OR 4.39; IC 95% 1.60–12.01; $p = 0.004$), bronchiectasis (OR 3.61; IC 95% 1.40–9.30; $p = 0.008$), hospital admission in the previous three months (OR 3.12; IC 95% 1.24–7.87; $p = 0.016$) and antifungal drugs against *Candida* spp. in the previous month (OR 3.18; IC 95% 1.16–8.73; $p = 0.024$. Nineteen percent of patients with influenza admitted to the ICU presented an IA, with a higher incidence noted when the patients were immunocompromised (32%). Influenza has been found to be an independent factor for IA (OR 5.19; 95% CI 2.63–10.26; $p < 0.0001$).[13] In patients with lung cancer or lung metastases, the presence of the anatomical neoplasic lung alterations and local and systemic factors affecting the immune response seem to contribute shaping the predisposition of these patients to IA.[8,9]

The nature of the immune suppression (degree, duration, and type of immunodeficiency) influences the pathogenesis of disease; aspergillosis thus manifests as a spectrum of disease involving predominantly airway (e.g., tracheobronchitis), lung (bronchopneumonia, IA, or chronic necrotizing aspergillosis) or both. In the presence of angioinvasive disease, *Aspergillus* spp. can disseminate beyond the respiratory tract to multiple different organs, including brain, eyes, liver, kidneys and skin.[2] Several reports have highlighted a possible link between ibrutinib therapy and the development of IA, with a distinct predilection for invasive cerebral disease and disseminated forms.[14,15] Risk factors for IA included ≥3 prior antitumor regimens and receipt of corticosteroids at any time during the course of ibrutinib.[15,16]

IA mortality in all those new populations of risk remains unacceptably high (>40%) and is mainly conditioned by refractory respiratory failure, patient age and renal replacement therapy.[12]

The standard of care for IA diagnosis requires the combined use of risk evaluation, radiological pattern examination and microbiological techniques.[10,11,17] In these emerging populations at risk, diagnosis is especially challenging, because the clinical presentation of IA may be atypical or insidious and initiation of diagnostic examinations is often delayed due to low clinical suspicion. Radiological findings, as with disease manifestations, can be variable and largely depend upon the host's immunitary status and type of aspergillar infection. The presence of well-circumscribed nodules with or without the halo sign in an immunocompromised host is more suggestive of IA.[18] Nevertheless, any kind of lung lesion should raise the possibility of IA in a susceptible host. In non-neutropenic patients other manifestations, such as consolidation or ground-glass opacity, may be the predominant feature.[2,5,11,19] In a recent study including COPD patients, an alveolar infiltrate was the most common radiological presentation.[6] A picture of

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bronchial wall thickening with centrolobular nodules, designated as tree-in-bud, is a hallmark of bronchopulmonary aspergillosis and is frequently observed in lung transplant recipients or in IA related to influenza infection.[13,18,19]

The definitive diagnosis is established with a histopathologic evidence of fungal infection and through identification of the causative agent. Complementary techniques have been validated for clinical use in immunocompromised patients. Because of the limited sensitivity of all these diagnostic procedures and concerns about specificity of some of them, a combination of various testing strategies is the hallmark of IA diagnosis.[10,11,17–19] The diagnostic value of isolating *Aspergillus* spp in respiratory tract specimens is not straightforward, principally because of difficulties in distinguishing colonization from disease.[6,7,20] In a study including nonselected patients with isolation of *Aspergillus*, the probability of aspergillosis is 12%, although the probability depended on the underlying condition: 72% for patients with neutropenia, 55% for solid organ transplant recipients, 28% for critically ill patients, and 22% in patients with COPD.[12] In a Spanish study, 25.9% of GOLD II COPD patients with at least two positive respiratory cultures presented IA, suggesting that this group of patients should not be neglected since mortality was significantly higher in GOLD II patients with IA than in GOLD II patients with colonization (42.9% vs. 5.0%). It is expected that this disease will become more prevalent in the future, considering the growing population of elderly patients and the increase in GOLD III-IV patients due to the improved management of COPD.[6]

The application of diagnostic algorithms adapted to these patients, in whom activation will depend on the isolation of *Aspergillus* in a respiratory specimen, is the most efficient diagnostic methodology.[10] Among the diagnostic approaches, the determination of galactomannan (GM) in bronchoalveolar lavage (BAL) is the most useful diagnostic test.[10,19] GM in BAL is more sensitive than culture for diagnosis of IA, with a sensitivity of 100% and a specificity of 90.4% was defined at cut-off of 1.[11] *Aspergillus* PCR has been applied mostly to blood and BAL fluid. The diagnostic performance of PCR in BAL fluid is acceptable and comparable to that of GM in BAL fluid. Moreover, the combination of the GM test and PCR in BAL increases the sensitive and specific diagnosis of IA.[10,11,17] The presence of 1–3-β-D-glucan (BDG) in serum indicates the presence of fungal invasion but it is not specific for *Aspergillus* species. Several studies carried out in critically ill patients coincidentally found that the diagnostic accuracy of this test is inferior to of BAL GM and comparable to serum GM. Tests such as serum GM, BDG in BAL and specific PCR should be interpreted with caution.[10] In clinical laboratories, species identification to complex level is recommended for all clinically significant isolates and antifungal susceptibility testing of *Aspergillus* isolates should be performed in patients with invasive disease due to the increasing number of resistances.[10,11,17,19]

Once the clinical suspicion is established, antifungal treatment should be started as soon as possible.[11,17,19] Current recommendations are extrapolated from those trials that enrolled mostly onco-hematologic patients in non-critical condition. Voriconazole and isavuconazole should be considered the drugs of choice for treatment of IA in all patients.[11,17] Although voriconazole is the drug with the most scientific evidence, having demonstrated to be an independent variable of survival in different studies, it has been related with adverse effects, interactions and pharmacokinetic difficulties in these populations.[11,17,19] Isavuconazole achieves a high concentration in lungs and is a suitable alternative for voriconazole in critically ill patients with IA, but current information about its use in this subset of patients is scarce.[19] The better tolerance in comparison to voriconazole, with fewer study-drug related adverse events (especially those related with hepatobiliary disorders, eye disorders, and QT elongation), less interactions (moderate CYP3A4 inhibitor and sensitive CYP3A4 substrate) and availability of a water-soluble solution for intravenous administration make this agent more easy to use in critically ill patients.[19] There are no definitive recommendations about the need of monitoring serum levels of isavuconazole, but to monitoring is recommended with voriconazole, even though this triazole is administered intravenously.[11,17] Liposomal amphotericin B is an alternative for primary or salvage treatment for patients who are intolerant, had hepatitis or are refractory or resistant to voriconazole or isavuconazole or when triazole use is not desirable due to drug interactions. There is limited data supporting the use of echinocandins for primary treatment of IA. Antifungal combination therapy should not be generally recommended for primary treatment of IA, but it could be considered in selected patients with documented IA.[11,17] It is worth mentioning that 40–60% of the critically patients included in observational studies received combination therapy for IA. Nebulized antifungal administration is an attractive option for IPA management, especially in intubated patients.[19] Regrettably, no clinical trial has been conducted to determine its efficacy and safety.

In general, global response is defined as surviving the episode and documenting improvements in fungal disease-related alterations, including clinical, radiological and mycological (histological and/or conventional mold isolation) evidence of infection.[10,11,17] However, this evaluation of therapeutic response may be difficult, since response criteria are often based on subjective assessments. Duration of antifungal therapy for invasive aspergillosis is not well defined.[10–12,17,18] There are no studies specifically addressing this issue. Therefore, recommendations emerge mainly from randomized clinical trials that focus on the safety and efficacy of several antifungal agents for the treatment of IA. Several factors influence the decision of determining when to stop antifungal therapy, such as the persistence of the immunosuppressed status, the localization of the disease, and the response to therapy.[11,17] Thus, the decision should be individualized.

In the near future, we will have to decide which patients included in these new populations at risk of aspergillosis should receive prophylaxis, and also in what moment, for how long and with which drug, taking into account the existing options and its particular limitations, such as pharmacologic interactions.

In summary, at present, more than 40% of IA occurs in non-hematological patients with a moderate degree of immunosuppression. A more insidious clinical presentation that often implies a delay in diagnosis and a higher mortality is often observed. On the other hand, choice of treatment in these patients is conditioned by a greater number of drug interactions and toxicities. We must be aware of these new populations at risk of AI, be alert to diagnose the infection as early as possible and to treat it appropriately to reduce as much as possible its high mortality. An era of new challenges in fungal infection has just begun.

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