

Pulmonary Infections in Lung Transplant Recipients

a report by

Krisztina Czebe¹, Balazs Antus¹, Eszter Csizser¹ and Ildiko Horvath²

1. Department of Pulmonology; and 2. Department of Pathophysiology,
National Koranyi Institute for Tuberculosis and Pulmonology

During the last two decades lung transplantation has become an accepted therapeutic modality for end-stage diseases of the lungs and the pulmonary circulation. Depending on the underlying disease, single or double lung transplantation or heart–lung transplantation can be performed. According to the registry of the International Society of Heart and Lung Transplantation (ISHLT), a total number of 1,703 lung transplants were performed in 2003, and one-, three- and five-year survival rates were 76%, 60% and 49%, respectively. In 2005 in the Eurotransplant region (Austria, Belgium, Germany, Luxemburg, The Netherlands and Slovenia) 444 lung transplantations were performed.

It is well known that infectious complications are the most common cause of morbidity and mortality at all time-points after lung transplantation. Infection rates among lung transplant recipients appear to be higher than those encountered in other solid organ transplant populations; for example, they may occur twice as frequently as in heart recipients.

The likelihood of developing a pulmonary infection is particularly high in the first half-year after transplantation, due to the augmented immunosuppression. In the later years, when bronchiolitis obliterans syndrome (BOS) develops, infectious complications are again more frequent. Pathologically, bronchiolitis obliterans (BO) is characterised by mononuclear cell infiltration, followed by the disturbance of the respiratory epithelium and progressive accumulation of fibroblasts and fibrous connective tissue in the airways. In patients with BOS, obliteration of the small airways, development of bronchiectasis and the enhanced immunosuppression, which is believed to slow down the obliterative process, are additional risk factors for infections. Death of BOS patients is usually related to respiratory failure due to recurrent respiratory tract infections or sepsis.

Epidemiology

Bacterial Pneumonia

Bacterial pneumonia is the most common infection in

lung transplant recipients during the first post-operative months. The reported incidence range is 35–70%. Gram-negative organisms pre-dominate as the cause of these infections, and they can often be cultivated from the donor lung. Therefore, it is very important to know precisely the medical history of the donor (occult pre-transplant infection such as tuberculosis (TB) and duration of mechanical ventilation).

Before transplantation, bacteriological examination of the bronchial washings of the donor lung should be performed in all cases. After transplantation, the recipient's own bacterial flora may become a source of infection. The native lung in single lung recipients and the trachea and the para-nasal sinuses in all transplant patients can serve as a good reservoir for various micro-organisms such as gram-negative bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA), *Candida*, *Aspergillus* and non-tuberculous mycobacteria. This is especially true for patients with cystic fibrosis (CF), whose native airways and sinuses are chronically infected with virulent bacterial pathogens. Nonetheless, there is now evidence that CF patients have no excessive risk of post-operative infections. Some points with this unique patient population, however, have to be considered. First, CF patients should repeatedly undergo rigorous infection screening together with antibiotic sensitivity testing before transplantation. Furthermore, it is recommended to perform a sinus CT scan and, if necessary, sinus surgery before transplantation to improve the drainage of infected para-nasal sinuses. Colonisation with *Burkholderia cepacia* has been associated with high risk of severe post-operative infections and, consequently, with inferior survival rate. Therefore, many centres limit offering lung transplantation to CF patients with *Burkholderia cepacia*. In those CF patients colonised with other multi-resistant bacterial strains – *Pseudomonas sp.*, *Stenotrophomonas maltophilia* – synergy test should be performed. If effective antibiotic combinations against these multi-resistant organisms cannot be assessed, the patient cannot be accepted for lung transplantation.

To reduce the risk of post-operative bacterial pneumonia, early prophylactic application of broad-spectrum antibiotics has been initiated in most

Krisztina Czebe is responsible for the care of lung transplant patients at the Hungarian Lung Transplantation Program at the National Koranyi Institute in Budapest. From 2002 to 2004 she worked in the transplantation group of the University of Vienna, Austria with the help of a scholarship from the Hungarian Respiratory Society. Dr Czebe is trained in pulmonary medicine and bronchology and obtained her medical degree from the Medical University of Debrecen, Hungary in 1998.

Balazs Antus is a pulmonologist and researcher at the National Koranyi Institute in Budapest. Prior to this, Dr Antus was a member of the department of pathophysiology at Semmelweis University in Budapest. During his training he spent two years in University Hospital Essen, Germany with a DAAD scholarship. His research interest is in the field of clinical and experimental transplantation and tissue fibrosis. Dr Antus is author/co-author of over 25 scientific papers in national and international journals. He obtained his medical degree from the Semmelweis University Budapest in 1997 and completed his PhD thesis in 2001.

Eszter Csizser is the Head of the IV Department of Pulmonology at the National Koranyi Institute. She is specialist in internal medicine, pulmonology and oncology. She has led the team for care of lung transplant recipients for six years. Dr Csizser is author/co-author of 35 scientific publications.

Ildiko Horvath is the Head of the Department of Pathophysiology at the National Koranyi Institute, studying airway diseases with special interest in exhaled biomarkers. She spent three years involved in research at the National Institutes of Health, Bethesda, US and one year at Imperial College and Royal Brompton Hospital in the department of thoracic medicine led by Professor Peter J Barnes. She is the author of around 100 scientific publications and book chapters.

transplant centres. At first, antibiotics are selected on the basis of pre-operative culture-results. These results can then be modified into culture-results obtained from the donor lung or the bronchoalveolar lavage performed routinely on the first post-operative day. Using this policy, the frequency of post-operative bacterial pneumonia has recently declined to <10%.

The so-called atypical bacterial infections (*Mycoplasma pneumoniae*, *Chlamydia pneumoniae* and *Legionella sp.*) are rarely seen, but should be suspected in patients with severe pneumonia.

Mycobacterium TB

TB is an infrequent but important complication after lung transplantation, affecting 1–6% of patients. It usually occurs in the first six months post-transplant, and may be due to reactivation of tubercle bacilli in the remaining native lung after single lung transplantation or transmission by the transplant. In transplant recipients, TB can often be fatal. If it is clinically suspected, the polymerase chain reaction (PCR) method is recommended to confirm the diagnosis as early as possible. Classical culture techniques are also required. For prophylactic purposes, Mantoux test and sputum culture analysis cannot be left out from standard investigations before transplantation.

Non-tuberculous Mycobacteriosis

Non-tuberculous mycobacteria are very rarely found after lung transplantation. They usually present as an indolent disease and respond well to treatment.

Viral Infections

Cytomegalovirus

The second most frequent infection, after bacterial infection, is caused by cytomegalovirus (CMV). Previously, the prevalence of this infection was found to be 53–75%, but this number has declined markedly. Due to the routine administration of prophylactic ganciclovir, or more recently valganciclovir, for 100 days after transplantation plus the administration of CMV-hyperimmunoglobulins, not only the number but the clinical picture of this infection has changed. The incidence of fulminant CMV-infection has decreased to approximately 4% and latent and sub-clinical CMV-reactivations became more frequent. The infection is most frequent in cases of donor+/recipient- CMV-antigen matches, so-called 'sero-mismatch', but the infection can also reactivate in other patients, especially after the end of prophylactic treatment. CMV infection/reactivation is not always accompanied by pneumonitis and radiographic changes. Routine blood or bronchoalveolar lavage tests

for CMV antigen or PCR analysis are important to reveal CMV infection. Differential diagnosis between acute rejection and CMV infection is based on the histological investigation of bronchial biopsies. CMV infection is confirmed by the presence of typical epithelial 'owls-eye cells' and the demonstration of immediate early antigen with monoclonal E13 antibody. The importance of CMV-replication is given by its potential to initiate acute and/or chronic rejection, therefore leading to graft function loss and as a consequence increase in mortality.

Epstein-Barr Virus

The infection caused by Epstein-Barr virus (EBV) has a role in the development of post-transplant lymphoproliferative disease (PTLD), affecting the lungs, gastrointestinal tract and the nervous system. Peak incidence of EBV infection is in the first year after transplantation. The diagnosis is based on serological reactions.

Respiratory Viral Infections

Infections caused by this group of viruses (influenza, para-influenza, respiratory syncytial virus (RSV) and adenovirus) occur seasonally and do not show relation to time after transplantation. Clinically they may appear as banal cases or be associated with mild loss of lung function, but could present themselves as severe diseases, causing dyspnoea and hypoxaemia. During the early post-operative period they may cause fulminant, therapy-resistant severe rejections and bacterial and/or fungal super-infections resulting in early death. Later they can induce chronic rejection, and BOS is frequently associated with viral infections. Diagnosis is made from bronchoalveolar lavage and needle biopsy by immunofluorescent and PCR techniques.

Fungal and Yeast Infections

Fungal infections are of central importance in terms of morbidity and mortality. Colonisation occurs in 22–85%, and invasive aspergillosis appears in 14–45% of lung transplant recipients, the latter having a mortality rate of 30–75%. In the immunocompromised host, the severity of problems caused by *Aspergillus* and *Candida* species may vary widely; from simply colonisation to necrosis, ulceration at the anastomosis, mediastinitis, life-threatening invasive diseases and systemic fungal sepsis associated with high mortality rate. Most frequently they develop during the first six months following transplantation. Therefore, prophylactic use of nebulised amphotericin-B is justified for three months and for high-risk patients, systemic anti-mycotic treatment is also administered.

When BOS appears, invasive aspergillosis has to be

considered if cavernous changes appear on X-ray. Bronchial biopsy or lavage samples can be used to establish the diagnosis. Treatment of fungal pneumonia and invasive aspergillosis is conventionally based on intravenous amphotericin-B, but there are also newer drugs available.

Protozoal Infections

Typically, these infections are caused by *Pneumocystis carinii*, *Toxoplasma gondii* and *Nocardia sp.*, although nowadays as the result of the prophylactic treatment with trimethoprim-sulphamethoxazole *Pneumocystis carinii* – caused pneumonia is infrequent. PCR is used for diagnosis from bronchial samples.

Diagnostic Possibilities

The central aim of the protocols for patient care, developed by different transplant centres, is regular monitoring of patients for early detection of potential infections and/or rejections, proper monitoring of medication (with special attention paid to potential interactions and adverse reactions) and recognition of development of malignant diseases. Most importantly, investigations aiming to diagnose or exclude infections as part of routine controls as indicated by the clinical picture are listed in Table 2.

The gold standard for the differential diagnosis of infections and rejections is bronchoscopy. This investigation, however, is invasive and costly. There is a need for newer, possibly non-invasive methods. At our institution, measurement of exhaled nitric oxide (FENO) is part of the routine in the follow-up assessment of lung transplant recipients. FENO level has increased due to upper and/or lower airway infections.¹⁸ Other groups, however, have reported that FENO levels increase in BOS, therefore the potential of this measurement for differential diagnosis seems to be more questionable and its evaluation needs further study.

Conclusion

Infectious complications are still an important limitation to patient survival after lung transplantation. To improve survival and quality of life after lung transplantation appropriate patient selection, proper immunosuppression and infection prophylaxis with well-managed infection control are of central importance. Development of even faster, more sensitive diagnostic tests and newer antimicrobial agents can facilitate this process and research in these areas may have important clinical impact. ■

Acknowledgement

FENO measurements are supported by the Hungarian

Table 1: Most Frequent Pathogens Causing Infections After Transplantation

	Frequent species	Time after transplantation	
Bacteria	Gram-negative bacteria	First three months and if BOS develops	
	<i>Pseudomonas aeruginosa</i>		
	<i>E. coli</i>		
	<i>Klebsiella</i>		
	<i>Haemophilus</i>		
	<i>Proteus</i>		
	<i>Stenotrophomonas</i>		
	Gram-positive cocci	First three months	
	<i>Staphylococcus (MRSA)</i>		
	<i>Streptococcus</i>		
Mycobacteriumok:	<i>M. tuberculosis</i>		
	Atypical tuberculosis	First half year	
	Viruses	Herpes family	
		CMV	>3 month and BOS
EBV		First year	
HSV		First weeks	
	VZV	First few months	
Respiratory Viral	Influenza	Seasonal	
	Parainfluenza		
	Adenovirus		
	Rhinovirus		
	RSV		
	Fungi and yeast	<i>Aspergillus flavus</i>	First half year and BOS
<i>Aspergillus nigger</i>			
<i>Candida albicans</i>			
<i>Mucor</i>			
Protozoons	<i>Toxoplasma gondii</i>	First year	
	<i>Pneumocystis carinii</i>		
	<i>Nocardia sp.</i>	Any time	

Table 2: Investigations to Diagnose Infections

Routinely practised	Indicated by clinical picture	Newer developments
Blood cell count, CRP, kidney and liver function	Procalcitonin	Measurement of exhaled nitric oxide
Serology: CMV, EBV	Virus serology	Assessment of exhaled breath condensate
Chest X-ray, CT	Fungi serology	
Lung function, blood gases	MR	
Bronchoscopy, lavage and biopsy	Culture (blood, lavage, sputum) investigations	
	Antibiotic resistance test	
	Antibiotic synergy test	
	Protected brushing (bronchoscopy)	
	Open lung biopsy	

Scientific Research Foundation (grant number: T43396 and F46526).

A version of this article containing references and additional table can be found in the Reference Section on the website supporting this briefing (www.touchrespiratorydisease.com).