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Therapeutic approach to respiratory infections in lung transplantation

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ABSTRACT

Lung transplant recipients (LTRs) are at life-long risk for infections and disseminated diseases owing to their immunocompromised state. Besides organ failure and sepsis, infection can trigger acute and chronic graft rejection which increases mortality. Medical prophylaxis and treatment are based on comprehensive diagnostic work-up including previous history of infection and airway colonisation to reduce long-term complications and mortality. Common bacterial pathogens include *Pseudomonas* and *Staphylococcus*, whilst *Aspergillus* and *Cytomegalovirus* (CMV) are respectively the commonest fungal and viral pathogens. Clinical symptoms can be various in lung transplant recipients presenting an asymptomatic to severe progress. Regular control of infection parameters, daily lung function testing and lifelong follow-up in a specialist transplant centre are mandatory for early detection of bacterial, viral and fungal infections.

After transplantation each patient receives intensive training with rules of conduct concerning preventive behaviour and to recognize early signs of post transplant complications. Early detection of infection and complications are important goals to reduce major complications after lung transplantation.

1. Introduction

Due to their chronic immunocompromised state lung transplant recipients (LTRs) are at increased lifelong risk of respiratory tract infections and other severe complications (Table 1). Immunosuppressive regimes include a combination of calcineurin inhibitor (cyclosporine or tacrolimus), an anti-proliferative agent (mycophenolate mofetil (MMF), azathioprin or sirolimus) and prednisone. Impaired mucociliary function and cough reflex, altered lymphatic drainage and donor-transmitted pathogens encourage infections besides the immunosuppressive state [1]. The clinical course of upper and lower respiratory tract infections varies in these patients. They may present with systemic symptoms such as fever, myalgia and fatigue or localized upper or lower airway symptoms with or without deteriorated lung function. Development of any such symptoms necessitates urgent evaluation at the transplant centre. Diagnostic work-up includes patient history and physical examination, laboratory results, blood gas analysis, lung function testing, chest radiography in conjunction with either sputum samples or bronchoscopy with bronchoalveolar lavage (BAL) and possibly transbronchial biopsies. In the initial period after lung transplantation (LTx), infections tend to be bacterial, followed by fungal microorganisms and viruses [2,3].

Immediate and appropriate treatment is essential in preventing complications such as septicaemia, acute respiratory distress syndrome (ARDS), acute graft rejection and death. Infections and acute cellular rejection (AR) can trigger chronic lung allograft dysfunction (CLAD) [4–6].

CLAD is an emerging umbrella term encompassing all different forms of chronic graft dysfunction. Traditionally CLAD has been considered as an obliterative bronchiolitis (OB) characterized by fibroproliferative processes in smaller airways along with peribronchial and perivascular inflammation leading to an obstructive ventilatory defect [2,7,8]. In attempting to grade graft dysfunction, The International Society for Heart and Lung Transplantation

Abbreviations: ARDS, acute respiratory distress syndrome; AR, acute cellular rejection; BAL, bronchoalveolar lavage; BCC, Burkholderia cepacia complex; CARV, community-acquired respiratory viruses; CF, cystic fibrosis; CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; IA, invasive aspergillosis; ISHLT, The International Society for Heart and Lung Transplantation; LTRs, lung transplant recipients; MMF, mycophenolate mofetil; NRAD, neutrophilic reversible allograft dysfunction; OB, obliterative bronchiolitis; PCR, polymerase chain reaction; PTLD, posttransplant lymphoproliferative disorder; RAS, restrictive allograft syndrome; SOTr, single organ transplantation recipients; TMP-SMX, trimethoprim-sulfamethoxazole.

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Table 1
Cause of death in LTRs; modified from ISHLT register report 2011 (between Jan. 1992 and Jun. 2010).

Cause of death	0–30 days ($n = 321$), no. (%)	31 days–1 year ($n = 249$), no. (%)	>1–3 years ($n = 223$), no. (%)
Bronchiolitis	0	6 (2.4)	50 (22.4)
acute rejection	3 (0.9)	8 (3.2)	4 (1.8)
Lymphoma	0	8 (3.2)	11 (4.9)
Malignancy, other	0	4 (1.6)	12 (5.4)
Infection	52 (16.2)	81 (32.5)	67 (30.0)
Graft failure	92 (28.7)	54 (21.7)	34 (15.2)
Cardiovascular	25 (7.8)	11 (4.4)	20 (9.0)
Technical	71 (22.1)	9 (3.6)	2 (0.9)
Other	78 (24.4)	68 (27.3)	23 (10.3)

(ISHLT) defined the term bronchiolitis obliterans syndrome (BOS) as an irreversible decline in FEV1 to less than 80% of baseline [9]. Treatment options in CLAD remain both limited and unpredictable and include immunomodulation with oral macrolides (azithromycin or clarithromycin), a leukotriene receptor antagonist (montelukast) and extracorporeal photopheresis [10–15].

Neutrophilic reversible allograft dysfunction (NRAD) represent a possible sub-set within CLAD, with patients initially fulfilling BOS criteria along with demonstrating profound BAL neutrophilia, that reverses completely after initiating azithromycin. In contrast, another recently described CLAD form known as the restrictive allograft syndrome (RAS) is characterized by a progressing restrictive ventilatory defect and peripheral lung fibrosis. This form generally exhibits a rapid, treatment refractory course and is inevitably associated with high mortality [16].

The development of these complications affects the long-term survival of LTRs and therefore needs to be identified.

2. Bacterial infections

Impaired cough reflex, swallowing and hypoventilation after surgery may increase the risk of pneumonia. Common pathogens include *Pseudomonas aeruginosa*, *Staphylococcus aureus* as well as other gram-negative organisms with important resistance profiles [2].

Management of these infections requires comprehensive work-up, including microbiological cultures, molecular tests, detection of urinary antigens for *Legionella* and *Pneumococcal* with interim broad-spectrum empirical antibiotic prophylaxis until all results are available. Each work-up should include bronchoscopy with bronchoalveolar lavage (BAL) for microscopy, culture and polymerase chain reaction (PCR) testing and when indicated transbronchial biopsies.

Preoperative airway colonization with gram-negative organisms e.g. in Cystic Fibrosis (CF) patients increases pneumonia risk in LTRs [17]. Increasingly this refers to multi-resistant gram-negative (MRGN) organisms which present considerable challenges to treating physicians in deciding upon appropriate antibiotic regimes.

Mycobacterial infection in LTRs is rare and largely due to non-tuberculous mycobacteria [3,18]. Diagnosis should be considered especially in areas with high prevalence.

Pneumocystis jirovecii pneumonia in solid organ transplantation recipients (SOTr) is extremely serious and can cause significant loss in graft function and often requires intensive care admission. Mortality remains at around 60% despite treatment with high-dose trimethoprim-sulfamethoxazole (TMP-SMX) [19]. In suspected pneumocystosis urgent work-up including BAL with PCR should be performed and treatment started immediately. Given the high risk of infection among SOTr, lifelong TMP-SMX *P. jirovecii* prophylaxis is recommended and has proven very effective [20–22] (Fig. 5).

For many years, patients with Burkholderia cepacia complex (BCC) were considered unsuitable transplant candidates due to an unacceptably high risk of lethal infection after transplant. Improved detection has identified different species with varying pathogenicity. Subsequently restrictions in transplant suitability have been reduced to include only subtypes including Burkholderia cenocepacia (genomovar III) and Burkholderia gladioli, which represent the main mortality risk after transplantation [23–25].

Nocardia spp. are gram-positive, aerobic actinobacteria causing life-threatening infections, predominantly amongst immunosuppressed patients. *Nocardia asteroides* type IV (*Nocardia cyriacigeorgica*) is the commonest pathogen leading to pulmonary or disseminated extrapulmonary nocardiosis that is often lethal. Nocardiosis may present with a variety of radiological findings (Figs. 1–3) making differentiation from other pathogens and diseases difficult. Nocardia spp. pneumonia is found in approximately 2% in LTRs and *Nocardia farcinica* is associated with poor outcome [26,27].

Tissue necrosis is occasionally associated with the granulomatous response and may imitate histoplasmosis or tuberculosis. The treatment of choice is protracted TMP-SMZ, second-line therapy is imipenem and amikacin. Treatment should be started immediately and may last for 6 months or longer in pulmonary or systemic nocardiosis to prevent relapse and failure of treatment [28].

3. Fungal infections

Aspergillus species (*Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus flavus* and *Aspergillus versicolor*) or *Candida* species (*Candida albicans*, *Candida glabrata* and *Candida krusei*) represent the predominant fungal infections. All can be identified by BAL cytological evaluation, serum antigen levels or occasionally are suspected in macroscopic endobronchial lesions observed at bronchoscopy and subsequently confirmed on microscopic assessment of mucosal biopsies.

Fungal infections in LTRs may reflect localized airway involvement, invasive forms involving lung parenchyma or disseminated disease.

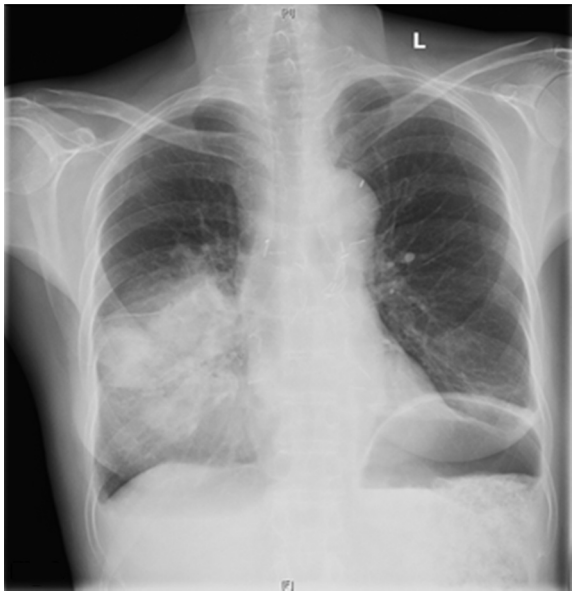

Fig. 1. Pulmonary nocardiosis in a 59 year-old-female double-lung transplant recipient two years after transplantation. Chest x-ray image shows enlarged infiltrations in the right lower lobe. BAL culture revealed *Nocardia farcinica*.