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Current and future therapies for invasive aspergillosis

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ABSTRACT

Invasive fungal infections have increase worldwide and represent a threat for immunocompromised patients including HIV-infected, recipients of solid organ and stem cell transplants, and patients receiving immunosuppressive therapies. High mortality rates and difficulties in early diagnosis characterize pulmonary fungal infections. Invasive pulmonary aspergillosis has been reviewed focussing on therapeutic management. Although new compounds have become available in the past years (i.e., amphotericin B lipid formulations, last-generation azoles, and echinocandines), new diagnostic tools and careful therapeutic management are mandatory to assure an early appropriate targeted treatment that represents the key factor for a successful conservative approach in respiratory fungal infections.

1. Introduction

Aspergillus spp. belongs to saprophytic fungi that grow on organic debris. Although hundreds of species have been recognized, only few are implicated in human disease. In particular, 90% of cases of pulmonary disease are caused by *Aspergillus fumigatus* due to its production of small spores that can penetrate inside the alveoli [1]. Amongst other species, *Aspergillus terreus* is responsible for less than 5% of invasive forms and *Aspergillus niger* and *Aspergillus flavus* can cause pulmonary and sinus disease.

Autopsy studies have shown the emergence of *Aspergillus* as a major pathogen due to an expansion of the spectrum of patients at risk for invasive aspergillosis (IA). An observational study over a 12-year period in a patient population at an academic hospital evidenced an increase of IFI from 2.2% to 5.1% that was mainly in association with a growth in the rate of *Aspergillus* infection [2]. Nevertheless, the real incidence of IA is difficult to estimate due to the challenges in discriminating between *Aspergillus* colonization and infection, a low number of autopsies performed that can prove definite diagnosis, and the absence of specific radiological signs especially in non-neutropenic patients.

Considering that *Aspergillus* virulence factors are of a multifactorial origin, the principal element linked to the disease presentation and progression remains the host immune status [3]. Specifically, the alveolar macrophages have a conidiocidal activity that may be impaired by steroid suppression [4]. Furthermore, the second line of defence from conidia that have germinated into hyphae is constituted by neutrophils that may be lacking or not functioning in case of chemotherapy or leukaemia [5]. Finally, T-cell dysregulation contribute to persistent and invasive *Aspergillus* infection [6].

Thus, *Aspergillus* species produce a spectrum of diseases that may present with features typically related to host factors [7]. Besides disseminated and invasive aspergillosis, other forms include allergic bronchopulmonary aspergillosis, aspergilloma, chronic necrotizing aspergillosis, tracheobronchitis, and acute invasive rhinosinusitis.

Aggressive forms of IA typically occur in immunocompromised patients. Conversely, chronic forms of pulmonary aspergillosis such as chronic necrotizing pulmonary aspergillosis or fibrocavitary aspergillosis that progress over months to years are more often seen in patients without severe immune deficiency and may complicate existing lung diseases associated with cavities or bullae.

1.1. Acute invasive pulmonary aspergillosis (IPA)

Aggressive forms of acute invasive aspergillosis typically occur in patients with impaired immune systems such as haematological patients, recipients of solid organ transplant, and, less commonly, patients with advanced HIV infection [8].

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Typical features include the presence of hyphal angioinvasion with vascular thrombosis and tissue infarction. Normally, scant inflammatory response is present due to the lack of immune activation. Possible evolution is represented by lung cavitation. The main risk factors for this acute clinical presentation is represented by neutropenia (i.e., acute leukaemia, stem cell transplant, chemotherapy).

Clinical signs and symptoms are often nonspecific. Fever is commonly present and may be associated with dry cough, chest pain, and occasionally haemoptysis [9].

Recipient of solid organ transplant, characterized mainly by T-cell impairment in the first 6 months post-transplant, often present with acute inflammatory pneumonia. In particular, chronic necrotizing aspergillosis and tracheobronchitis affecting the anastomotic site can progress causing dehiscence in lung-transplant recipients [10].

In HIV-infected patients progressed to AIDS, acute to slowly progressive necrotizing pneumonia due to *Aspergillus* infection may present variable histologic findings with neutrophilic infiltrates, vascular invasion, pulmonary abscesses, and cavitation.

1.2. Chronic pulmonary aspergillosis

Other chronic forms of *Aspergillus* infection of the lung have been described, namely chronic necrotizing pulmonary aspergillosis (CNPA), symptomatic pulmonary aspergilloma, and *Aspergillus* pseudotuberculosis. The distinction between subacute IPA, CNPA, and aspergilloma has not been well defined, and an overlap in clinical and radiological features among these different forms exists. Subacute IPA has been associated with advanced HIV-infection, chronic granulomatous disease, diabetes mellitus, alcoholism, and corticosteroid therapy [11]. Subacute and chronic forms of pulmonary aspergillosis (e.g., chronic necrotizing pulmonary aspergillosis or fibrocavitary aspergillosis) typically occur in patients without severe immune impairment where the inflammatory response plays a role into disease progression. Developing pneumonia is generally characterized by pyogranulomatous inflammation without hyphal vascular invasion or coagulative necrosis. Weight loss, chronic cough (often with hemoptysis and shortness of breath), fatigue, and chest pain represent the most common symptoms.

A study has recognized three distinct radiological patterns of non-acute infection: chronic cavitary pulmonary aspergillosis, characterized by the formation and expansion of multiple cavities possibly containing fungus balls; chronic fibrosing pulmonary aspergillosis, with an extensive pulmonary fibrosis; subacute IPA, with enlargement of a single cavity, usually with a thin wall, occurring slowly over months or rapidly in weeks [12]. Since risk factors such as diabetes and corticosteroid use are commonly associated to these forms, it is estimated that chronic pulmonary aspergillosis has a high global disease burden and is associated with significant under diagnosis. Furthermore, other risk groups for IA include patients with chronic obstructive pulmonary disease (COPD) and patients with cirrhosis due to a generalized depressed phagocytosis status. The analysis of a group of 16 patients with COPD receiving steroid treatment who had proven or probable IA required ICU admission and displayed poor outcomes [13]. Furthermore, with the introduction of new monoclonal immunosuppressive agents it is expected that new categories at risk for IA will arise [14].

1.3. Epidemiology

The classic risk factors for IA have been highlighted by the EORTC/MSG [15,16], but nowadays they do not represent the broadeness of immunesuppression caused by, for example, structural lung diseases, HIV and critical illnesses [17] together with the issue of hospitalization. Patients with pulmonary or invasive aspergillosis may have a complex interplay between the host, the underlying disease and the immune function at a molecular and cellular level, often with the addition of systemically administered setroids. In one study with 94 biopsy-proven severe alcoholic hepatitis episodes, 16% were diagnosed with aspergillosis after a median of 26 days by the diagnosis of hepatitis [18].

In the ICU most of patients who develop IA are not neutropenic [19–21] and COPD and solid-organ transplant are more common underlying condition, not limited by parenchymal disease but including tracheobronchial disease [19,22–24]. There are studies showing that IA may be equally recognized in the ICU patients with COPD or immunocompromised [25], that Aspergillus isolation should raise the suspicion of IA not just in patients with GOLD III–IV classes [24] and also that, in addition to steroids, risk factors include treatment with at least three antibiotics during hospitalization and antibiotic treatment for at least ten days [26] (Table 1). The issue of aspecific radiological signs, compared to neutropenic patients, needs to be considered with special reference to angioinvasive or airway-invasive pulmonary aspergillosis and the timing of disease or of the chest CT scanning [27,28].

Meersseman et al. divided into three categories the risk factors for IPA in ICU patients: high, intermediate and low risk [29], well recognizing that the latter category is very broad, and also a clinical algorithm was suggested and externally validated on the basis of positive respiratory cultures [30,22]. By the algorithm, a new diagnostic category of "putative" IPA was described, mainly representing frequent aspecific clinical and radiological signs which may delay diagnosis and treatment, with difficulties in differentiating between colonization and infection [27,31,32]. Interestingly, the algorithm judged 38% of patients to have putative IA and 47% colonization, achieving a 32% higher diagnosis rate and probably encompassing a broader proportion of the true IPA burden in the ICU [22].

The issue of invasive aspergillosis during hospitalization in patients with acute or chronic liver failure has been highlighted in a recent study where 5% of 787 patients developed IA [33], with independent risk factors including older age, encephalopathy and steroid use. It is well known that construction, renovation or demolition in the hospital or around the hospital may be linked to at least half of nosocomial aspergillosis outbreaks [34], even suggesting that in the ICU setting the indoor air concentration of *Aspergillus* spp. conidia might be a potential determinant of the frequency of IPA [35].

Table 1
Risk factors for IPA.

Recent history of severe neutropenia (<500/microl for >10 days)
Allogeneic stem cell transplant
Prolonged steroid use (>0.3 mg/kg/day prednisone equivalent > 3 weeks)
T-cell immunosuppressant treatment during the previous 3 months (e.g. cyclosporine, TNF-alpha blockers, specific monoclonal antibodies, or nucleoside analogues)
Inherited severe immunodeficiency
"Additional risk factors"
Chronic obstructive pulmonary disease (COPD)
Acquired immunodeficiency syndrome (ARDS)
Solid-organ transplant (SOT) recipient
Decompensated liver disease
Severe alcoholic hepatitis
Critically ill patients with severe sepsis
H1N1 critically ill patients
Critically ill patients with ECMO support
"Environmental risk factors"
Fungal contamination of indoor air: construction or demolition works in the hospital or its environment

Adapted from Ref. [17].