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Review

Antifungal prophylaxis in lung transplantation

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ABSTRACT

Lung transplant (LTx) patients have an increased risk of developing invasive fungal infections (IFIs), particularly invasive aspergillosis. Rapid identification of the causative fungal pathogen, to allow for early administration of appropriate initial antifungal therapy, in LTx patients has been challenging due to the limited sensitivity and specificity of the diagnostic tools. Hence, there is increasing emphasis on antifungal prophylaxis in the LTx setting, given the high mortality rates and substantial cost of treating IFIs. Evidence for the optimal antifungal prophylactic approach in this setting, however, remains scant and inconsistent. This review will briefly discuss the epidemiology, risk factors, timing and clinical manifestations of fungal infections in LTx patients and will focus primarily on the available evidence related to the efficacy, safety and practicality of current prophylactic strategies in LTx recipients as well as challenges and gaps for future research.

1. Introduction

Infectious complications following lung transplantation are common, partly due to the immunosuppressive therapy used to prevent graft rejection. According to the International Society for Heart and Lung Transplantation (ISHLT), infections are the leading cause of death, responsible for 38.4% of all deaths in the first year post-lung transplantation [1]. Although fungal infections are less common than bacterial or viral infections in lung transplant (LTx) recipients, they are associated with higher morbidity and mortality [2–4]. Approximately 15–35% of patients develop fungal infections post-LTx, with an overall mortality of nearly 60% [4]. It is vital, therefore, that LTx patients who are at risk of fungal infections should be identified early and managed appropriately. Whilst diagnostic tools for early detection of invasive fungal infections (IFIs) among LTx patients are evolving, they are not without their shortcomings. Hence, antifungal prophylactic therapy appears to be an attractive strategy for reducing the incidence of IFIs and IFI-related mortality in this patient population. A uniform approach, however, has not been established as no randomised controlled trials (RCTs) have been conducted to investigate the optimal agent, route of administration or duration of prophylaxis in LTx recipients [5]. Accordingly, this review will provide a brief overview of the epidemiology, risk factors, timing and clinical manifestations of fungal infections in LTx patients. It will then focus on current evidence associated with antifungal prophylaxis in LTx setting, including the challenges and gaps for future research.

2. Fungal infections in lung transplant patients

2.1. Epidemiology of fungal infections

At present, aspergillosis is the most common IFI (44–63%) among LTx patients [5–8], with *Aspergillus fumigatus* being the most common causative pathogen [6,8]. *Candida* infections remain the second most common causative pathogen (23–23.9%) in the LTx setting, whilst mould infections caused by *Scedosporium* spp. and *Fusarium* spp. are increasing (9.7–19.8%) [6,8].

2.2. Risk factors for fungal infections

A good understanding of the risk factors for developing fungal infection can help to identify high-risk candidates for prophylaxis during their most at-risk period. Direct exposure of the transplanted lungs to the environment, along with impaired defences due to decreased cough reflex and mucociliary clearance, increases

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the risk of invasive aspergillosis (IA) in LTx recipients [9]. Single lung transplantation [10], pre- or post-LTx airway fungal colonisation [11–14], chronic rejection [3] and cytomegalovirus (CMV) infection [15,16] are common predisposing factors for IA in LTx patients. The risk is further enhanced by hypogammaglobulinaemia [17], relative ischaemia at the anastomosis site [18] and bronchial stent placement [19]. Other risk factors include the use of high-dose corticosteroids, anti-lymphocyte therapy, renal impairment, older donor age, longer ischaemic time and use of daclizumab induction [5,20–22]. In contrast, predisposing factors for *Candida* infections or emerging mould infections have not been well described in the LTx setting.

2.3. Timing of fungal infections post-lung transplant

Apart from the assessment of individual risk factors for each LTx patient, the relative chronology of fungal infections plays an important role in determining the use and duration of prophylactic and pre-emptive strategies. The timeline for fungal infections in LTx patients is similar to that in other solid-organ transplant recipients [23–26]. *Candida* spp. are responsible for most infections that occur within the first month post-transplant, due to technical and surgical complications, donor-derived infections and nosocomial risk factors [24,25]. *Aspergillus* infections are uncommon during this period, even in the setting of pre-transplant colonisation [27]. Fungal infection between 1 month and 6 months post-LTx is usually dominated by *Aspergillus* spp. [24], primarily due to intensive immunosuppression [24,25,28]. The time period beyond 6 months post-LTx is complicated by chronic rejection (i.e. bronchiolitis obliterans syndrome) resulting in the need to augment immunosuppression; thus, fungal infections due to endemic fungi [23,29] are reported. In addition, late-onset aspergillosis has been noted in elderly patients with single lung transplantation [30].

2.4. Definitions and clinical manifestations of fungal infections

The European Organisation for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) updated the diagnostic criteria for IFI in 2008 [31]. The updated definitions, however, do not take into consideration the unique clinical syndromes (e.g. colonisation, tracheobronchitis/bronchial anastomotic infection) that are commonly observed in LTx patients. Furthermore, the category of possible IFI appears not to be applicable in the LTx setting [32]. As a result, a working group of the ISHLT has standardised the definitions for fungal infections related to cardiothoracic transplant recipients [32], which will allow for comparisons between studies conducted in LTx recipients.

Of all *Aspergillus* infections, tracheobronchitis or bronchial anastomotic infections are the most common clinical syndromes (33–58%) [30,33,34], with a median time to onset of 2.7 months post-LTx [30]. The mortality rate of LTx recipients with *Aspergillus* tracheobronchitis or *Aspergillus* bronchial anastomotic infections ranges from 23.7% to 29% [7]. Approximately 5–32% of the *Aspergillus* infections in LTx recipients are related to invasion of the lung parenchyma [30,35,36], which then may become disseminated [30]. The median time to onset of IA in LTx recipients has increased from 5.5 months (reported in 2005) [7] to 16.1 months post-LTx (reported in 2009) [5] owing to the widespread use of antifungal prophylaxis [37]. The occurrence of invasive candidiasis remains low, with candidaemia being more common in heart–lung transplant patients, occurring within 18–36 days post-transplant [38]. The incidence of *Scedosporium* infections is higher in LTx recipients compared with other organ transplant patients [39] and these are mostly invasive or disseminated in nature [22,40–43].

Early diagnosis of fungal infections is important to ensure timely and appropriate antifungal treatment for improving patient outcomes. Despite recent advances in diagnostic tools, early and accurate diagnosis of fungal infections in LTx patients remains challenging given the limited sensitivity and specificity of these tools [34,44,45]. Given that fungal infections are associated with high mortality, and the treatment of IFI is often related with a significant cost burden [46], use of antifungal prophylaxis in LTx recipients is now common practice in most LTx centres. Apart from understanding the epidemiology of IFI post-LTx and identifying LTx patients who are at risk of developing IFI, it is also important to evaluate the efficacy and safety of the antifungal agent(s) prescribed for prophylaxis.

3. Antifungal prophylaxis in lung transplant patients

3.1. Definition of antifungal prophylactic strategies

Antifungal prophylactic therapy is defined as the administration of an antifungal agent in order to prevent infection to patients who are neither infected with nor manifesting symptoms of fungal infection [47]. In the LTx setting, various terminologies (e.g. universal, pre-emptive/targeted) have been used in studies involving antifungal prophylaxis (Table 1). If antifungal prophylaxis is given to all recipients regardless of the presence of risk factors or immediately after LTx [48,49], it is known as universal prophylaxis. Alternatively, some authors advocate pre-emptive/targeted prophylaxis in LTx patients whom are at very high risk for developing IFI [50]. These high-risk LTx recipients include those with airway fungal colonisation [48,49,51], underlying cystic fibrosis [49], hyperacute rejection/acute graft failure [24], CMV infection [24] and bronchial ischaemia [24].

3.2. Evidence for and types of antifungal prophylaxis

The evidence for antifungal prophylaxis in reducing the incidence and risk of IA in LTx recipients has been conflicting [4,52,53]. At present, there is no consensus among LTx centres with respect to the choice of antifungal agent, dose and duration owing to the paucity of data from multicentre RCTs evaluating the various prophylactic strategies [24]. The dearth of data has been identified as one of the possible reasons for high mortality in LTx patients [4]. As LTx recipients show significant and sustained rates of infection, antifungal prophylaxis is often thought to be desirable [54]. Consequently, well-controlled trials with clinically relevant endpoints to demonstrate the efficacy and safety of antifungal agents used prophylactically in the LTx setting are warranted.

To date, 27 studies have investigated the efficacy and/or safety of antifungal prophylaxis in the LTx setting (Table 1). Most were retrospective reviews, case series, uncontrolled trials or comparisons with historical controls, with a limited number of prospective, single-centre, non-comparative studies [16,35,48,55–78]. Of the studies listed in Table 1, most were related to universal prophylaxis; only five evaluated pre-emptive/targeted antifungal prophylactic use [35,57,63,74,78] and another three compared universal prophylaxis with pre-emptive/targeted prophylaxis [48,73,76].

There have been debates regarding the most suitable type of antifungal prophylactic strategy to use in the LTx setting. Extensive use of universal prophylaxis may increase exposure to potential toxicities of the antifungal drug, the risk of drug–drug interactions, the risk of developing antifungal drug resistance and costs [79]. Conversely, pre-emptive/targeted prophylaxis may not be feasible as high-risk LTx recipients are not readily identifiable, the diagnostic tests to be used in the strategy are not well defined, and the period of vulnerability to *Aspergillus* infections in these patients always extends over several months [50].