Review

Invasive pulmonary Aspergillosis in organ transplants – Focus on lung transplants

Christian Geltnera,⁎, Cornelia Lass-Flōrlb

aDepartment of Pulmonology, Academic Hospital Klinikum Klagenfurt am Wörthersee, Feschnigstr. 11, A-9020 Klagenfurt, Austria
bDivision of Hygiene and Medical Microbiology, Medical University of Innsbruck, Innsbruck, Austria

Abstract

Infections with filamentous fungi are common in transplant recipients. The risk for aspergillosis and other invasive pulmonary mycosis (IPM) is high in patients undergoing stem cell and lung transplantsations. The mortality rates range from 20% to 60% and depend on a number of risk factors. The typical manifestations of IPM are lung infiltrates, consolidations, and fungal tracheobronchitis. The most common infectious agent is Aspergillus fumigatus. Infections caused by non-Aspergillus molds are more frequent for various reasons. The species distribution of non-Aspergillus molds varies in different locations. Furthermore, infections caused by Mucor and Penicillium are increasing, as are infections caused by species resistant to azoles and amphotericin B. Most centers use antifungal prophylaxis with inhaled amphotericin B or oral azoles. Early diagnosis and therapy is crucial. Reliable information on the local microbiological spectrum is a prerequisite for the effective treatment of molds with primary or secondary resistance to antymycotic drugs.

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1. Introduction

The number of patients with acquired immunodeficiency due to transplantations, antitumor chemotherapies, antirheumatic drugs, and various lymphocytotoxic monoclonal antibodies is increasing. The results of solid organ transplantations for end-stage disease are promising, and the overall incidence of these procedures is increasing worldwide. In the United States, the total number of organ transplantations performed has reached 90,000 per year. In 2013, more than 3800 lung and 4200 heart transplantations were performed worldwide [1,2].

The overall 5-year survival rates range from 70% for lung transplantations to >90% in heart and kidney transplantations. This survival benefit and the favorable outcome mainly result from improvements in immunosuppression, antifungal treatment, and surveillance strategies. Among a wide range of adverse effects and complications after solid organ transplantations, infections are very common and potentially life threatening. The most problematic infectious agents are viral and fungal pathogens.

Unlike in North and South America, where endemic fungal infections such as cryptococcosis and blastomycosis occur with a high incidence, in Europe and Eastern Asia pulmonary fungal infections are common in immunosuppressed patients with acquired or iatrogenic immunosuppression. Invasive pulmonary aspergillosis (IPA) is almost exclusively a disease of compromised immunity typically occurring in transplant recipients and patients with acquired immunodeficiency syndrome; however, it is also increasingly seen in chronic steroid therapy, anti-tumor necrosis factor therapy, prolonged critical illness, severe chronic obstructive pulmonary disease (COPD), and after cardiothoracic and vascular surgery [3].

2. Incidence and frequency of filamentous fungal infections in solid organ and stem cell transplantations

In an incidence study on aspergillosis, Morgan et al. [4] presented results for invasive fungal disease. Lung transplant (cumulative incidence [CI], 3.5%/year) followed by allogeneic (CI, 2.3%/year) and autologous stem cell transplant (CI, 0.8%/year) and other organ transplant recipients were the most common patients affected by fungal infections. The mortality rate of invasive pulmonary mycosis was 53% and 76% in autologous and allogeneic hematopoietic stem cell transplantation (HSCT), respectively, whereas the mortality rate in solid organ transplant (SOT) patients ranged from 20% to 66%. A prospective 2-year nationwide Austrian Aspergillosis registry study [5] gives an insight into the local epidemiology, which depends very much on the respective transplant unit, and the local endemic situation and prevalence. This study also showed that patients with acute myeloid leukemia (AML), non-Hodgkin lymphoma, acute lymphatic leukemia, and various organ transplants are also prevalently affected. All patients had lung involvement; a third of the patients had proven, probable, or possible aspergillosis of the lung according to the international EORTC/MSG (European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group) classification [6,7]. The risk factors for the development of invasive fungal disease were neutrophil count <500 cells/mm³, immunosuppressive therapy, and corticosteroid therapy. Of the patients, 43% received antifungal prophylaxis for >7 days, of whom 30% (24 patients) had a breakthrough fungal infection [2]. Most of the detected fungal pathogens were Aspergillus spp. (67%), followed by mucormycetes (28%) and others (4%). Mortality depends on comorbidity. Among SOT patients, hepatic insufficiency, malnutrition, and central nervous system disease were poor prognostic indicators [8].

3. Aspergillosis and filamentous fungi after lung transplantation

An overall increase of fungal infections is observed in lung transplant recipients. In 2003, Singh [9] described a prevalence of 6.5% of invasive fungal infections with a mortality rate of 52%, the common sites of infection being the bronchial...
anastomoses. Invasive and disseminated fungal diseases occurred in 34% and 22%, respectively.

The local epidemiology is crucial: the largest German lung transplantation program in Hannover describes fungal colonization in 28% of patients and invasive fungal infection in 5.6%; this fact led to a comprehensive oral prophylaxis withitraconazole or voriconazole [10]. Other centers describe a reduction of incidence from 25% to 5% by means of a chemotherapeutic prevention. The Austrian registry mainly included lung-transplanted patients from Innsbruck with a very high incidence of *Aspergillus terreus* as well as an increasing number of non-*Aspergillus fumigatus* fungal infections. The occurrence of infections after lung transplantation (analogous to other SOT) can be assigned to time. There is a frequency distribution in the occurrence of infections depending on the time of transplantation (Fig. 1), and the risk of IA in organ transplant recipients correlates with the intensity of immunosuppression [11]. Cytomegalovirus (CMV) infection and renal dysfunction are immunomodulatory conditions known to heighten the immunosuppressive state [12].

Infection with filamentous fungi is an independent risk factor for the development of oblitative bronchiolitis (bronchiolitis obliterans syndrome, BOS) and correlates with progressive organ failure [13]. The authors hypothesized that colonization with small *Aspergillus conidia* is associated with a greater risk of BOS, based on an increased likelihood of deposition in small airways [14]. The lung itself is an open system connected to environmental air and microbes. It serves as an immunologically active organ; hence, a high immune suppression is usually necessary to control acute and chronic rejection. This explains the high incidence of infectious complications compared with other organ transplant recipients. The use of antifungal prophylaxis (mostly withitraconazole, voriconazole, and inhaled amphotericin B) compared with preemptive antifungal therapy showed a clear benefit concerning the reduction of colonization rates [15].

### 4. Appearance of fungal infection in the lung

In immunocompetent patients, saprophytic aspergillosis may be present in preformed pulmonary cavities (aspergilloma) or as small nodules. Allergic bronchopulmonary aspergillosis is a hypersensitivity lung disease that is associated with inflammatory destruction of airways in response to *Aspergillus* species. It typically occurs in immunocompetent patients associated with IgE elevation, allergic asthma, and bronchiectasis. Compared with immunocompetent patients, the clinical manifestation of fungal infection can vary in cases of immunosuppression.

Lung involvement is present in all SOT recipients, stem cell transplant (SCT) recipients, and other immunocompromised hosts. Systemic disease, fungal sepsis, and multiorgan failure can be a fatal complication. *Aspergillus* infections in the lungs and other pulmonary mycoses have different appearances.

#### 4.1. Airway colonization

The significance of fungal colonization especially in transplant recipients is unclear. However, at any time, colonization may progress to IA. In immunocompromised patients, treatment recommendations are based on the presence of risk factors.

#### 4.2. Invasive pulmonary aspergillosis

- Proven IA (biopsy proven, demonstration of fungal elements in infected tissue).
- Probable IA (host factor+clinical factor+microbiological culture).
- Possible IA (host factor+clinical factor).

The criteria for host and clinical factors mentioned in the guidelines for the diagnosis of IA lead to the secure management of these patients.

#### 4.3. Tracheobronchial aspergillosis and anastomositis

This manifestation of a semi-invasive and potentially invasive form of Aspergillus infection in lung transplant recipients covers plaques, lawn fungus, ulcerations, pseudo-membranes, and granulation tissue within the bronchial system. This manifestation form of aspergillosis is typical for lung transplant recipients.

As frequent laboratory monitoring and bronchoscopies are routinely performed in lung transplantations, 80% could be classified as “proven IA.” The features of invasive fungal disease are shown in Fig. 2.

Bronchoscopic examination is the gold standard in diagnosing bronchial aspergillosis and fungal invasion. The anastomotic region is the predominant site of infection. Fig. 3 shows typical endoscopic views of different anastomotic diseases after lung

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**Fig. 1 – Timeline of infectious complications after solid organ transplantations (especially lung transplantations).** The risk for bacterial pneumonia is greatest in the first 4 weeks and decreases after 3 months, whereas the risk for cytomegalovirus infection peaks after the discontinuation of antiviral prophylaxis similar to pneumocystis. Molds, yeasts, and parasites mainly occur in the first 3–12 months. CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein-Barr virus; PTLD, post transplant lymphoproliferative disease; PCP, pneumocystis carinii pneumonia. Modified from Ref. [35].

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transplantation. A “normal” anastomosis with tissue necrosis and some granulation is often present in the first months after transplantation (Fig. 3-3). This has to be distinguished from the rare surgical complication of anastomosis dehiscence where fistulae to the mediastinum sometimes become visible. Mold infection, colonization with Aspergillus, or other invasive pathogens are shown in Fig. 3-2. The worst scenario is a deep necrotizing bronchitis with bacterial and fungal superinfection and destroyed bronchial mucosa, and sometimes necrosis of the entire bronchial wall (Fig. 3-1).

Singh et al. showed that clinical outcomes were better in lung transplant recipients with nodular than nonnodular presentations of IA. The mortality rate ranged from 25% to 64%, respectively. Usually, cases of IA in lung transplant recipients appear as pulmonary disease; disseminated aspergillosis occurs infrequently. Indeed, the rates of disseminated disease are generally lower in lung transplant recipients than in other organ transplant recipients [16].

Recently, immunoreconstitution syndrome (IRS) was described as a new pathomechanism of lung disease. After the reduction of immunosuppression in case of the occurrence of invasive fungal disease, an enhancement of symptoms and infiltrates has been demonstrated [17]. Host defense against Aspergillus and other molds is mediated through T-helper cells. Th1 (CD4+ cells) (protection and enhancement of the antifungal activity of polymorphonuclear cells against Aspergillus) and Th2 cells (CD8+) (facilitation of disease progression by inhibition of phagocyte-mediated hyphal damage, oxidative burst, and Th1 neutralization) are necessary for a sufficient antifungal defense of the immune system [18,19]. The typical manifestations of IRS in lung transplants include the new onset or progression of pulmonary infiltrates, consolidation, pleural effusions, cavitation, or respiratory failure.

5. Diagnostic measures in invasive pulmonary aspergillosis

Radiologic examination supports the diagnosis of suspected aspergillosis (possible or probable IA), and computed tomography
A 54-year-old male patient was treated with unilateral lung transplantation (left) for α-1-antitrypsin-deficiency (phenotype ZZ). The immunosuppressive regimen consisted of daclizumab induction, tacrolimus, mycophenolate mofetil, and tapered steroids. Four months after the transplantation, he developed post transplant lymphoproliferative disease (PTLD) and therefore received antitumor chemotherapy (R-CHOP) and alemtuzumab. As complication of the augmented immunosuppressive therapy an infection with an invasive mold occurred. The disease started with a coin lesion. Later disseminate pulmonary infiltrates developed. Final diagnosis and cause of mortality was invasive pulmonary mycosis due to Penicillium chrysogenum [24].

### 6.4. Case 4

Case 4 demonstrates a 52-year-old female patient who underwent bilateral lung transplantation in 2006 for COPD and emphysema. Three years after the transplantation and routine immunosuppression with daclizumab, tacrolimus, mycophenolate, and steroids, PTLD (Epstein–Barr virus+,...
CD20+ non-Hodgkin lymphoma occurred. Treatment with rituximab caused a high level of immunosuppression and was probably the basis for the development of invasive fungal disease despite antifungal prophylaxis with posaconazole (200 mg tid). Bronchoscopic examination revealed invasive mold infection due to Absidia corymbifera (Fig. 5).

7. Mycological spectrum and emergence of non-Aspergillus species

The most common filamentous fungi are A. fumigatus followed by Aspergillus niger, A. terreus, and A. flavus. The occurrence of non-A. fumigatus species is crucial, and knowledge about these species is important for therapeutic decisions and outcome, especially in case of fungal invasion. A. terreus is genuinely resistant to amphotericin B. In the last years, a shift to non-Aspergillus fungi has often been demonstrated in several studies. A retrospective analysis of 2898 SOT recipients by Stelzmüller et al. showed 12 patients with a non-Aspergillus infection in 2008 [25]. Rare species such as mucormycetes, Mucor sp., Pseudallescheria sp., and Alternaria sp. occurred. Treatment with antithymocyte and antilymphocytic monoclonal antibodies for PTLD was found to be the main risk factor. Concomitant diseases and host factors such as graft-versus-host disease (GvHD), diabetes, and chronic renal failure complicated the postoperative course and led to higher levels of immunosuppression. In lung transplant recipients, a similar trend was seen: 24% of a total of 25 patients with invasive pulmonary mycosis showed infection with mucormycetes and Penicillium species [26]. In these patients, a temporarily increased immunosuppression occurred because of refractory acute rejection or post transplant lymphomas. Of the 25 patients with proven invasive pulmonary mycosis, 14 had classic fungal disease with A. fumigatus, 5 with other Aspergillus species (A. terreus and A. niger), and 6 presented with non-Aspergillus molds (Absidia sp., Scedosporium sp., Penicillium sp., and Mucor sp.). The Hannover lung transplant group described an emergence of mucormycetes as colonizers in 65 of 580 patients after lung transplantation. Several of these colonized patients developed invasive diseases [27]. The treatment of fungal diseases in the presence of primary or secondary resistant pathogens in patients without host defense is challenging.

In 1995, cases of mucormycosis were described in a kidney transplant recipient for the first time. A shift to lung transplants occurred later, and was published recently [28]. These molds are naturally resistant to voriconazole and echinocandins. The frequent use of these new antifungals for prophylaxis and/or treatment and high levels of immunosuppression are probably responsible for the widespread occurrence of azole-resistant filamentous fungi in immunosuppressed patients [29].

8. Prophylaxis in HSCT

In all HSCT patients, prophylaxis with posaconazole (200 mg tid orally) or fluconazole (400 mg daily) is usually recommended [30]. Posaconazole is the drug of choice for the prophylactic treatment in allogenic SCT with GvHD and for AML. Fluconazole alone can be given for allogenic SCT recipients without signs of GvHD. There is an IIIB recommendation for inhaled amphotericin B in neutropenic patients.

Breakthrough infections after or during prophylaxis with posaconazole occur in up to 17% of patients. As seen in other immunocompromised patients, a shift to infections with non-Aspergillus molds such as mucormycetes, e.g., Mucor or Penicillium spp., is observed [31].

9. Prophylaxis in SOTs

Usually, inhaled prophylaxis with amphotericin B or liposomal amphotericin is given in centers performing lung transplantations. The duration of treatment is at least 3 months and/or until the complete healing of the anastomoses (see Fig. 3). Some centers have changed to oral prophylaxis with voriconazole or posaconazole in the first month up to 1 year. Prophylaxis is recommended in case of augmented immunosuppression during treatment of rejection, concurrent viral infection, especially CMV reactivation, administration of monoclonal antibodies (anti-CD54 or anti-CD20), or antilymphocytic substances. Surveillance and frequent bronchoscopies facilitate an early diagnosis.
10. Therapeutic considerations

The strategies for prophylaxis and for preemptive therapy depend on the local epidemiology and the risk of infection. The Infectious Diseases Society of America guidelines for the treatment of invasive pulmonary mycosis provide recommendations for the diagnosis and treatment in these cases [33]. Knowledge of the endemic situation and the resistance profile of pathogens involved in infections are essential for early intervention. Pathogen specification is usually not available at the time of radiological or clinical suspicion of invasive disease. The occurrence of amphoterin B-resistant molds such as A. terreus, or the emergence of secondary resistance to voriconazole or posaconazole, challenges the choice of antifungal drugs applied as first-line treatment. In lung transplant recipients, the early commencement of a sufficient antifungal pharmacotherapy is essential. Several epidemiologically based studies display a high rate of primarily resistant molds responsible for fungal infections (25%), e.g., mucormycetes or A. terreus. At our institution, the rate of non-Aspergillus molds is 25%, and the rate of A. terreus (primarily resistant to amphoterin B) is up to 20%. Therapeutic algorithms have to be adapted bearing these regional influences in mind (Fig. 6). The primary drug approach has to be set depending on the probability of fungal invasivity and the individual risk situation of the patient. The first-line use of echinocandins is recommended if Candida is more likely than Aspergillus. Voriconazole is recommended in the case of probable or possible IA. In case of countable risk of infections with non-Aspergillus fungi, an upfront combination therapy can be discussed unless typing and resistance profile is done. De-escalation and modification of therapy starts after the final diagnosis of the underlying pathogen, and with the availability of resistance profiles.

11. Innate drug resistance of non-A. fumigatus species and therapeutic implications

Several of the molds mentioned have innate resistance to various antifungal drugs. Aspergillus spp. other than A. fumigatus are resistant to amphoterin B (especially A. terreus). The antymycotic drugs of choice are therefore voriconazole, posaconazole, or echinocandins. Mucomycetes are resistant against voriconazole and have low sensitivity to echinocandins. According to ECIL-3 (Third European Conference on Infections in Leukemia) guidelines, the options for the first-line chemotherapy of mucormycosis include liposomal amphoterin B and amphoterin B lipid complex. Posaconazole and a combination therapy of liposomal amphoterin B or amphoterin B lipid complex with caspofungin are options for second-line treatment. Surgery is recommended for rhinocerebral and skin and soft tissue diseases [34]. Penicillium spp. are mostly sensitive to voriconazole and posaconazole but do not respond to amphoterin or amphoterin lipid complex.

The first-line therapy is difficult, and combination therapies can be useful. As the exact typing of these molds is usually not available at the time chemotherapies should be started, the choice of drugs has to be influenced by local epidemiology. The combination of two new drugs is recommended until susceptibility testing is available.

12. Summary

Invasive pulmonary fungal infections are common in immunosuppressed patients (SCT and lung transplant recipients). Depending on the local epidemiology, an increase of non-Aspergillus infections with mucormycetes, Alternaria sp., and Penicillium sp. are on the rise. These pathogens are difficult to treat; hence, early diagnosis is required. Prophylaxis is recommended in specific cases.

Conflict of interest

Christian Geltner received honoraria for lecturing and travel fees from Eli Lilly, Böhringer Ingelheim, Menarini, Novartis; Cornelia Lass-Flörl was funded by Pfizer, Gilead Sciences, Merck Sharp and Dohme, Astellas and Schering Plough and received honoraria for lecturing and advisory.
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