13 Special Issue: Fungal Infection in Patients with Organ Transplantation

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13.1 Introduction

The ubiquitous presence of fungal spores leads to a continuous contact of inner and outer body surfaces to these potential pathogens. The immunological defense system of healthy individuals effectively protects the body against fungal infections. But an impairment of the immunologic system is one of the main factors, which makes patients prone to suffer from fungal colonization and topic or invasive fungal infections. Immunocompromised patients are found in the settings of hematological or solid cancer diseases, human immunodeficiency virus (HIV) infection, stem cell transplantation, solid organ transplantation (SOT), and neonatology as well as prolonged intensive care dependency after major trauma, surgery, or burns.

13.2 Solid Organ Transplantation (SOT)

Each year over 120,000 organ transplantations were performed worldwide. Due to high surgical expertise and a steady progress in the management of possible transplant candidates as well as of transplant recipients, the constantly improving outcomes of organ transplantations led to a common acceptance of more liberal indications for these lifesaving procedures. Subsequently the number of transplant recipients, suffering from severe comorbidities, belonging to extreme age groups, exhibiting an increased immunological risk profile, or simply undergoing re-transplantation, is tremendously rising. Despite a more individualized and closely monitored immunosuppressive therapy, the recipients of organ grafts are prone to infections. The combination of the impairment of the immune status, major surgery, intensive care dependency, extracorporeal organ replacement therapy, and a preexisting chronic illness is responsible that posttransplant infections are still one main cause of mortality in these patients. Also donor-derived fungal infections are described; their incidence is very low [1]. Between 2005 and 2011, only 31 confirmed transmissions of donor-derived fungal infection were reported in the USA. In the same time period, almost 200,000 organ transplantations were performed in the USA [2].

Among SOT recipients the overall 1-year cumulative incidence of invasive fungal infections (IFI) is 5.6% [3]. Invasive candidiasis (IC) is the most frequent IFI and is diagnosed in 1.9–4.0% of all SOT patients during the first 12 months after transplantation [4]. About 50% of these fungal infections were caused by *Candida albicans*, followed by *C. glabrata*, and less frequent by *C. krusei* and *C. guilliermondii* [4]. The incidence of invasive aspergillosis (IA) in SOT is 0.65–15% [3, 5]. To a far lesser extent,

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IFI are caused by *Cryptococcus* spp., non-*Aspergillus* molds, *Mucormycetes*, or other rare fungi.

The time of onset of IFI in SOT mostly follows a specific pattern depending on the etiologic fungus and the transplanted type of organ. Whereas IC occurs early after transplantation (median, 179 days after transplantation), IA shows a more delayed onset (median, 400 days after transplantation) [6]. Infections due to *Cryptococcus* spp., *Mucormycetes*, and other rare fungi generally occur later after SOT. It is important to keep in mind that these time patterns are not valid in the setting of re-transplantation.

In SOT recipients the diagnosis of fungal infections is hindered by several influencing factors. On one hand the typical immunologic response to pathogens is depressed by the immunosuppressive therapy, and on the other hand, the surgical trauma during implantation or the rejection of the transplanted graft causes reactions like fever and/or an increase of inflammatory markers. The broad use of antibiotics and of antifungal prophylaxis interferes with the results of antigen or (1-3)-β-D-glucan tests. Also high-resolution computer tomography, PCR-based diagnostics, and galactomannan assays may be helpful in certain clinical situations; definitive diagnosis can only be achieved by blood cultures or cultures of sterile tissue, liquid, and biopsy samples.

13.2.1 Immunosuppressive Therapy in SOT

To achieve the necessary grade of host tolerance to protect the transplanted organ against rejection, a combination of different immunosuppressive agents is applied. At the time of transplantation, the induction therapy is facilitated by the use of corticosteroids, polyclonal antibodies (i.e., antithymocyte globulins), or monoclonal antibodies (i.e., basiliximab, alemtuzumab, etc.). Mostly the immunosuppressive maintenance therapy consists of three pillars: the concomitant application of corticosteroids, calcineurin inhibitors (cyclosporin A, tacrolimus), and proliferation inhibitors (azathioprine, mycophenolate acid, mTOR inhibitors) is widely used to reduce side effects and provoke sufficient immunosuppression. In the case of rejection episodes, corticosteroids, antithymocyte globulins, or murine monoclonal anti-CD3 antibodies (OKT3) are in use to save the transplanted graft.

Corticosteroids suppress the production of pro-inflammatory cytokines as prostaglandins, tumor necrosis factor (TNF-α), interleukins (IL-1, IL-2, IL-6), and many others. Calcineurin inhibitors (CNI) block the production of IL-2 and in consequence the activation of B-cells and T-cells. The proliferation of these cells as well as the DNA synthesis of other proliferating cells is markedly impaired by agents like mycophenolate or azathioprine [7].

All these mechanisms to prevent rejection of a transplanted organ interfere with the ability of the human body to protect itself from infection and invasion of pathogens like bacteria, viruses, and fungus.

Many interactions between immunosuppressive agents and concomitant administered medications are well known. In the context of fungal infections, the effect of azoles in SOT is of special importance. All azoles cause increased levels of calcineurin inhibitor serum concentrations. Therefore the dosage of calcineurin inhibitors has to be adjusted. With exception of isavuconazole, all azoles cause a prolongation of the QT time, an effect that is intensified by concomitant administration of tacrolimus. Because liver transplant recipients exhibit a high incidence of QT-time prolongation, the described effect is of special interest in this patient population.

13.2.2 Kidney Transplantation

Despite the longest waiting time for organ transplantation and the dependency on renal replacement therapy (RRT), sometimes over many years, recipients of a renal graft have the lowest incidence of invasive fungal infections (IFI) compared to all other SOT groups. The onset of IFI occurs in kidney transplantation typically late. A delay of more than 2 years between transplantation and the diagnosis of an IFI is not uncommon

[6, 8]. Over 90% of observed IFI are due to *Candida* spp. The overall incidence of IFI in these patients is stated with 1.3% [3]. The incidence of invasive aspergillosis (IA) is as low as 0.7% [9]. Typically invasive infections only occur in highly immunosuppressed patients and in the setting of re-transplantation or are facilitated by other infective or surgical complications and prolonged intensive care dependency. Although the incidence of IFI in kidney transplantation is low, the mortality of these infections exceeds 75%. Nevertheless universal antifungal prophylaxis in the setting of kidney transplantation is not recommended [10].

More frequent than from IFI, the kidney recipients suffer from candiduria, with an incidence of 3–11% [11]. The treatment of candiduria consists, besides the removal of indwelling urinary catheters and ureter stents, of systemic application of antifungals, which penetrate well into the urinary tract [12]. In selected cases antifungal bladder irrigation may be appropriate.

For systemic treatment of urinary tract infections caused by fluconazole-susceptible organism in this population, fluconazole (3–6 mg/kg, daily for 24 days) is recommended. Fluconazole-resistant organism should be treated with amphotericin B (AmB) deoxycholate (0.3–0.6 mg/kg, daily for 1–7 days), with oral flucytosine (25 mg/kg, four times daily for 14 days), or with a combination of AmB deoxycholate and oral flucytosine [12]. One major drawback of AmB deoxycholate in this setting is its nephrotoxicity, which can limit the use of AmB especially in patients receiving CNI for immunosuppression. In severely immunocompromised patients and in suspected systemic dissemination of the infection, antifungal therapy should be expanded with an echinocandin without delay. AmB deoxycholate (50 mg/L sterile water) is recommended for daily bladder irrigation for a period of 5 days [12].

13.2.3 Pancreas Transplantation

The incidence of fungal infections in pancreas transplant recipients is between 3.4 and 38% [3, 8, 9, 13]. Almost all infections are caused by *Candida* spp. [3]. General risk factors are long-standing diabetes, concomitant renal insufficiency with RRT, enteric pancreas drainage, and induction therapy with antithymocyte globulins. Special risk factors for fungal infections are vascular graft thrombosis, posttransplant pancreatitis, posttransplant re-laparotomy, enteric anastomosis insufficiency, and re-transplantation [10]. It is recommended to use a universal prophylaxis for all pancreas recipients with fluconazole (4–6 mg/kg q24 h) [4, 10]. Due to the interaction of fluconazole and the CNI levels, the increase in fluconazole-resistant candida species, as well as the growing number of patients exhibiting special risk factors for IFI, the use of an echinocandin in the prophylactic setting appears as reasonable.

13.2.4 Liver Transplantation (LT)

The population of liver transplant recipients shows a large heterogeneity related to the risk profile for IFI. Transplant candidates with oncological indications (i.e., hepatocellular carcinoma), who present with a normal liver function and who did not undergo prior abdominal surgery, exhibit no increased risk for IFI. On the other hand, patients, who were referred to transplantation because of acute or acute on chronic liver failure and who are treated on intensive care units prior to transplantation, show a tremendous risk for suffering from fungal infection. IFI in LT recipients are despite maximal antifungal therapy accountable for mortality rates up to 72% [14, 15].

The overall incidence of fungal infection in liver transplant recipients is described as high as 5–42% [14, 16]. In recent published studies, the incidence of IFI in LT declines due to improved perioperative management and broader use of antifungal prophylaxis. An analysis of 386 LTs performed between 2006 and 2013 at one single center showed without using universal antifungal prophylaxis an overall incidence of IFI of 10.1% and an incidence of 4.1% in the group of low-risk recipients [17]. Most fungal infections in the setting of LT are caused by *Candida* spp. (80%),

followed by *Aspergillus* spp. (15%), and other rare fungi. Within the *Candida* spp. infections, an increase of IFI due to non-*albicans Candida* species is reported. *Infections due to Candida* spp. occur earlier after LT then caused by *Aspergillus* spp., *Mucormycetes*, *Cryptococcus* spp., or other filamentous fungi. Despite the later onset of infections due to filamentous fungi, up to 75% of IFI due to *Aspergillus* spp. were diagnosed within the first 6 months after LT [6]. In a retrospective study, Raghuram et al. demonstrated that within 1, 3, and 6 months after LT, 67%, 81%, and 91%, respectively, of the IFI were observed [14].

Risk factors for IFI in patients undergoing LT were identified by many authors and are accepted as basis for decisions to initiate antifungal prophylaxis. The following factors predispose LT recipients for fungal infections: re-transplantation, prolonged operation time, need for re-laparotomy, transfusion requirements ≥40 blood products, impaired graft function, renal insufficiency, RRT, pretransplant ICU dependency, choledochojejunostomy, model of end-stage liver disease (MELD) score ≥25, prior fungal colonization or infection, pretransplant treatment with antibiotics, prior spontaneous bacterial peritoneal infections, and CMV infections, accumulating more than 6 g of prednisone within the first 12 weeks after LT [10, 14, 18, 19].

Considering these factors it is possible to grade the risk for fungal infections of the potential LT recipients into a low- and high-risk group. Universal antifungal prophylaxis should only be applied to patients belonging to the high-risk group. The recommended antifungal prophylaxis can be maintained with an echinocandin or a lipid formulation of amphotericin B. The prophylaxis should be applied for 2–4 weeks and should not be terminated if the risk factors did not resolve [10].

Early treatment of suspected fungal infections in LT recipients is crucial. Because of the high mortality rates due to IFI in these patients, also empiric treatment should be initiated with antifungals which exhibit broad activity against *Candida* spp. After identification of the fungus, a step-down therapy, if possible, is recommended. In cases where the transplantation was done more than 3 months before the onset of the suspected fungal infection, an agent with activity against *Aspergillus* spp. should be considered. Despite the possible hepatotoxicity of antifungal agents, the number of therapy discontinuations in LT recipients is low. The highest number of discontinuation of antifungal treatment has been described for AmB formulations and for itraconazole [20]. The rise of liver enzymes in conjunction with the use of echinocandins is reversible and in the clinical setting of LT is mostly irrelevant (Fig. 13.1).

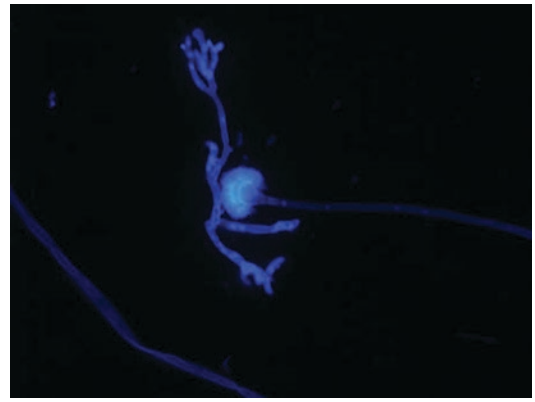

Fig. 13.1 Mixed fungal infection with *Aspergillus* spp. and *Mucormycetes* in a highly immunocompromised patient after liver re-transplantation. Courtesy of Dr. Maria Aigner, Division of Hygiene and Medical Microbiology, Medical University of Innsbruck, Innsbruck, Austria

13.2.5 Heart Transplantation

Besides kidney transplantation the recipients of heart transplants show the lowest incidence of fungal infections. In the literature the overall incidence of IFI in heart transplantation (HT) is described with 5% to 10.7% [9, 21, 22]. The majority of fungal infection is caused by molds. In up to 77% of heart recipients suffering from IFI, *Aspergillus* spp. can be diagnosed as responsible pathogen. The highest incidence of IFI in HT is seen within the first 3 months after transplantation [23]. Because of the comparatively low incidence of IFI, there is no recommendation for universal antifungal prophylaxis. In high-risk HT recipients, prophylaxis with an antifungal

agent which exhibits activity against *Aspergillus* spp. (i.e., voriconazole, itraconazole, posaconazole, isavuconazole, or amphotericin B) is indicated [10]. Identified risk factors for fungal infection in HT are reoperation, delayed chest closure, pre- or perioperative mechanical circulatory support, RRT, concomitant CMV infection, colonization with *Aspergillus* spp., rejection episodes, and prolonged leukopenia after induction therapy [10, 23, 24].

Many patients were bridged to HT by implantation of a left ventricular assist device or by using other mechanical circulatory support. The number of patients treated with any circulatory support device exceeds 5000 per year in Europe and the USA, and the time patients stay on such a device extends constantly [25]. The prevalence of IFI in patients on mechanical circulatory support decreased over the last decades and is now 4.4% [25]. In contrast to HT recipients, most fungal infections in these patient groups are caused by *Candida* spp., a fact that should be considered for empirical therapy in this setting. Patients with implanted devices suffering from IFI should be treated as patients with fungal endocarditis. After successful treatment an antifungal suppressive therapy with an azole should be considered as long as the device is in place [12].

13.2.6 Lung Transplantation

The continuous open contact of the airways to the environment facilitates colonization and infection of lung transplant recipients with fungal spores. So, not surprisingly, the incidence of all IFI is as high as 15–35%, and the incidence of IA was described to reach a portion of up to 60–72% [9, 26]. Recent data show a decline in the incidence of all IFI (26%) as well as in the incidence of IA (44%) in lung transplantation [3]. At the same time, the number of non-*Aspergillus* mold infections is increasing. This trend might be caused by the broader application of a universal antifungal prophylaxis in the setting of lung transplantation. IFI and especially IA cause a tremendous mortality rate (IA up to 68%) in this population.

Besides the permanent exposure of the airway mucosa to inhaled pathogens and an impaired mucociliary clearance, other risk factors for the development of IFI in lung recipients were identified: pre- and posttransplant colonization with *Aspergillus* spp., re-transplantation, unilateral lung transplantation, prolonged bronchial anastomotic ischemia or insufficiency, induction therapy with antithymocyte globulins or monoclonal antibodies, rejection therapy, concomitant cytomegalovirus (CMV) infection, or tracheobronchial stent placement [5, 9, 10, 26].

The strong recommended prophylaxis for lung transplant recipients consists of inhaled nebulized AmB lipid complex or nebulized liposomal AmB. A weaker recommendation for universal prophylaxis with voriconazole also exists. The duration of the prophylactic therapy is indefinite but should, depending on the persistence of risk factors, last for a minimum of 4 months with voriconazole and 12 months with nebulized AmB formulations.

13.2.7 Small Bowel Transplantation

Of all SOT patients, the recipients of small bowel transplantation (SBT) show the highest incidence of both all-cause infections and fungal infections. This group of patients is characterized by long-standing diseases with the need of frequent hospitalizations, parental nutrition, and recurrent infections of central vein catheters. Immunosuppression in SBT consists of a highly effective induction therapy followed by immunosuppression at a higher level as in any other SOT. Due to these factors, the incidence of infectious complications in SBT is 100% [27]. Fungal infections were reported to occur in 40–62% of SBT recipients with a preponderance of yeast infections [3, 27, 28]. The share of candida infections exceeds 80% of all fungal infections with a high number of non-*albicans Candida* species [28].

Besides the underlying predisposition for IFI, several additional risk factors have been identified. A delayed or poor graft function, repeated abdominal surgery, insufficiency of the

bowel anastomoses, rejection episodes, or RRT further increases the probability of manifestation of IFI [10].

Universal antifungal prophylaxis should be administered to all SBT recipients. Also fluconazole is still one recommended options, the use of echinocandins for prophylactic treatment seems reasonable due to the high number of non-*albicans Candida* spp. in SBT [10].

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